ABSTRACT
Targeted tumor necrosis factor-α antagonists, first approved by the FDA in 1998, have had a significant impact on the treatment of patients with rheumatoid arthritis. In general, the benefit/risk ratio for these agents and the IL-1 receptor antagonist, anakinra, has been quite favorable. However, infrequent adverse events can be serious and require continued pharmacovigilance. Infections, particularly tuberculosis and less commonly fungal infections, are among the most serious adverse events, especially given delays in diagnosis due to subtle or atypical presentations. Questions have also arisen regarding whether anti-TNF-α agents increase the risk of lymphoma, a complicated issue confounded by the multiple risk factors for lymphoma in patients with rheumatoid arthritis and low observed incidence rates of lymphoma, requiring prolonged monitoring. Additional rare reported complications include systemic lupus erythematosus-like syndromes, congestive heart failure and demyelinating syndromes (including cases resembling progressive multifocal leukoencephalopathy). Ongoing post-marketing surveillance of these and other serious adverse events is necessary to determine the true incidence rates, and whether a reassessment of the overall risk-benefit of tumor necrosis factor-α antagonists will be required.

Introduction
Three tumor necrosis factor (TNF)-α antagonists that neutralize TNF-α are available for clinical use: etanercept, a protein composed of two p75 TNF-α receptors fused to the Fc portion of IgG1, is approved for rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis, and juvenile chronic arthritis; infliximab, a chimeric IgG1α monoclonal antibody binding TNF-α, is approved in the U.S. for RA and Crohn’s disease; and adalimumab, a fully humanized IgG1α monoclonal antibody, is approved for RA. Worldwide prescription data through December 2002, reported at the FDA advisory meeting March 2003, indicate that patient exposure for infliximab is estimated at 400,000, etanercept at 150,000 (1), and 2,468 in clinical trials for adalimumab (2).

These biologic agents have had a marked impact in the treatment of RA, demonstrating efficacy in reducing disease activity in patients who have incomplete responses to conventional disease-modifying antirheumatic drug (DMARD) treatment and in retarding radiographic progression (1). Controlled phase III trials during clinical development for TNF-α antagonists did not show an increase in overall serious adverse events above active comparator controls. However, clinical trials do not include sufficient numbers of patients or sufficient time to detect unusual adverse events. Since the conclusion of the clinical trials, post-marketing reports (MedWatch program: www.fda.gov/medwatch) of tuberculosis, opportunistic infection and lymphoma, have led to FDA-mandated label changes (1).

This article focuses on serious adverse events reported since the time of the introduction of these biological agents and reviews the best available evidence by which to judge the overall safety of TNF-α blockade. More detailed discussions concerning infection – particularly tuberculosis (3), demyelination (4), lymphoma (5), congestive heart failure (6) and drug induced lupus (6) – are provided elsewhere in this supplement.

Infections
Serious infections are well-known to occur in untreated RA patients and in patients treated with both traditional DMARDs and TNF-α antagonists (2, 11-11). At the March 2003 Arthritis Advisory Committee meeting, 2782 cases of infections for etanercept and 1100 for infliximab were reported through August 2000 (13). Although there may
be a bias toward increased spontaneous reporting of adverse events shortly after the introduction of novel agents, the evidence does support an increased risk conferred by TNF-α antagonists for the development of certain infections (13). Three recent review articles have addressed the spectrum of infections noted during TNF-α antagonist therapy (2, 8, 9), and a new review included in this supplement (3). The most common infections reported are illustrated in Table I and are discussed below.

**Mycobacterium tuberculosis**

The infection that appears to be most increased relative to usual occurrence rates in post-marketing data has been Mycobacterium tuberculosis (TB). Through December 2002 in the United States, TB was reported to have developed in 39 patients treated with etanercept, with at least one fatal outcome, and in 335 patients who took infliximab, with at least 12 deaths (1, 11, 14, 16). During adalimumab clinical trials, 13 cases of TB were observed in 2,468 patients, most of which developed before implementation of TB surveillance (2). The baseline TB incidence rate in patients with RA in the United States has been estimated at 6.2 per 100,000 per year (15), although the rate in patients with RA may be higher. Wallis et al. recently analyzed the FDA Adverse Event Reporting System database and calculated an estimated 144 TB cases per 100,000 infliximab-treated patients and 35 TB cases per 100,000 etanercept-treated patients based on cases reported from 1998 through the third quarter of 2002 (11).

