

Safety Update on TNF- α Antagonists:

Infliximab and Etanercept

**Food and Drug Administration
Center for Biologics Evaluation and Research**

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I. 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 (InfliximabTM) 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 (EtanerceptTM), 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).

II. 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. **Table 2** and **Figure 1** show the major categories of adverse events reported with etanercept and infliximab as of June 2001.

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 is common which often prove inaccurate. 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. Adverse events reported in these categories are shown in Table 3. 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. Demyelinating Disease and 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).

- Report #00060425 describes a 43 year old man with psoriatic arthritis in an investigator-sponsored IND who developed numbness and tingling of his hands and feet 8 months after starting etanercept 25 mg sc biw. Follow-up examination 6 months later showed loss of dexterity and numbness in both hands and hypoactive reflexes. MRI of the spinal cord showed an abnormal signal consistent with transverse myelitis or demyelinating disease. MRI of the brain showed multiple lesions consistent with MS. The patient continued on etanercept and was given no therapy for his neurologic symptoms.
- Report #98050033 describes a 48 year old woman with RA who developed lower trunk and lower extremity sensory and spasticity changes 15 months after beginning etanercept therapy. Thoracic and brain MRI were reported as consistent with MS. Etanercept was discontinued temporarily and patient was treated with interferon beta 1b.

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

- Report #00010721 describes a 56 year old woman with RA and previous neurologic signs and symptoms who experienced left-sided numbness after 12 months on etanercept. Twenty-six years previously, the patient had an episode lasting 24 hours where she was unable to read a printed page and had difficulty swallowing. MRI at that time showed a brain lesion, but no diagnosis of MS was made. With the recent episode, an MRI showed an abnormal focus at T2 and lumbar puncture showed oligoclonal bands. A diagnosis of MS was made and the symptoms subsided upon treatment with prednisone.
- Report #99110062 describes a 40 year old woman with a past history of optic neuritis with demyelination who developed numbness in the legs, facial and peripheral paresthesias and visual disturbances after approximately 8 months on etanercept. An MRI showed multiple active lesions and she was diagnosed with MS. Consulting neurologists diagnosed mild relapsing remitting MS. She was treated with interferon alpha-1a and subsequently glatiramer, a synthetic copolymer consisting of the amino acids glutamic acid, alanine, lysine and tyrosine that is indicated for reduction of the frequency of relapses in patients with relapsing-remitting MS. Etanercept was stopped temporarily then restarted at once weekly doses. On follow-up, the patient stated that her muscle control was satisfactory, but her eyesight was still affected.

Five additional cases were submitted:

- Case #00030099 was a 37 year old man with RA who developed an altered mental status after 3 months on etanercept. He presented with confusion, difficulty writing and difficulty drawing a clock face. An MRI showed a large area of signal intensity in the left parietal and occipital lobes consistent with an old infarction or with demyelinating disease. A stereotactic biopsy of the brain showed demyelination. Etanercept was discontinued. Symptoms improved after 5 days of IV methylprednisolone. Repeat MRI showed inflammatory demyelination with lesions in the left parietal and occipital areas. LP was negative for oligoclonal bands. He received oral dexamethasone with a taper. Symptoms returned upon subsequent reintroduction of etanercept. Follow-up indicates that patient has a permanent neurologic deficit consisting of an inability to do simple math, with higher math function unaffected.

Reviewer comment: This case is 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 hardly typical. The patient was left with residual deficits. It is particularly notable that the patient had a positive etanercept rechallenge, although the concomitant discontinuation of corticosteroids makes attribution of the worsening difficult.

- Case #00040265 is a 49 year old man with RA who presented with altered mental status, difficulty walking, muscle rigidity and respiratory distress requiring intubation after 4 months on etanercept. MRI showed an area of increased signal in the left frontal lobe and white matter changes consistent with demyelination. A brain biopsy showed spongiotic changes in the white matter. Repeat MRI showed extensive

leukodystrophy involving entire white matter. He gradually improved on methylprednisolone. He was discharged from the hospital with residual left-sided weakness and dysphagia.

Reviewer comment: This case describes a catastrophic neurologic event characterized by leukodystrophy involving the entire white matter with altered mental status, muscle rigidity, and eventual partial recovery.

- Report #00010699 describes a 37 year old man with psoriatic arthritis who developed dysesthesias of the feet, which ascended both legs to the mid thigh after 2 months on etanercept. An MRI showed demyelination of the cervical spine. LP showed an increased protein, but no demyelinating profile. A repeat MRI showed resolution of the cervical demyelination. Etanercept was discontinued.

Reviewer comment: This case does meet the clinical criteria for MS, for neurologic signs and symptoms to be separated in time and space.

- Case #00050658 describes a 43 year old man with RA who was hospitalized with optic neuritis and papilledema following 2 and ½ months on etanercept. No other information is available.

Reviewer comment: Optic neuritis can be the initial presentation of MS, but in this case no additional information is available to make a definitive diagnosis at this time.

- Case #00050732 describes a 48 year old woman with psoriatic arthritis and a history of Lhermitte's symptom who developed recurrence of numbness in the lower legs when flexing the neck shortly after starting etanercept. Lhermitte's symptom is a momentary electric-like sensation evoked by neck flexion, other neck movements, or coughing, which is experienced as a shooting phenomenon that travels down the spine and into the legs. Lhermitte's symptom is common in MS. C-spine MRI was negative, as was a myelogram. A brain MRI showed increased uptake at the optic nerve consistent with optic neuritis, although there were no symptoms to go along with that diagnosis. Visual evoked potentials were prolonged. Etanercept was discontinued.

Reviewer comment: Symptoms and results of imaging studies are consistent with MS but are not adequate to establish a diagnosis of MS. The described symptoms following initiation of etanercept are difficult to evaluate since they were present prior to initiating etanercept therapy.

B. Review of the Literature

Considerable data suggested that TNF α 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 (cases #00060425 and #99110062). Another case (#00030099) worsened on reinstating etanercept therapy (positive rechallenge), however the worsening 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.

IV. Demyelinating Disease and Infliximab

The attached manuscript (Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-TNF α 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.

V. Seizures and Etanercept

A. Summary of Adverse Events

The sponsor submitted 14 reports of seizures or convulsions from post-licensure adverse event reports on etanercept. In two cases (#99040019 and #99080056), 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. They are as follows:

- Report # 99080668: 52 year old woman with diabetes mellitus, hypertension, and RA, who developed nocturnal tonic-clonic seizures during the first month on etanercept. No prior history of seizures. Seizures stopped after discontinuing etanercept. EEG was abnormal, consistent with epilepsy.
- Report # 99100644: 33 year old woman with RA who developed a seizure after 1 month on etanercept. EEG showed generalized epileptiform discharges. Etanercept

was discontinued and no further seizures were observed. No recent head injury and no h/o seizures. She does drink alcohol, but had had no recent heavy alcohol consumption.

- Report # 00010703: 46 year old woman with RA who was hospitalized for 2 epileptiform events after 4 weeks on etanercept. No h/o seizures. Etanercept was restarted without reoccurrence of seizures.
- Report # 00040296: 27 year old woman with RA who experienced a grand mal seizure 1 week after starting etanercept. No h/o seizures. CT scan negative. EEG was consistent with a seizure disorder. Placed on Dilantin and etanercept discontinued with no further seizures. No h/o head trauma, recent medication change or alcohol or recreational drug use.

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.

VI. Aplastic Anemia and Pancytopenia in Etanercept Therapy

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. The aplastic anemia cases are as follows:

- Mfg report #: 00070362

Case: 78 year old woman with no prior history of blood dyscrasia before etanercept. Began etanercept 12/1/99. On 4/6/00, developed diffuse petechiae. WBC 4,200, Hct

29.9, Hb 9.8 and plt 16,000. Bone marrow biopsy showed <10% cellularity. She received corticosteroids and equine ATG and lymphocyte immune globulin but showed no improvement. She died of sepsis on 5/15/00.

Time from onset of etanercept therapy: 4 months

Other immunosuppressive medications: None

Prior history of blood dyscrasia: No

Outcome: Death

Attribution: Temporal association with beginning etanercept therapy. No other factors predisposing to aplastic anemia are apparent.

- Mfg report #: 00070516

Case: 34 year old woman with RA, DM and renal failure requiring dialysis, hospitalized with aplastic anemia after 2 months on etanercept. A bone marrow biopsy showed all 3 cell lineages at < 5% cellularity. She was treated with sargramostim with some improvement in cell counts. She developed a sinus infection with aspergillosis, precluding the use of ATG or bone marrow transplantation. She died.

Time from onset of etanercept therapy: 2 months

Other immunosuppressive medications: None

Prior history of blood dyscrasia: None

Outcome: Death

Attribution: Associated in time with beginning etanercept. No other factors predisposing to aplastic anemia are apparent.

The pancytopenia cases are as follows:

- Mfg report #: 00090320

Case: 51 year old woman with RA who developed pancytopenia, olecranon bursitis and bacteremia 3 wks after beginning etanercept. Also on methotrexate 26 mg qw. Blood cultures were positive for staph aureus. On admission, WBC were 3,100, plt 213,000 and WBC fell to 500 and plt to 25,000. A bone marrow biopsy showed 15-20% cellularity with hypoplasia of all 3 elements. Patient died of sepsis. Blood counts had been normal in July, 2000. She had experienced transient thrombocytopenia and anemia associated with intraoperative bleeding during a hip arthroplasty in March 2000.

Time from onset of etanercept therapy: 3 wks

Other immunosuppressive medications: Methotrexate

Prior history of blood dyscrasia: Thrombocytopenia and anemia with surgery

Outcome: Death

Attribution: Associated in time with beginning etanercept. Other potentially confounding factors which may induce bone marrow suppression include methotrexate use and sepsis.

- Mfg report #: 00080228

Case: 74 year old woman was hospitalized with pancytopenia, erythema multiforme and renal insufficiency after 4 doses of etanercept. BUN was 53 and creatinine 2.1. Patient was also receiving methotrexate and captopril. She had previously been treated with azathioprine and, most recently, leflunomide until 2 months prior to beginning etanercept. After treatment with filgrastim and IV antibiotics, blood counts returned to normal. During leukopenia, patient experienced polymicrobial bacteremia. Bone marrow biopsy showed markedly hypocellular bone marrow with reduction in all 3 elements, consistent with hypoplastic anemia. CBC was Hb 8.8, WBC 580, platelet count 19,000. Also developed respiratory failure with diffuse pulmonary infiltrates requiring intubation, renal failure.

Time from onset of etanercept therapy: 2 weeks

Other immunosuppressive medications: Methotrexate, prior leflunomide and azathioprine

Prior history of blood dyscrasia: No

Outcome: Recovered

Attribution: Pancytopenia associated in time with beginning etanercept, however the development of renal insufficiency while receiving methotrexate may also have contributed. In addition, patient was recently on leflunomide and this may have contributed, given that drug's prolonged half-life. The fact that patient presented with erythema multiforme raises the question of whether both clinical features are due to drug hypersensitivity. According to Harrison's Online, most drug reactions of the skin occur within 1 to 2 weeks of initiating therapy, consistent with this timeframe. There are case reports of erythema multiforme and aplastic anemia/pancytopenia presenting together as a drug reaction. However, erythema multiforme also has non-drug causes, including herpes simplex infection.

- Mfg report #: 00020630

Case: 71 year old woman with RA who developed a decreased WBC count 1 month after beginning etanercept. Other medications include azathioprine and celcoxib. 6 weeks before beginning etanercept, WBC was 4.1. After 1 month on etanercept, WBC was 2.6. A bone marrow biopsy showed a hypocellular bone marrow with granulocytic hypoplasia and cellularity approximately 20%. WBC counts recovered slowly after discontinuing etanercept, azathioprine and celcoxib. After celcoxib was reintroduced, WBC fell from 4.6 to 2.9, then recovered spontaneously.

Time from onset of etanercept therapy: 1 month

Other immunosuppressive medications: Azathioprine

Prior history of blood dyscrasia: None reported

Outcome: Recovered

Attribution: Granulocytopenia associated in time with initiation of etanercept.

Although Felty's syndrome also causes granulocytopenia in RA patients, the bone marrow biopsy results are not consistent with Felty's. Concomitant use of azathioprine makes it difficult to attribute this specifically to etanercept.

- **Mfg report #: 99110105**

Case: 41 year old man with RA developed leukopenia and thrombocytopenia after 3 months on etanercept. Patient was also on stable 6-mercaptopurine and had ulcerative colitis and hepatitis C. WBC fell to 1,000 and platelet count to 40,000. A bone marrow biopsy showed hypoplasia. After receiving steroids and IVIg, plts rose to 100,000 and WBC to 4,500.

Time from onset of etanercept therapy: 3 months

Other immunosuppressive medications: 6-MP

Prior history of blood dyscrasia: Prior history of anemia, splenomegaly

Outcome: Recovered after steroids, IVIg

Attribution: Leukopenia and thrombocytopenia associated in time with beginning etanercept. However, other factors may contribute as well, including concomitant 6-MP, splenomegaly, ulcerative colitis and hepatitis C.

- **Mfg report #: 99070643**

Case: 58 year old man with RA and vasculitis of the lungs who presented with pneumonia, respiratory failure and pancytopenia after 2 months on etanercept. Prior to this admission, patient had been hospitalized with severe vasculitis and was discharged on cyclophosphamide and high dose corticosteroids. He was not closely monitored on this regimen. Platelet count was 74,000, WBC 324, Hb 11. Patient died shortly after arrival at the hospital ER. The reporter attributed this event to cyclophosphamide.

Time from onset of etanercept therapy: 3 months

Other immunosuppressive medications: Cyclophosphamide, high dose corticosteroids

Prior history of blood dyscrasia: None

Outcome: Death

Attribution: Pancytopenia and pneumonia most likely associated with cyclophosphamide.

- **Mfg report #: 99080380**

Case: 78 year old man with h/o COPD and RA was hospitalized with sepsis, pancytopenia and renal insufficiency. Patient had been on etanercept for an unknown period of time. Other meds included methotrexate and prednisone. WBC was 0.6, plt 97,000, BUN 110 and creatinine 3.2. Patient was treated with antibiotics, but died within 24 h of admission.

Time from onset of etanercept therapy: Unknown

Other immunosuppressive medications: Methotrexate

Prior history of blood dyscrasia: Not reported

Outcome: Death

Attribution: Pancytopenia and sepsis in patient on etanercept for unknown period of time. Factors which may have contributed to pancytopenia include sepsis as well as methotrexate use in the setting of new onset renal insufficiency. It is difficult to attribute this case of pancytopenia to use of etanercept.

- **Mfg report #: 99090656**

Case: 77 year old woman with RA developed pancytopenia after 3 weeks on etanercept. Patient developed mouth ulcers after 5 doses of etanercept, prompting laboratory evaluation. Patient also received cephalexin for unstated reasons 10 days before CBC was measured. Testing showed platelet count 8,000 and WBC 2.0 with 30% polys and 25% eosinophils. WBC and platelet count were in normal range before beginning etanercept. A bone marrow biopsy showed marked granulocytic hypoplasia, numerous megakaryocytes, erythroid hyperplasia, lymphoid hyperplasia with an increase in eosinophils, consistent with a drug reaction. Patient was treated with filgrastim and transfusions and recovered her blood counts.

Time from onset of etanercept therapy: 3 weeks

Other immunosuppressive medications: None

Prior history of blood dyscrasia: None reported

Outcome: Recovered

Attribution: Granulocytopenia and thrombocytopenia associated in time with initiation of etanercept. However, these hematologic abnormalities were also associated with eosinophilia and recent initiation of cephalexin. Therefore, the clinical picture is consistent with a hypersensitivity to cephalexin.

B. Conclusions

Two definite cases of aplastic anemia have been 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 because of the seriousness, including pancytopenia in the **WARNINGS** section appears warranted.

C. 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.

VII. Intestinal Perforation and Etanercept

A. Summary of Adverse Events

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

- Case #99120366 was a 66 year old man with a long history of RA and diverticulitis, who developed a ruptured diverticulum after 4 weeks on etanercept. Blood cultures were positive for Morganella but there was no sepsis. Patient recovered. Etanercept was restarted.
- Case #00010399 is a 54 year old woman with RA who developed a ruptured diverticulum after an unknown time on etanercept. When she was hospitalized with pneumonia, she was discovered to have an enterovaginal fistula. Etanercept was stopped. She had surgical repair and etanercept was restarted. She also has a history of IgA nephropathy and developed proteinuria of 9.3 gm/24 h (fell to 6 gm/24 hr after sulindac was discontinued) while on etanercept. She also developed a fungal infection of the right hand and forearms that was treated with griseofulvin.
- Case #000401470 is a 57 year old man with RA who developed ruptured diverticuli during a hospitalization for hyperglycemia and septic arthritis after approximately 4 months on etanercept. He was receiving concomitant methotrexate and prednisone. The patient was initially hospitalized for sepsis that was believed to have come from an abscess at a venipuncture site. His presentation was also complicated by septic emboli of the lungs. His colon was resected and had a prolonged recovery. One week after discharge, patient was readmitted with SIRS (systemic inflammatory response syndrome). He developed multisystem failure requiring mechanical ventilation and hemodialysis. At the time of the report, the patient remained on a ventilator, but the physician believed he would ultimately be discharged.
- Case 00060319 is a 65 year old woman with RA and no prior history of diverticulitis, who required emergency surgery for ruptured diverticuli after approximately eight months on etanercept. She had a full recovery. Etanercept was discontinued and she remains off etanercept.