The majority of TNF-α antagonist associated TB cases are believed to be the result of reactivation of latent disease. Nearly 50% of the TB cases associated with TNF-α antagonists were extrapolmonary and/or disseminated disease. The diagnosis may therefore be delayed due to atypical presentation, with many patients requiring an invasive procedure for diagnosis. It should be noted, however, that even in the absence of TNF-blockers, there may be an increased risk of TB in rheumatoid arthritis patients. For example, a recent study from Spain of 788 biologically naïve RA patients had a 4-fold increased risk of developing TB compared with the general population (134 per 100,000 versus 23 per 100,000 per year, respectively (18).)

Because many TB infections following TNF-α antagonist treatment appear to be cases of reactivation, routine tuberculin skin testing before initiating treatment has been recommended (2, 7, 15, 19, 21). However, in an FDA-sponsored study surveying various practices in the United States, rates of tuberculin skin testing before administration were only 31% for infliximab and 10% for etanercept as of June 2002 (22). Evidence from a review of infliximab clinical trials for spondyloarthropathy as well as from a surveillance study suggests that meticulous screening with chest roentgenograms and a two-step Mantoux skin test along with prophylaxis for latent TB has been effective in reducing reactivation of TB (23, 24).

There are no published data, however, that confirm the effectiveness of isoniazid prophylaxis in patients with a positive tuberculin skin test before treatment with TNF-α antagonists. Indeed in 2 patients treated with infliximab, 6 months of isoniazid did not prevent the reactivation of pansensitive TB (25, 26). Physicians must be alert to false-negative tuberculin skin testing as described in RA patients, as well as atypical presentations of TB.

**Fungal and other opportunistic infections**

Through June 2002, opportunistic infections were reported in 337 patients treated with either infliximab or etanercept for various indications, leading to at least 21 deaths. Reported organisms have included other mycobacteria, fungi such as Histoplasma capsulatum and Coccidioides immitis, *Pneumocystis jirovecii* (carinii), yeasts such as *Cryptococcus neoformans* and Candida species, molds such as Aspergillus, bacteria such as *Listeria monocytogenes* and *Nocardia*, the protozoan parasite *Toxoplasma*, *Brachiola algerae* and cytomegalovirus (1, 7, 11, 12, 27, 28). Awareness of risk factors, endemic areas, atypical presentations, specialized diagnostic tests, and antimicrobials for these infections are important in minimizing morbidity and mortality (Table I). Patients should be educated to avoid live vaccinations (29), and unpasteurized dairy products as a potential source of *Listeria* (30). Physicians should be vigilant for unusual presentations of infections before initiating biologics. In one reported case, a patient treated with TNF-patients antagonists developed disseminated sporotrichosis that initially masqueraded as synovitis of an autoimmune etiology (31).

With regard to the underlying mechanisms, one recent study demonstrated a decreased Th1 immune response in *vitro* against *H. capsulatum* by host defense cells treated with infliximab (32).

In TNF-deficient mice, impaired granuloma formation is seen, with increased susceptibility to TB and increased dissemination (33, 34). Because TNF-α also plays a central role in granuloma formation, the production of cytokines and adhesion molecules, the release of enzymes, and the migration and maturation of inflammatory cells, the neutralization of TNF-α may contribute to an increased susceptibility to infections (9, 35). There is no experimental evidence that the three available TNF-α antagonists differ in this regard, and therefore susceptibility to infection should be viewed as a class effect.

**Bacterial infections**

Although attention has been drawn to opportunistic infections, common bacteria have also led to serious infections and fatalities in patients treated with TNF-α antagonists. One study compared serious bacterial infections in patients treated with TNF-α antagonists to patients treated with conventional DMARDs, identified 2 years before biologics, calculating an incidence of 0.181 per year for TNF-α inhibitors and 0.008 per year for traditional DMARDs (36). On reviewing each case, C-reactive protein appeared to be a more sensitive marker of infections than temperature, the erythrocyte sedimentation rate, or the white blood cell count, and rose before evidence of infection in several cases. Although sepsis has been seen with all available TNF-α antagonists to date,
Table I. FDA reported cases of opportunistic infections associated with TNF-α antagonists.