- Case #00100629 is a 55 year old man with _____, who developed multi-organ failure, bone marrow suppression, pneumonia and sepsis and died from a perforated colon 2 days after received his second etanercept injection. _____ had been diagnosed earlier in the year and the patient was treated with cyclophosphamide. Post-mortem exam showed the perforated colon was most likely due to ulceration of a compromised bowel. The reporting physician believed the events were unrelated to etanercept and were all processes related to his _____ that were all in train before he received etanercept.
- Case #00100174 is a 72 year old woman with RA and no prior history of diverticulitis, who was hospitalized for diverticulitis, ruptured colon and peritonitis after 10 days on etanercept. She was receiving concomitant prednisone. She recovered with surgery.
- Case #99030077 is a 28 year old woman with psoriatic arthritis who developed a perforated colon 4 days after her first dose of etanercept. Patient reported having severe abdominal pain the day prior to taking etanercept.

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:

- In one case, the patient presented with abdominal pain and was found to have cecal perforation. She had surgery and had a full recovery.
- The 2nd patient had a history of ulcerative colitis. She presented with diarrhea and was found to have a perforated sigmoid colon and severe ulcerative pancolitis. She had a full recovery after surgery.
- The 3rd patient had diverticulitis and a perforated sigmoid colon. She was recovering uneventfully from surgery when she had a cardiac arrest and died.
- The 4th patient had GI bleeding and a sigmoid colon perforation secondary to supratherapeutic anticoagulation. He had a complicated post-op course and died of cardiac arrest.

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.

Reviewer comment: 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 perforation 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.

VIII. Cutaneous Lupus Rash and Etanercept

A. Summary of Adverse Events

The sponsor submitted four adverse event reports:

- Report # 99060679: 65 year old man with RA who developed a red papulosquamous rash with annular and plaque morphologies on the forearms and back 3 months after starting etanercept. A biopsy was compatible with subacute cutaneous lupus. Anti-SSA antibodies were positive. Rash went away when etanercept was discontinued.
- Report # HQ4798305NOV1999: 50 year old woman with RA who developed discoid lupus after a few weeks on etanercept. She had itching and erythema on the upper neck, back, face and extremities, with red papules and slight scaling. ANA and anti-histone antibody were negative. Skin biopsy consistent with lupus erythematosus. No signs of systemic lupus erythematosus.
- Report # 99090592: 69 year old woman with RA who developed an increase in CRP (80 to 399), thrombocytosis (959,000), an increased ESR and elevation in anti-dsDNA antibodies after 6 doses of etanercept. Upon rechallenge with etanercept, CRP and platelets and fatigue increased. Patient recovered on discontinuation of etanercept.
- Report # 99110310: 47 year old man with RA who develop a subacute cutaneous lupus erythematosus rash 4 months after starting etanercept. Etanercept was stopped and rash subsided. Rash recurred on restarting etanercept.

B. Conclusions

Three of these reports represent 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.

C. 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.

IX. 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 reports may have resulted for many reasons, including the manufacturer instituting a phone number for users to report adverse events. 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 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 types of opportunistic infections seen on etanercept and on infliximab are shown in Table 4. 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 and 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 cases resulted in death. 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 and 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. The case reports are summarized below:

- 54 year old woman with RA on prednisone and MTX, with a history of significant exposure to sister's TB as a child who developed an axillary mass and a positive PPD after 1 year on etanercept. In addition, patient had been caregiver for sister dying of cancer who developed suspected reactivation of TB. Patient's biopsy showed non-caseating granulomas and presumed TB (US-IL).
- 9 year old girl with JRA on prednisolone, who was diagnosed with TB of L ankle, culture confirmed, after 3 months on etanercept (UK)
- 59 year old woman with RA with lymphadenopathy and culture positive TB after 3 months on etanercept (Netherlands)
- 52 year old woman with RA on prednisone developed abdominal pain, granulomatous hepatitis, and culture positive TB after 4 months on etanercept. Patient had significant foreign travel history: India (6 years ago), Malaysia (2 years ago) and Germany (6 months ago). Family members may have been exposed to TB. Consultant believed TB probably a reactivation due to immunosuppression (US-WV).
- 59 year old woman with RA and a history of insulin-dependent diabetes mellitus and a history of possible exposure to TB in childhood presented with interstitial pneumonia and a lung biopsy positive (including positive culture) for TB after 7 months on etanercept. Etanercept was discontinued. Further information unavailable. (Sweden)

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. MMWR cites an incidence of 5.6 per 100,000 person-years. 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, as follows.

- Report #00010555: 45 year old woman with

[REDACTED]

Reviewer comment: Etanercept is not licensed for _____, and it is not known whether the safety profile is similar to that for RA. Although etanercept may have played a role in this infection, the high dose corticosteroids and immunosuppressants this patient received are clearly associated with opportunistic infections, such as aspergillus.

- Report #00020377: 49 year old man (France) with RA who developed severe diffuse vasculitis and sepsis 5 months after beginning etanercept. After 4 months, etanercept was discontinued due to lack of efficacy. One month thereafter, patient presented with a decline in his general health status, fever and cachexia. A muscle biopsy showed vasculitis. The patient was treated for candidiasis during hospitalization; he died of a suspected pulmonary embolism.

Reviewer comment: Diffuse vasculitis in this case is temporally related to use of etanercept. The attribution of the candidiasis is difficult. It would be helpful to have more information about concomitant medications (only minocycline is listed) including corticosteroids and cytotoxic agents, and HIV status in view of declining general health status and cachexia. It is also not stated what organs were associated with candidiasis, e.g. internal organ system involvement vs. oral, esophageal.

- Report 00030716: 60 year old woman with _____ developed ARDS after 2 months on etanercept and methotrexate. Hospital course was

complicated by DVT, MI, septic shock, multi-organ system failure leading to her death. At autopsy, cultures of lungs and liver grew *Candida torulopsis* and *Candida glabrata*.

Reviewer comment: Etanercept is not licensed for _____, and it is not known whether the safety profile is similar to that for RA. Infectious complications, including opportunistic infections, are common in _____. It is difficult to determine whether etanercept contributed to the ARDS in this patient. It is also difficult to determine whether the Candida infections seen at post-mortem were responsible for the initial presentation, or developed during a long and complicated hospital course.

- Report #90040383: 58 year old man with RA who developed thrombocytopenia and leukopenia after 2 months on etanercept. Platelets fell to 133,000 and WBC to 6300. Skin abscesses grew mycobacterium marinum. The source of the infection was believed to be his fish tank. The cytopenias resolved after treatment with ethambutol and rifampin. When etanercept was restarted, the patient developed new lesions.

Reviewer comment: Mycobacterium marinum is an uncommon infection and cytopenias are not described as a part of the infection. The positive rechallenge with etanercept is additional evidence suggesting a causative role for the product in predisposing to this infection.

- Report #99050391: 72 year old woman hospitalized with presumed viral pneumonia after 4 months on etanercept. Developed respiratory failure requiring mechanical ventilation. Sputum and blood cultures were negative. There were high titers of influenza B and parainfluenza viruses. Viral cultures were negative and a lung biopsy showed interstitial pneumonitis. She was treated with cyclophosphamide and high dose steroids without response. She died 5 weeks after presentation. Post-mortem lung cultures was positive for cytomegalovirus (CMV). Examination of the lungs showed CMV inclusion.

Reviewer comment: The role of CMV in this case is problematic since viral cultures of the lung pre-mortem were reported as negative. Since the patient was treated with high doses of corticosteroids and cyclophosphamide, it is possible that the CMV infection arose during the hospitalization.

- Report #99070115: 66 year old man with severe RA and COPD who died after being hospitalized with a collapsed lung. He was on etanercept for 6 months, then stopped 6 weeks before the event. Patient had surgery, but developed respiratory failure and pneumonia and died. Pleural fluid cultures were positive for mycobacterium avium intracellulare.

Reviewer comment: Although etanercept treatment may have been a contributing factor in this case of pulmonary MAI, there are clearly other factors. COPD is a known predisposing factor for MAI. In addition, etanercept was stopped 6 weeks before presentation, so much of the product would have cleared.

- Report #99070193: 62 year old woman with RA who developed diffuse bilateral lung infiltrates after 2 months on etanercept. The patient is believed to have had _____ as a pre-existing condition. She originally presented with episcleritis, chondritis and polyarthritis (RF positive and ANCA negative; the patient's physician believed that the ANCA result was falsely negative). After 2 months on etanercept, she developed lower lung infiltrates, treated with prednisone with partial clearing. The infiltrates worsened and etanercept was discontinued. She was treated with prednisone and cyclophosphamide. Three months after stopping etanercept, she developed an abnormal CXR diagnosed as pneumocystis carinii. Serologies were positive for CMV. The patient died.

Reviewer comment: This patient appears to have had _____ pre-existing the starting of etanercept. The PCP and CMV may be more likely related to cyclophosphamide treatment and _____, since opportunistic infections of this type are common complications in this situation.

- Report #99080647: 46 year old woman with RA developed Herpes simplex 2 infection after 4 months on etanercept. Presented with stomatitis and difficulty swallowing. Exposed to husband's lip herpes just prior. Hospitalized for IV acyclovir and hyperalimentation. Esophagogastroduodenoscopy normal. Patient recovered. Etanercept discontinued.
- Report #99090281: 76 year old woman with RA developed Candida esophagitis after 8 months on etanercept. Hospitalization notable for complications of gastroduodenoscopy and her pre-existing CHF.
- Report # 99100258: 67 year old woman with long-term methotrexate and high dose prednisone use for RA developed PCP after 3 doses of etanercept. She is slowly recovering on Bactrim.
- Report # 99100637: 35 year old man with RA developed pulmonary aspergillosis after 6 weeks on etanercept. For several weeks before, patient had been self-medicating with high doses of prednisone (30 mg qd). Presented with high fever, hypoxia and 20 lb weight loss. Condition initially diagnosed as vasculitis and treated with high dose corticosteroids. During hospitalization, he developed complications including line sepsis with staph aureus and an infection with vancomycin-resistant enterococcus and died.

Reviewer comment: Fatal pulmonary aspergillosis temporally associated with initiation of etanercept therapy. Other contributing factor is patient's self medication with high doses of corticosteroids. Mistaken diagnosis of pulmonary vasculitis may have contributed to fatal outcome.

D. Conclusions Supporting Change to Etanercept Package Insert

Infrequent reports of a variety of opportunistic infections have been seen on etanercept. Review of many of these cases show 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 (#90040383). 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.

E. 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. RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ETANERCEPT. 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.

X. 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. Thirteen 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, a rate likely to be significantly lower than the true incidence rate owing to underreporting under passive surveillance.

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. The 10 cases are summarized in Table 5.

- **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, interleukin-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). The 12 cases are summarized in Table 6.

- **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.

C. 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.

D. 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 AND A CHEST X-RAY. 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.

X. 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.

Table 1: Characteristics of Infliximab and Etanercept

| Characteristic | Infliximab (Remicade) | Etanercept (Enbrel) |
|---|--|--|
| molecular description | chimeric monoclonal antibody, human constant and murine variable regions | recombinant human protein, ligand binding portion of 75 kilodalton TNFR fused to Fc portion of IgG1 |
| molecular weight | 149 kilodaltons | 150 kilodaltons |
| mechanism of TNF- α inhibition | binds to TNF- α and prevents infliximab-bound TNF- α from binding with TNFR | decoy receptor for TNF- α |
| association constant | 10^{10} M^{-1} | (not described in product labeling) |
| affinity for TNF- β (lymphotoxin α , which also binds to TNFR) | NO | YES |
| lysis of cells expressing transmembrane TNF- α | YES, in vitro | NO |
| elimination half-life | 210 hours | 115 hours |
| clinical indication | moderate to severe or fistulizing Crohn's disease; adjunctive use with methotrexate in rheumatoid arthritis refractory to methotrexate alone | moderate to severe rheumatoid arthritis, second line therapy in moderate to severe polyarticular juvenile rheumatoid arthritis |
| dosage and administration in RA | 3 mg/kg (intravenous) initially and at 2 and 6 weeks, then every 8 weeks thereafter | 0.4 mg/kg (25 mg in adults) twice weekly (3 to 4 days apart) as a subcutaneous injection |
| dosage and administration in CD | 5 mg/kg as a single intravenous infusion; in fistulizing disease, repeat doses at 2 and 6 weeks | (not a labeled indication in CD) |
| patients treated, worldwide* | 147,000 (10/1998 - 3/2001, 29 months) | 102,000 (11/1998 - 4/2001, 29 months) |
| patients treated, US | 121,000 (82% of worldwide) | 96,000 (94% of worldwide) |
| patients treated, non-US | 26,000 (18% of worldwide) | 6,000 (6% of worldwide) |
| phone number to facilitate adverse event reporting | NO | YES |

*manufacturers' estimates

Table 2: Major Categories of Reports for Etanercept and Infliximab

| Advere Event Category | | Etanercept | Infliximab | Etan / Influx |
|----------------------------------|---------------------------------|------------|------------|---------------|
| Approximate Total Cases Reported | | 18500 | 2300 | 8.0 |
| Category | Organ System | % of Total | % of Total | Number Ratio |
| 1 | Neurologic | 13 | 20 | 5.4 |
| 2 | Psychiatric | 2.3 | 5.0 | 3.7 |
| 3 | Cardiac | 5.6 | 15 | 3.1 |
| 4 | Vascular | 4.6 | 19 | 1.9 |
| 5 | Pulmonary | 10 | 30 | 2.7 |
| 6 | Gastrointestinal | 13 | 24 | 4.5 |
| 7 | Hepatobiliary | 0.7 | 4.0 | 1.4 |
| 8 | Renal | 1.5 | 4.6 | 2.6 |
| 9 | Reproductive | 1.4 | 1.2 | 9.3 |
| 10 | Musculoskeletal | 11 | 17 | 5.3 |
| 11 | Dermatologic | 18 | 22 | 6.3 |
| 12 | Hematologic | 2.5 | 7.0 | 2.8 |
| 13 | Endocrine | 0.3 | 0.6 | 3.9 |
| 14 | Metabolic | 2.2 | 4.0 | 4.6 |
| 15 | Immunologic | 0.6 | 8.0 | 0.6 |
| 16 | Infection | 22 | 26 | 7.1 |
| 17 | Neoplastic | 1.9 | 5.6 | 2.8 |
| 18 | General and Administration Site | 45 | 34 | 11 |
| Categories per Reported Case | | 1.6 | 2.5 | 0.6 |

Table 3: Post-Licensure Safety Surveillance of Infliximab and Etanercept *
(Licensure through June 30, 2001, US and Foreign) *

| Adverse Event Reports | Infliximab | | | | Etanercept | | | |
|--------------------------|------------|-------------------|-------|----------------|------------|-------------------|--------|----------------|
| | Deaths | % Deaths of Total | Total | % Total of All | Deaths | % Deaths of Total | Total | % Total of All |
| All Reports | 201 | 9 | 2,300 | 100 | 290 | 2 | 18,400 | 100 |
| Demyelination | 1 | 100 | 1 | 0.04 | 0 | 0 | 15 | 0.08 |
| Aplastic Anemia | 0 | na | 0 | 0 | 5 | 71 | 7 | 0.04 |
| Intestinal Perforation | 3 | 75 | 4 | 0.2 | 0 | 0 | 3 | 0.02 |
| Systemic Lupus | 1 | 100 | 1 | 0.04 | 1 | 4 | 25 | 0.14 |
| Infections | 228 | 25 | 901 | 39 | 291 | 6 | 5,143 | 28 |
| Sepsis | 67 | 52 | 130 | 6 | 72 | 50 | 145 | 0.8 |
| Pneumonia | 51 | 35 | 145 | 6 | 124 | 22 | 553 | 3 |
| Bacterial Infections | 181 | 29 | 616 | 27 | 228 | 12 | 1,941 | 11 |
| Mycobacteria | 16 | 17 | 93 | 4 | 5 | 28 | 18 | 0.1 |
| Listeriosis | 4 | 25 | 16 | 0.7 | 1 | 100 | 1 | 0.01 |
| Fungal Infections | 24 | 28 | 86 | 4 | 13 | 7 | 186 | 1 |
| Histoplasmosis | 1 | 7 | 15 | 0.7 | 0 | 0 | 1 | 0.01 |
| Aspergillosis | 3 | 75 | 4 | 0.2 | 3 | 60 | 5 | 0.03 |
| Candidiasis | 8 | 29 | 28 | 1 | 5 | 7 | 73 | 0.4 |
| Coccidioidomycosis | 0 | 0 | 2 | 0.1 | 0 | na | 0 | 0 |
| Cryptococcosis | 0 | na | 0 | 0 | 1 | 25 | 4 | 0.02 |
| P. Carinii Pneumonia | 6 | 38 | 16 | 0.7 | 3 | 60 | 5 | 0.03 |
| Viral Infections | 7 | 7 | 94 | 4 | 19 | 3 | 553 | 3 |
| Organism Undefined | 11 | 12 | 92 | 4 | 28 | 1 | 2,443 | 13 |
| Lymphoma | 2 | 20 | 10 | 0.4 | 4 | 15 | 26 | 0.1 |
| Congestive Heart Failure | 10 | 53 | 19 | 0.8 | 11 | 17 | 66 | 0.4 |

* The figures reflect number of reports in AERS with the adverse event identifier. These figures, therefore, are larger than the actual numbers of cases due to: (1) duplicate and follow up reports for the same case being counted as separate reports, and (2) a particular report may include multiple adverse event terms.