<table>
<thead>
<tr>
<th>Opportunistic infections</th>
<th>Presentation in reported cases</th>
<th>Transmission</th>
<th>Modes of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium tuberculosis (n=374)</td>
<td>Pulmonary Extrapulmonary (over 40% of cases) Disseminated, lymph nodes, tonsils, pleura, peritoneal, meninges, enteric, paravertebral, bone, genital, bladder</td>
<td>Reactivation or Inhalation of tubercle bacilli</td>
<td>♦ TST ♦ Chest radiograph ♦ Culture specimens ♦ Tissue biopsy (extrapulmonary)</td>
</tr>
<tr>
<td>Histoplasma capsulatum (n=42)</td>
<td>Constitutional symptoms, Pneumonia: nodular, interstitial, BOOP (*note: CXR can mimic TB) Pancytopenia, hepatosplenomegaly</td>
<td>Inhalation of contaminated soil with bat and bird guano in endemic areas such as the Ohio and Mississippi River valleys</td>
<td>♦ Urine/serum antigen OR ♦ Culture ≥ 3 specimens improves yield ♦ Histochemistry of tissue or fluids with Gomori methenamine or Grocott silver stains</td>
</tr>
<tr>
<td>Candida species (n=90)</td>
<td>Sepsis, esophagitis</td>
<td>Comensal organism</td>
<td>♦ +Hyphae on superficial scraping ♦ Culture of biopsy or body fluid</td>
</tr>
<tr>
<td>Listeria monocytogenes (n=38)</td>
<td>Meningoencephalitis, sepsis, cholecystitis, brain abscess, septic joint</td>
<td>Ingestion of delicatessen ready-to-eat meats, soft cheeses, turkey frankfurters, gravad or cold-smoked trout, pate, raw vegetables, raw milk, fish, &amp; poultry</td>
<td>♦ Gram stain – variable ♦ Culture at site typically sterile ♦ Microbial biochemical assays ♦ MRI to detect brain involvement</td>
</tr>
<tr>
<td>Aspergillus fumigatus (n=39)</td>
<td>Invasive Pulmonary aspergillosis</td>
<td>Inhalation of Aspergillus spores</td>
<td>♦ Culture of sputum, BAL or biopsy ♦ Detection of hyphae in sputum ♦ Chest radiograph ♦ IgG titer detects colonization</td>
</tr>
<tr>
<td>Cryptococcus species (n=19)</td>
<td>Disseminated, Pulmonary, Pancytopenia</td>
<td>Primary inhaled fungi Potential source-pigeon droppings or Reactivation</td>
<td>♦ Serum cryptococcal Ag detection ♦ Culture ie blood, urine, prostate secretion, skin, sputum ♦ Tissue methenamine silver, periodic acid-Schiff, mucicarmine stain (High opening pressure on lumbar puncture, CSF cryptococcal Ag)</td>
</tr>
<tr>
<td>Nocardia species (n=11)</td>
<td>Note: Details of presentation not described</td>
<td>Soil-borne, traumatic inoculation of skin, has been isolated from secretions in patients with COPD</td>
<td>♦ Biopsy with special staining (Brown-Brenn, modified Fite), &amp; ♦ Culture ♦ Rose spots ♦ Cultures of stool, urine, bone marrow, and gastric or intestinal secretions.</td>
</tr>
<tr>
<td>Salmonella species (n=11)</td>
<td>Septicemia</td>
<td>Contaminated food or water</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma species (n=5)</td>
<td>Central Nervous System</td>
<td>Oral route, Cat feces Reactivation of latent infection or exogenous sources such as blood or transplanted organs</td>
<td>♦ Toxoplasma IgM, IgG, IgA titers ♦ Isolation of the parasite from blood or other body fluids after sub-inoculation of the sample into the peritoneal cavity of mice.</td>
</tr>
<tr>
<td>Brucella species (n=2)</td>
<td>Note: Details of presentation not described</td>
<td>Ingestion of untreated milk or milk products; raw meat (i.e., blood) and bone marrow.</td>
<td>♦ Combination of potential exposure, consistent clinical features and significantly raised levels of Brucella agglutinin</td>
</tr>
</tbody>
</table>
only two cases of septic arthritis have been reported (37, 38). The first was in a 12-year-old girl with group A-hemolytic streptococci, multifocal septic arthritis, and osteomyelitis, whose left toe abscess recurred despite surgical drainage, appropriate antibiotics, and discontinuation of etanercept. The second was a case of bilateral septic hip arthritis with Staphylococcus aureus in a 27-year-old woman who had an 11-year history of RA, after treatment with 4 months of etanercept. Currently, no clinical studies have been conducted in patients with RA who were taking biologics to establish perioperative guidelines. Given the potential risk of septic arthritis and the indeterminate effect on wound healing, withholding biologics 1 week before and after surgery may be prudent (39, 40).