**Table 4: Opportunistic Infections in Etanercept or Infliximab Therapy
(Post-Licensure Reports, US and Foreign, as of September 2000)**

| Infection | Etanercept (N=2782) | Infliximab (N=226) |
|------------------------------|----------------------------|---------------------------|
| Herpes Zoster | 82 (2.9%) | 2 (0.9%) |
| Fungal Infections NOS | 52 (1.9%) | 5 (2.2%) |
| Herpes Simplex | 42 (1.5%) | 10 (4.4%) |
| Candida (all types) | 35 (1.3%) | 5 (2.2%) |
| Meningitis | 9 (0.3%) | 0 |
| Tuberculosis | 3 (0.1%) | 17 (7.5%) |
| PCP | 3 (0.1%) | 6 (2.6%) |
| Aspergillosis | 3 (0.1%) | 4 (1.8%) |
| Cryptococcosis | 3 (0.1%) | 0 |
| Histoplasmosis | 0 | 3 (1.3%) |
| Listeriosis | 0 | 3 (1.3%) |

Table 5: Ten Cases of Life-Threatening Histoplasmosis after Immunotherapy Using Infliximab or Etanercept

| Case | Age Sex | Indication Agent | State | Dose | * Number of Doses | * Time (days) | Clinical Presentation and Course | Diagnostic Biopsy, Culture, or Test |
|------|---------|------------------|-----------|---------|-------------------|---------------|---|---------------------------------------|
| 1 | 52 F | RA infliximab | Ohio | 3 mg/kg | 3 | 50 - 60 | fever, dyspnea, weight loss, diffuse interstitial pneumonitis; recovered | transbronchial biopsy |
| 2 | 61 M | RA infliximab | Alabama | 3 mg/kg | 3 | 50 - 60 | fever, malaise, cough, dyspnea, abnormal CXR, BOOP; outpatient management, recovered | transbronchial biopsy |
| 3 | 45 F | RA infliximab | Iowa | 3 mg/kg | 1 | 30 - 40 | malaise, pneumonia, hilar lymphadenopathy, hypotension, acute renal failure; recovered | transbronchial biopsy |
| 4 | 78 F | RA infliximab | Wisconsin | 3 mg/kg | 6 | 10 - 20 | fever, malaise, weight loss, interstitial pneumonitis, CHF, shock; patient expired | open lung biopsy |
| 5 | 67 F | RA infliximab | Tennessee | 3 mg/kg | 1 | 10 - 20 | dyspnea, neutropenia, thrombocytopenia, abnormal LFT; recovered | transbronchial & liver biopsies |
| 6 | 11 M | CD infliximab | Tennessee | 5 mg/kg | 2 | 5 - 10 | fever, sinusitis, interstitial pneumonitis, acute HC exposure; recovered | open lung biopsy |
| 7 | 19 M | CD infliximab | Louisiana | 5 mg/kg | 2 | 130 - 150 | fever, cough, night sweats, HSM, anemia, thrombocytopenia; recovered | liver & marrow biopsies |
| 8 | 38 M | CD infliximab | Kentucky | 5 mg/kg | 5 | 150 - 180 | fever, malaise, cough, myalgia, neutropenia, pulmonary nodules, DIC; recovered | transbronchial biopsy & blood culture |
| 9 | 42 M | CD infliximab | Ohio | 5 mg/kg | 2 | 50 - 60 | fever, cough, pulmonary nodules, right flank pain, abnormal LFT, cytopenias, DIC; recovered | transbronchial biopsy & blood culture |
| 10 | 38 M | RA etanercept | Indiana | 25 mg | 95 | 320 - 350 | fever, malaise, weight loss, abnormal LFT, pancytopenia; recovered | blood anti-HC IgM urine HC antigen |

Footnotes for Table 5

* When more than one dose of infliximab were given, the approximate time interval in days to clinical presentation was measured from the first dose. Indic = indication for infliximab; CD = Crohn's disease; RA = rheumatoid arthritis; CHF = congestive heart failure; CXR = chest X-ray; BOOP = bronchiolitis obliterans and organizing pneumonia; HC = *Histoplasma capsulatum*; HSM = hepatosplenomegaly; DIC = disseminated intravascular coagulopathy; LFT = liver function tests; NIR = not reported.

Case 2: The histoplasmosis in this patient was more indolent than in the other 9 patients. The patient required hospitalization only for bronchoscopy and biopsy, after which he was managed successfully as an outpatient with itraconazole. Tissue histopathology was interpreted initially as idiopathic BOOP before a definitive diagnosis of histoplasmosis was made.

Case 4: The single fatality occurred in the 78 year old woman with RA and multiple other immunosuppressive risk factors: Grade I infiltrating tubular carcinoma of the breast, resected 1984; large cell lymphoma of the kidney, resected 1988; cardiomyopathy secondary to adriamycin therapy for lymphoma; chronic renal insufficiency; osteoporosis with fractures. Histoplasmosis in this patient was treated with itraconazole to avoid renal toxicity anticipated with amphotericin B therapy.

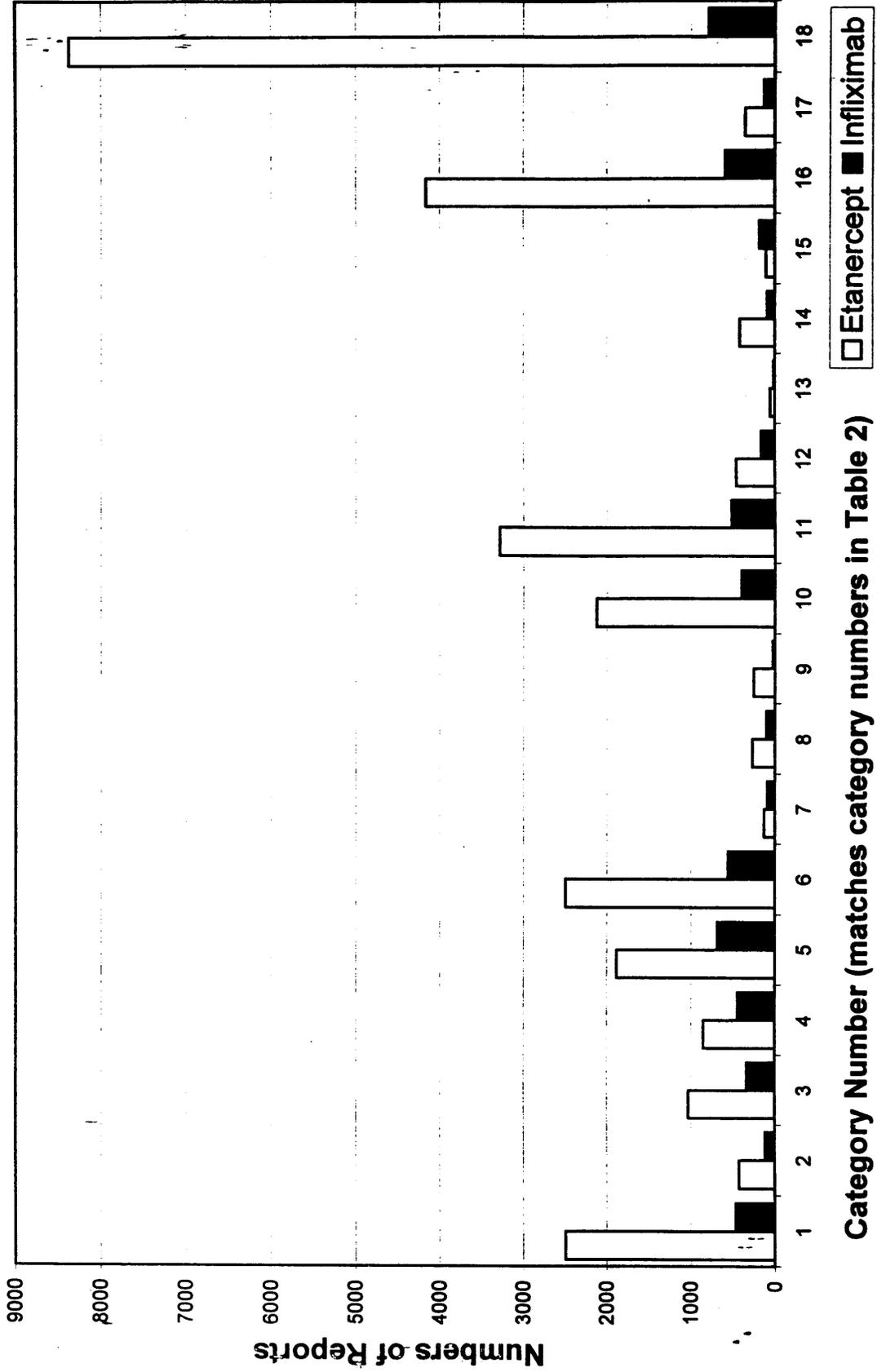
Case 6: The patient's fistulizing CD improved remarkably with a single dose of infliximab. The patient reported cleaning an old barn which housed many pigeons; within 24 hours of cleaning the barn, he began to have fevers unresponsive to antibiotics. His rapidly deteriorating condition required management in the intensive care unit within 10 days of receiving infliximab. Upon recovery with amphotericin therapy, the patient's fistulizing CD worsened and the patient requested repeat infliximab therapy despite the prior life-threatening histoplasmosis. The patient is doing well on infliximab therapy as of June 2001 (31 months after recovering from infliximab-related histoplasmosis).

Case 10: The only case of etanercept-related histoplasmosis case reported to FDA as of June 2001. As with the 9 infliximab-related cases, the patient resided in an HC endemic region (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.