**Lymphoma**

An increased incidence of lymphoma among patients with RA had been reported ranging from 2 to 25-fold, even before the introduction of TNF-α antagonists (41-48). To what extent the disease alone and/or concomitant therapies such as azathioprine and methotrexate (49, 50) may contribute to this increased risk has not been well delineated. Brown et al. (51) reviewed MedWatch reports of 26 cases of lymphoma through December 2000 in patients who were treated with infliximab from May 1999 and in patients treated with etanercept from November 1998. The main indication for treatment was RA, followed by Crohn’s disease, and psoriatic arthritis. From these data, a crude extrapolation of the lymphoma incidence for etanercept was 19 cases per 100,000 persons treated. For infliximab, a crude rate of 6.6 cases per 100,000 persons treated was calculated. These rates alone do not indicate an increased risk for developing lymphoma with TNF-α antagonists, because the annual incidence in the general population is 2.48 per 100,000 for men and 1.77 per 100,000 persons for women (52). Furthermore, comparing such rates is difficult due to an imprecise estimation of patient drug exposure used to calculate the incidence rates. Despite the low rates, salient features in these cases raised concern. Fifty-four percent of the patients developed lymphoma within 8 weeks of initiation of treatment, and regression of lymphoma occurred in 2 patients whose only intervention was discontinuation of medication, one with etanercept and one with infliximab (51). Three deaths occurred, 2 in patients with fulminant recurrence of lymphoma that had been in remission. In an addendum to this article, 68 new cases of “probable/possible” medication-associated lymphoma were reported to MedWatch during November 2001 to September 2002.

Information concerning the risk of lymphoma in patients treated with TNF-α antagonists was reviewed at an Arthritis Advisory Committee meeting in March 2003 (1). Nine cases of lymphoma occurred among 3,389 patients treated with etanercept in clinical trials, including patients in extension studies, treated for a median of 2.2 years, resulting in a standardized incidence ratio of 3.47 (95% CI, 1.58 to 6.59). For infliximab, 4 cases were observed among 555 patients with RA in the ATTRACT trial (standardized incidence ratio, 6.35; 95% CI, 1.73 to 16.26) and 2 cases occurred in Crohn’s disease trials (standardized incidence ratio, 8.7; 95% CI, 1.05 to 31.41). For adalimumab, 10 cases were reported over the 24-month clinical trial among 2,468 RA patients (standardized incidence ratio, 5.4; 95% CI, 2.6 to 10.0).

Comparing these incidence ratios is complex because of the absence of definitive information concerning lymphoma incidence ratios in the RA population (41-47). Three studies have been cited frequently to mitigate concerns about potential increased incidences with the biologics. A study by Backlund et al. (44) demonstrated a 25.8-fold increased risk for lymphoma in biologically naïve RA patients with high disease activity. The 95% confidence intervals CI for this odds ratio, however, were extremely wide (3.1 to 213.0), suggesting that more data are needed before definitive conclusions may be drawn. A study by Prior et al. (42) reported a 23-fold increased risk for lymphoma in RA patients. Because this involved a small patient population...
treated at a tertiary referral center, referral bias may have influenced the results. Lastly, in a 1994 study by Wolfe and Fries (53), a correction was made in the incidence death rate for leukemia/lymphoma in RA patients, reducing it from 8.02 to 1.78.

An important concern raised at the FDA Advisory Committee meeting in March 2003 was the absence of lymphoma in comparator groups in clinical trials of etanercept, infliximab, and adalimumab, although this suggests that the biologic agents increase the risk of lymphoma because the control group of RA patients with parallel disease activity not treated with TNF-α antagonists had a lower incidence. One rationale is that the control groups were considerably smaller and were followed only for brief periods. Therefore, the increased number of lymphoma cases in patients treated with TNF-α antagonists could have been the result of chance. Further data, including careful longitudinal assessment of treated patients, are required and are being collected to clarify the risk of lymphoma with TNF-α antagonists (4).

**Systemic lupus erythematosus-like syndromes**

Systemic lupus erythematosus-like syndromes and autoimmune serology conversion has been described with all the TNF-α antagonists. Of the confirmed cases of etanercept-associated systemic lupus erythematosus (SLE) from November 1998 to February 2002, 12 of 13 patients had complete resolution of symptoms by 1 to 4 months after discontinuation of the biologic agent (54). A caveat is the difficulty in detecting TNF-α antagonist-induced SLE because these features may be misinterpreted as symptoms resulting from RA (55). In a few recently reported cases of drug-induced SLE, patients initially had objective evidence of RA but vague symptoms and serologic findings typical of SLE. Treatment with TNF-α antagonists appeared to lead to the progression of subtle SLE manifestations (56), causing re-evaluation of the original diagnosis of RA.