Table 6: Twelve Cases of Listeriosis in Patients Treated with Infliximab or Etanercept

| Age Sex | TNF α & Indication | Dose | Number of Doses | Days to Event | Clinical History and Outcome | Listeria Culture |
|---------|---------------------------|---------|-----------------|---------------|--|-------------------------------|
| 34 F | infliximab, RA | 3 mg/kg | 2 | 290 | fever, headache, and abdominal pain; underwent cholecystectomy with post operative hemiparesis and dysarthria; cranial abscess on head CT; expired | blood |
| 60 M | infliximab, RA | 3 mg/kg | 2 | 35 | successful treatment of anal abscess yet remained ill; outpatient blood culture positive for Listeria, outpatient treatment intravenous ampicillin | blood |
| 73 M | infliximab, RA | 3 mg/kg | 1 | 41 | nausea, vomiting, headache, lethargy, and diarrhea for 3 days; Listeria monocytogenes meningitis treated with ampicillin/cephalosporine; recovered | cerebrospinal fluid |
| 74 F | infliximab, RA | 3 mg/kg | 6 | 240 | Listeria meningitis; expired 5 days after hospitalization | blood |
| 78 M | infliximab, RA | 3 mg/kg | 3 | 70 | fever, headache, confusion, atrial fibrillation, and pulmonary edema; on antibiotic therapy for Listeria meningitis | cerebrospinal fluid |
| 80 M | infliximab, RA | 3 mg/kg | 2 | not reported | fever, weakness, confusion; Listeria sepsis & meningitis; expired | blood and cerebrospinal fluid |
| F | infliximab, RA | 3 mg/kg | multiple | 100 | improvement of all joints after initiating infliximab therapy, except one; Listeria found in that joint | not reported |
| 17 F | infliximab, CD | 5 mg/kg | 1 | 4 | fever, lethargy, headache, hypotension 13 days after admission for leukopenia; antibiotic therapy for Listeria and Candida sepsis | blood |
| 39 F | infliximab, CD | 5 mg/kg | 3 | 80 | fever, headache, joint pain, confusion; Listeria meningitis treated with ampicillin; recovered but remains paralyzed in one eye | cerebrospinal fluid |
| 64 F | infliximab, CD | 5 mg/kg | 1 | 12 | initial presentation with fractured vertebra and Listeria sepsis; second hospitalization for pseudomembranous colitis; expired | blood |
| 67 M | infliximab, CD | 5 mg/kg | 3 | not reported | fever, weakness, lethargy, rigors, diarrhea, and Listeria sepsis; recovered | blood |
| 72 M | etanercept, RA | 50 mg | not reported | 30 | etanercept and methotrexate for one month; fever, chills, headache, dizziness; Listeria sepsis unresponsive to antibiotic therapy; pt expired | blood |

Figure 1: Relative Numbers of Etanercept and Infliximab Reports



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Title: Demyelination occurring during anti-TNF α therapy for inflammatory arthritides.

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Running head: Demyelination occurring during anti-TNF α therapy.

Abstract:

Objective: To review the occurrence of neurological events suggestive of demyelination during anti-TNF α therapy for inflammatory arthritides.

Methods: The Adverse Events Reporting System (AERS) of the FDA (Food and Drug Administration) was queried following a report of a patient with refractory rheumatoid arthritis (RA), who developed confusion and difficulty walking after 4 months on etanercept.

Results: Nineteen cases with similar neurological events were identified from the FDA database, 17 following etanercept (Immunex, USA) administration and 2 following infliximab (Centocor, USA) administration for inflammatory arthritis. All neurological events were temporally related to anti-TNF α therapy with partial or complete resolution on discontinuation. One patient exhibited a positive rechallenge phenomenon.

Conclusion: Further surveillance and studies are required to better define risk factors for and frequency of adverse events and their relationship to anti-TNF α therapies. Until more long-term safety data are available, consideration should be given to avoiding anti-TNF α therapy in patients with pre-existing multiple sclerosis and immediate discontinuation of anti-TNF α therapy when new neurological signs and symptoms occur, pending an appropriate evaluation.

Although the tumor necrosis factor (TNF)/TNF receptor (TNFR) system is ubiquitous in the human body, its various roles in normal physiological conditions and disease pathogenesis have not been fully elucidated. TNF α is produced in response to infection or immunological injury and effects multiple responses that extend beyond its well-characterized pro-inflammatory properties (1) to include diverse signals for cellular differentiation, proliferation and death (2). Some studies have indicated that the TNF/TNFR system is an important mediator of inflammation in both rheumatoid arthritis (RA) and multiple sclerosis (MS). Its role in mediating the arthritogenic response has been demonstrated by the improvement of arthritis lesions in anti-TNF α treated animal models of arthritis (3) and anti-TNF α agents have been reported to be safe and effective in the treatment of RA (4) (5). TNF α is also thought to play a significant role in the pathogenesis of inflammatory demyelinating disease of the central nervous system (CNS) as has been demonstrated in experimental autoimmune encephalomyelitis (EAE) (6), an established animal model for human MS, and in studies of MS in humans (7, 8).

We report a series of patients who developed new onset neurological signs and symptoms associated with demyelinating lesions of the CNS in most cases, while undergoing therapy with anti-TNF α agents, namely etanercept (Enbrel, Immunex, USA) or infliximab (Remicade, Centocor, USA). Etanercept is a p75TNFR fusion protein and infliximab is a chimeric monoclonal antibody against TNF α . These cases underscore the importance of a) clarifying further the interactions and functions of TNF/TNFR systems *in vivo* both in the periphery and within the CNS and b) the need for further surveillance and follow-up of patients being treated with anti-TNF α agents, in order to better define potential adverse events and prevent neurological damage.

Methods: The index patient was a 48-year-old male with RA who developed neurological signs and symptoms while on etanercept. We conducted a search of the medical literature and did not find any reports of neurological events associated with etanercept. This case was then reported to the MedWatch program (for the voluntary reporting by health professionals of adverse events and product problems as well as mandatory reporting of the same by drug manufacturers) of the Food and Drug Administration (FDA). The Adverse Events Reporting System (AERS) which is used to categorize reports of adverse events related to drugs was queried using the following terms from the MedDRA (Medical Dictionary for Drug Regulatory Affairs): *central nervous system infections and inflammatory disorders, cranial nerve disorders (excluding neoplasms), demyelinating disorders, encephalopathies (not otherwise specified), Guillain-Barre syndrome, mental impairment, MRI changes, neurological disorders of the eye, neurological signs and symptoms, peripheral neuropathies and spinal cord and nerve root disorders*. The information available in the MedWatch forms and available MRI scans was reviewed.

Results: Search of the AERS database identified seventeen patients following etanercept administration and 2 patients (patient #19 and patient #20) following infliximab administration, with neurological events suggestive of demyelination (Table 1). Reports to the AERS do not necessarily represent causal relationships between adverse events and drugs. In addition, under-reporting of adverse events occurs, and the reports may have missing data. Therefore these reports should be interpreted cautiously.

The index patient (patient #1) was a 48-year-old male with refractory RA for 10 years, who developed fever, confusion and gait disturbance after 4 months on etanercept (25mg subcutaneously, twice weekly). Physical examination was notable for altered mental status, mild left facial palsy (central) and ataxia. Etanercept was discontinued and the patient was started on

ceftriaxone, metronidazole, acyclovir and methylprednisolone for a presumed infection at a community hospital. CSF analysis was normal. Magnetic resonance imaging (MRI) revealed large areas of increased signal intensity on T-2 weighted images throughout the periventricular and subcortical white matter without abnormal contrast enhancement. At this juncture, the patient was transferred to Georgetown University Medical Center.

On admission, the patient was febrile (38.4C), responsive only to noxious stimuli; by the second day of admission he became unresponsive. Repeat CSF analysis revealed elevated protein of 79 mg/dl (normal range: 15-45 mg/dl). EEG showed diffuse slowing. Cerebral angiogram was normal. Repeat MRI revealed progression of the white matter signal abnormality such that it became confluent (Figure 1 [A&B])). Brain biopsy revealed spongiotic changes in the white matter with gross macrophage infiltration on H & E stain (Figure 2), raising the possibility of a demyelinating process. This prompted an investigation for demyelination as mentioned above. However, special stains (luxol fast blue for myelin) revealed preservation of myelin. The final reading of the biopsy was most consistent with a leukoencephalopathy. Differential diagnosis included toxic and metabolic injuries, cerebral edema and spongy degeneration. The patient improved gradually following 5 days of pulse methylprednisolone (1 gm/day). On discharge, he had residual left-sided weakness and dysphagia. His neurological status continued to improve and on follow-up visit 6 weeks later, he had normal mentation, 4/5 strength on the left side and normal speech and swallowing. He was also amnesic for the events of his hospital stay. A repeat MRI of the brain was planned at the 3-month visit. The patient has since been lost to follow-up.

Clinical presentation: The commonest presenting clinical symptoms among the 20 patients identified in the AERS search were paresthesias (13/20) followed by visual disturbance secondary to optic neuritis (8/20). Other signs and symptoms included confusion (5/20), gait

disturbance, apraxia, facial palsy, and Guillain-Barre' syndrome. One of the atypical features that occurred in 25% of patients was confusion, which is uncommon in MS. Four patients had a prior history of MS or an MS-like syndrome with flares of their previous symptoms. Patient #2 exhibited a positive rechallenge phenomenon, i.e., his neurological symptoms improved on discontinuation of drug and were exacerbated on re-exposure to etanercept 2 months later. He was being tapered off steroids at the same time. Etanercept was again discontinued and the patient is currently left with a permanent residual neurological deficit. 5/20 patients were reported to be on MTX and 1/20 patients were reported to be on leflunomide in addition to anti-TNF α therapy at the time of the neurological event. Most patients responded either partially or completely with clinical resolution of their neurological symptoms on discontinuation of anti-TNF α therapy. Other therapies that were tried with varying degrees of success included corticosteroids (pulse or rapidly tapering), plasmapheresis, interferon- β 1A and intravenous immunoglobulin (IVIG).

Tissue diagnosis and imaging: Lumbar puncture was reported in only one patient in the series and was normal. Brain biopsy was reportedly done only in 2 patients. Patient #1 had a picture suggestive of toxic encephalopathy and Patient #2 had demyelination. Imaging studies were reported in 17/20 patients. Among them 16 reported a pattern compatible with demyelination in different areas of the CNS, while the index case demonstrated an extensive, confluent, bilaterally symmetric pattern of signal abnormality in the periventricular, deep, and subcortical white matter. We were able to independently review MRI scans of the index case (Patient #1) and 4 of the other cases (Patients 3, 4, 5 and 7). The latter 4 cases demonstrated findings similar to each other, but different from the index case. These four patients had small

white matter lesions in the brain (3 patients) and spine cord (2 patients) most compatible with a demyelinating process.

Discussion: Assessing the likelihood of a causal connection between an environmental exposure and an adverse event is referred to as attribution analysis. Miller et al (9) reviewed the many methods that have been proposed to substantiate such associations. The criteria proposed by them (Table 2) were used to review the association of anti-TNF α therapy with the neurological event in our case series. In their review, the specified primary attribution elements are more critical than secondary attribution elements and include temporal association, the lack of likely alternative explanations, dechallenge (improvement in symptoms following discontinuation of the agent), rechallenge (reappearance or worsening of symptoms on re-exposure to the agent) and biologic plausibility (the likelihood of the agent causing the signs and symptoms based on its known in vivo and/or in vitro effects). Secondary attribution elements include analogy (prior published or unpublished reports of a similar disorder developing after the exposure), dose responsiveness (dose of agent related to the likelihood of developing the disorder) and specificity (similar symptoms, signs and laboratory features in previous cases after exposure to the same agent).

The following factors argue against a true association of events and etanercept use. a) A total of 77,152 patients were exposed to etanercept from November 1998 through May 2000, representing 55,313 person years of exposure (communication from Immunex Corporation); among them only 9 patients were identified with symptoms suggestive of a demyelinating disorder; the other cases including the 2 patients on infliximab were reported after May 2000. This compares with the natural incidence of MS of 4-6-cases/100,000-population/year (10). b) These events could possibly represent the unrelated, chance occurrence of a demyelinating

disorder (such as MS) in the setting of inflammatory arthritis and anti-TNF α therapy. c) Only 1/20 patients had a positive rechallenge phenomenon.

The 5 primary elements of the attribution analysis suggest a relationship between TNF- α blockage and demyelinating syndromes and are addressed below. 1) *Temporal relationship*: Average time between onset of therapy and symptoms was 5 months with a range of exposure times between 1 week and 15 months. 2) *Likely alternative explanations*: MTX has been associated with a variety of neurologic sequelae in the brain (such as demyelination and even necrosis) when used in combination with high doses of irradiation (11). However these changes have been reported only with the use of high-dose MTX (intravenous, intrathecal, intraventricular) in the treatment protocols for CNS prophylaxis of lympho- and myelo-proliferative malignancies. Similar events have not been reported with the use of leflunomide. A literature search for reports of demyelination associated with other concomitant medications (Table 1) was negative. 3) *Dechallenge*: Discontinuation of anti-TNF α therapy resulted in complete or partial improvement of symptoms in all patients. 4) *Rechallenge*: Reexposure to etanercept in Patient #2 caused worsening of his neurological status and MRI, though steroid taper at that point may have contributed to his clinical deterioration. Two patients remained on etanercept with continued symptoms. None of the other patients were reported to be reexposed to the drug. Rechallenge will be difficult to assess in the future due to the patient risk involved.

5) *Biologic plausibility*: Several studies suggest that a perturbation of the TNF/TNFR system by anti-TNF α agents can potentially precipitate or worsen an underlying demyelinating process. Elevation of TNF α is a recognized component of the pathophysiology of both RA and MS. TNF α was found to be a key coordinator of pro-inflammatory cytokines in RA (11). Similarly TNF α is overproduced in the serum and CSF of MS patients and by resident and

infiltrating cells at sites of CNS injury (8). TNF α also induces selective cytotoxicity of oligodendrocytes in vitro and myelin damage in brain slices (12).

Human studies: Due to the success of anti-TNF α therapies in animal models of MS, lenercept, a soluble dimeric p55TNFR-immunoglobulin fusion protein (Roche) was examined in a double-blind placebo controlled study of 168 MS subjects. The number of lenercept-treated patients experiencing exacerbations was significantly increased compared to patients receiving placebo and their exacerbations occurred earlier. Neurologic deficits tended to be more severe in the lenercept treatment groups, although this was not statistically significant. This finding resulted in the sponsor's decision to terminate the study and to release the treatment code halfway through the study (13). Two rapidly progressive MS subjects treated with infliximab (Remicade, Centocor) developed an increase in the number of gadolinium enhancing lesions on MR scan, CSF IgG index, and the CSF lymphocyte count after each infusion, although there was no reported clinical worsening of disease (14).

Little is known of the prevalence of other autoimmune diseases among population-based, unselected MS patients. Even less is known about the incidence and prevalence of MS in autoimmune diseases like RA. Two recent studies suggest a possible association between autoimmune diseases and MS. A hospital-based case-control study of 155 MS patients and 200 controls revealed a statistically significant more frequent coexistence of rheumatoid arthritis, psoriasis, and goiter when compared to controls (OR=2.96; 95% CI 1.23-7.66) (15). Another study of autoimmune diseases in families of French patients with MS suggests a possible familial association of MS and autoimmune disease (16). Conflicting case reports also exist of improvement or worsening of inflammatory arthritis when the patients were being treated for MS with interferon- β (IFN β) (17, 18, 19). Common loci for genes associated with EAE and pristane-

induced arthritis (PIA), suggest that common genes are likely to be involved in different autoimmune diseases (20). It is therefore conceivable that the patients in our series could have had a genetic propensity to develop MS, which may have been exacerbated by the administration of an anti-TNF α agent.

Animal studies: Recent studies in transgenic and knockout animals, where the pathogenic influence of genetically perturbed TNF α expression has been evaluated, indicate that several pathways of TNF/TNFR action may contribute independently or in concert to initiate, promote or down regulate disease pathogenesis. Overexpression of TNF in the CNS of transgenic mice causes spontaneous inflammatory demyelination, which is prevented if the p55TNFR is knocked out (21) (22). In EAE, anti-TNF α treatment completely prevents initiation of pathology and ameliorates the progression of established disease (23). On the contrary, when EAE was induced in mice lacking TNF α , they developed severe neurological impairment with high mortality and extensive inflammation and demyelination. Treatment with TNF α dramatically reduced disease severity suggesting TNF α is not essential for the induction and expression of inflammatory and demyelinating lesions and may have a neuroprotective function in the CNS (24). In transgenic mice with overexpression of p75TNFR, the high p75TNFR level has been shown to mediate its own inflammatory pathologic changes, independent of TNF α , lymphotoxin, and p55TNFR (25). Since the TNF/TNFR system acts as a complex network, mechanisms may exist by which TNF α blockade could augment those immune responses that contribute to demyelination.

In vitro studies: Soluble receptors influence TNF α activity in vitro and in vivo and maintain the balance between active, free TNF α and the inactive form bound to its soluble receptors. The soluble forms in high concentrations act as inhibitors by competing with its cell surface receptors; however, in lower concentrations, soluble receptors can prolong the biological

half-life of TNF α by functioning as a carrier protein and protecting TNF α from degradation, and therefore stabilizing its activity (26). A dominant role of p55TNFR has been shown in the induction phase of several TNF α mediated pathologies, including endotoxemic shock and several transgenic mice models of disease for arthritis (27) and demyelination (28). Elevated levels of p55TNFR have been detected in the serum of patients with MS (29). Levels of soluble TNFRs correlated with levels of the circulating adhesion molecules L-selectin and VCAM-1 which reflect lymphocyte/monocyte and endothelial cell activation occurring in the setting of acute inflammatory processes affecting the CNS (29). In contrast, there is ample in vitro evidence for a co-operative role for p75TNFR in p55TNFR-mediated responses, leading to the concept that p75TNFR plays an accessory role in p55TNFR signaling (30). Hence altering the ratio of pTNFR55 to pTNFR75 in the periphery by administering etanercept (p75 receptor fusion protein) may lead to altered signaling of the TNF/TNFR system that could potentially exacerbate a patient's underlying tendency to develop MS or cause a relapse in a patient with already diagnosed MS.

Analysis of the secondary attribution elements (Table 2) shows a positive analogous exposure occurring in the 2 MS patients treated with infliximab (14). The data on dose responsiveness and specificity of these symptoms to etanercept and infliximab is currently unavailable.

Despite the small number of patients in our series, the occurrence of these neurological events in the setting of TNF α blockade raises the possibility of a true association between demyelination and anti-TNF α therapy. Clinicians should consider avoiding anti-TNF α therapy in those patients who have a pre-existing diagnosis of MS and be cautious with its use in those

with a strong family history of MS. If a patient on anti-TNF α therapy develops new neurological signs and/or symptoms suggestive of demyelination, the following steps are warranted:

- a) Immediate discontinuation of anti-TNF α therapy pending further investigations
- b) A thorough neurological examination inclusive of a fundus examination for papilledema and optic neuritis with neurology consultation
- c) MRI of the brain with and without gadolinium
- d) Lumbar puncture for CSF studies, including oligoclonal bands and IgG levels.
- e) When the above investigations are inconclusive or the patient has rapid clinical and/or radiological progression, a brain biopsy may be helpful to delineate the differential diagnosis.
- f) Therapies used in MS such as glucocorticoids, IFN β , or IVIG should be considered.

This case series suggests the possible association of a demyelinating syndrome or other forms of white matter injury (leucoencephalopathy) with the use of anti-TNF agents in inflammatory arthritides. Due to the relatively small number of patients that have been exposed to anti-TNF α agents, further epidemiologic, clinical and laboratory studies are necessary to test the hypothesis. What occurs in vivo in the CNS when the TNF/TNFR systems are perturbed in the periphery will remain a matter of speculation until more is learned about the complex regulation of these cytokines across the blood-brain-barrier. Therefore it is critical to monitor patients on anti-TNF α therapy for the development of new neurological signs and symptoms and discontinue their use when clinical signs of white matter injury appear in order to prevent neurological damage.

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Table 1.

Cases of demyelination occurring during anti-TNF α therapy from FDA-AERS database.

| Case # | Age/ Sex | Diagnosis | Time on drug | Concomitant medications | Clinical signs and symptoms | MRI findings | Treatment | Follow-up |
|-------------------|-------------|-----------|--------------|---|---------------------------------|--|-----------------------|--|
| 1 (Index case) | 48M | RA | 4 mth | Acyclovir, metronidazole ceftriaxone, ranitidine | Confusion difficulty walking | White matter changes | Pulse Methpred | Partial resoln. at 6 wk. |
| 2 | 37M | RA | 3 mth | Naproxen sodium | Confusion, apraxia | Parietal & occipital demyelination | Pulse Methpred | Partial resoln. & positive rechallenge at 4 mths |
| 3 | 37M | PsA | 2 mth | MTX | Ascending dysesthesia | Demyelination of cervical cord | Oral dexamethasone | Complete resoln. with recurrence at 7mths |

| | | | | | | | | |
|---|-----|---------|---------|---|--------------------------------------|---------------------|--------------------------------|--|
| 4 | 43M | PsA | 4 mth | Prednisone | Paresthesia | Demyelination | Unk | Contd. symptoms while on contd. etanercept |
| 5 | 48F | Unknown | 15 mth | Unknown | Spasticity & lower trunk paresthesia | Thoracic & brain MS | Unk | Unknown |
| 6 | 43M | Unknown | 2.5 mth | Allopurinol, omeprazole, prednisolone, probenecid, propoxyphene | Optic neuritis papilledema | Normal | Unk | Unknown |
| 7 | 40F | RA | 10 mth | Prednisone, nabumetone, alendronate, hydrocodone | Optic neuritis, paresthesia | Demyelination | IFN β , IVIG, glatiramer | Partial resolu. at 4 mths |
| 8 | 56F | Unknown | 12 mth | Prednisone, Ranitidine | Paresthesia | Demyelination | Prednisone | Complete resolu. at 3 mths |

| | | | | | | | | |
|----|-----|-----|----------------------------|---|--|---|---|--|
| 9 | 53M | RA | 2.5 3 mth | Alprazolam, atenolol, fluoxetine, fentanyl patch | Progressive weakness & paresthesia | Normal | Plasmaphe resis | Partial resoln. |
| 10 | 48F | PsA | 5 mth | MTX, piroxicam, bupropion | Lhermitte's sign, leg numbness | Optic neuritis | Unk | Contd. symptoms at 6 mths |
| 11 | 21F | JRA | 9 mth | MTX, prednisone, piroxicam | Paresthesia | Cervical myelitis at C2 | Unk | Unknown |
| 12 | 41F | RA | Unk | Unknown | Paresthesia optic neuritis, hemiparesis | Multiple plaques | Pulse Methpred | Complete resoln. at 4 wk. |
| 13 | 47M | RA | 4 mth | MTX, dexamethason e, epoetin, calcium, iron, nandrolone | Altered mental status, personality & visual changes | Finger- like brain edema, barrier damage | Acyclovir, ampicillin, high dose cortisone | Partial clinical & MRI resoln. at 7 mths |

| | | | | | | | | |
|----|-----|-----|------------|--------------------------------------|---|---|--|---|
| 14 | 44F | RA | 7 doses | Prednisone | Transverse myelitis | Post. conus medullaris lesion | Methpred | Complete resoln. at 2 wk. |
| 15 | 51F | RA | 4 mth | Estradiol, zolpidem | paresthesias speech, gait, visual & cognitive disturbance, headache, back pain. | Demyeli nation | Fluoxetine | Contd. symptoms on contd. etanercept therapy |
| 16 | 21F | JRA | 7 mth | Lanzoprazole, cyclobenzapri ne | Visual loss due to optic neuritis | T2 abnorma lity, brain & C-spine enhance ment | IV steroids with steroid taper | Contd. symptoms with 2 new MRI lesions at 2 mths |

| | | | | | | | | |
|----|-----|-----|-------------|--|--|---|------------------|---------------------------------|
| 17 | 46F | RA | 1 mth | Prednisone, glatiramer, sulfasalazine, rofecoxib, hydrocodone | Incontinence visual, balance & cognitive difficulty, paresthesias | Unk | Unk | Partial resoln. at 3 mths |
| 18 | 50F | PsA | 5 mth | MTX | Gait & bladder difficulty | MS | Unk | Unknown |
| 19 | 53F | RA | 2.5 mths | | Diplopia, nystagmus weakness neurogenic bladder paresthesia | Demyeli nation in tectum and spinal cord | Methpred IVIG | Partial resoln. |
| 20 | 42M | RA | 1 dose | Leflunomide, prednisolone, amlodipine, bendrofluaide, tramadol, lansoprazole, coproxamol | Dysarthria | Demyeli nation | Unk | Unknown |

RA – Rheumatoid arthritis; PsA – Psoriatic arthritis; JRA – Juvenile rheumatoid arthritis;
 Methpred – methylprednisolone Unk - Unknown

Table 2

Elements of Attribution Analysis.

| Primary elements | Secondary elements |
|--|--|
| <ol style="list-style-type: none"> 1. Temporal association 2. Lack of likely alternative explanations 3. Dechallenge 4. Rechallenge 5. Biologic plausibility | <ol style="list-style-type: none"> 1. Analogy 2. Dose responsiveness 3. Specificity |
| <p>To publish findings of a possible causal relationship between an environmental (drug) exposure and a clinical syndrome, at least 4 of the 8 attribution elements and at least 3 of the 5 primary elements should be present. The 3 primary attribution elements should include temporal association, lack of likely alternative explanations, and at least 1 of the other primary elements.</p> | |

Legends:

Figure 1.

- A. Axial FLAIR image shows confluent signal abnormality in the periventricular and deep white matter.**
- B. Axial post-contrast T1-weighted image demonstrates no abnormal enhancement**

Figure 2.

H&E stain of brain biopsy of index case

Figure 3 (Patient #7)

- A. Axial FLAIR image demonstrates multiple small white matter lesions typical of a demyelinating process.**
- B. Axial post-contrast T1-weighted image demonstrates that some of the lesions abnormally enhance suggesting an active demyelinating process.**

**Table 4: Opportunistic Infections in Etanercept or Infliximab Therapy
(Post-Licensure Reports, US and Foreign, as of September 2000)**

| Infection | Etanercept (N=2782) | Infliximab (N=226) |
|------------------------------|----------------------------|---------------------------|
| Herpes Zoster | 82 (2.9%) | 2 (0.9%) |
| Fungal Infections NOS | 52 (1.9%) | 5 (2.2%) |
| Herpes Simplex | 42 (1.5%) | 10 (4.4%) |
| Candida (all types) | 35 (1.3%) | 5 (2.2%) |
| Meningitis | 9 (0.3%) | 0 |
| Tuberculosis | 3 (0.1%) | 17 (7.5%) |
| PCP | 3 (0.1%) | 6 (2.6%) |
| Aspergillosis | 3 (0.1%) | 4 (1.8%) |
| Cryptococcosis | 3 (0.1%) | 0 |
| Histoplasmosis | 0 | 3 (1.3%) |
| Listeriosis | 0 | 3 (1.3%) |