Although monitoring of autoantibodies may be important, the predictive value of seroconversion while taking biologics for developing SLE still needs to be determined. In a one-year randomized, controlled trial of RA patients treated with infliximab, antinuclear antibodies were detected in 29% of the patients before and in 53% after treatment, and approximately 10% of the patients developed IgM anti-dsDNA antibodies (pre-treatment anti-dsDNA levels were not reported). However, only one patient with all three isotypes (IgG, IgM, and IgA anti-dsDNA) was observed to develop a reversible lupus syndrome (57).

Positive dechallenge and rechallenge cases are the strongest evidence that these TNF-α antagonists induce features of SLE (54, 58). One proposed explanation for the development of autoantibodies is that administration of antibodies to TNF-α on the cell surfaces leads to apoptosis releasing nuclear antigens that promote the formation of antinuclear antibodies (57).

**Heart failure**

Questions have arisen concerning the possibility that TNF-α antagonists may cause new congestive heart failure (CHF) or worsen pre-existing disease (6). In clinical trials of infliximab for CHF, mortality and hospitalizations for heart failure were increased (1). A report from the MedWatch database described 47 cases of heart failure after initiation of TNF-α antagonists (59). These cases included new onset or exacerbations that were diagnosed a median of 3.5 months and 4 months respectively after the initiation of therapy. New-onset heart failure without a known risk factor occurred in 19 (50%) of these patients with a median ejection fraction of 0.2 (range, 0.1 to 0.45). For the 10 patients under age 50, 9 had stopped the TNF-α antagonist and received treatment for heart failure. Three patients completely resolved, 6 patients partially resolved, and one patient died. Despite the temporal association, no definitive conclusions can be made because coincidental occurrence cannot be ruled out with this small number of case series (59).

In response to the FDA warning of cases of heart failure in patients treated with etanercept or infliximab, Wolfe et al reviewed their National Data Bank for cases of heart failure in patients with RA. The most relevant information gleaned from this data is that there were no incidents of heart failure in 1,569 patients who were less than 50 years old and treated with TNF-α antagonists. However, heart failure associated with TNF-α antagonists appears to be a rare event, with only 47 cases reported to the FDA among approximately 270,000 patients exposed to TNF-α antagonists. Furthermore, there was a strong temporal association in the cases reported by the FDA, as the 9 patients who had no predisposition to cardiac disease had resolution of their depressed ejection fractions after withdrawal, as well as treatment for heart failure. Detection of cases of heart failure may have been limited, as 8% of their population declined to participate in the study. Approximately 0.017% of the FDA database patients developed heart failure. (60)

Because TNF-α is important for viral clearance (61, 62), a possible explanation for congestive heart failure in patients without a history of heart disease might be that myocardial decompensation is secondary to viral myocarditis. A study with TNF-deficient mice demonstrated decreased survival after infection with encephalomyocarditis virus, resulting from viral defects in clearance from the myocardium (63, 64). Survival improved with the administration of recombinant human TNF-α. These findings suggest that viral myocarditis may develop during treatment with TNF-α antagonists. Further evaluation for viral infection may help characterize new cases of heart failure in patients treated with TNF-α antagonists.

**Demyelination**

Twenty cases of patients developing neurologic symptoms with accompanying demyelination on MRI scans have been reported to the FDA database as a TNF-α antagonist-associated adverse event (4, 65). Although this complication has been attributed to possible precipitation of a multiple sclerosis-like demyelinating syndrome, a brain biopsy
from one index case demonstrated leukoencephalopathy. The patient’s symptoms and progressive lesions on MRI were consistent with progressive multifocal leukoencephalopathy. This report raises an intriguing possibility: namely, that some cases categorized as multiple sclerosis-like demyelinating syndromes could in fact represent progressive multifocal leukoencephalopathy. The organism responsible for progressive multifocal leukoencephalopathy is human JC papovavirus, which can be detected in the cerebrospinal fluid by the polymerase chain reaction (66-69). Cases of "demyelination syndrome" will require careful analysis to determine the etiology of the symptoms, and increased scrutiny is necessary to exclude progressive multi-focal leukoencephalopathy.

Conclusion

The introduction of TNF-antagonists has been a major advance for patients with inflammatory arthritis. The overall safety of these agents appears to be comparable to traditional DMARDs. However, patients may be at a small but increased risk for specific serious adverse events such as tuberculosis, opportunistic infection, and possibly lymphoma. In general, the perception by many patients and physicians that these agents also offer greater therapeutic benefit with respect to symptoms, quality of life and retardation of disease progression, has led to the widely held view that the benefit/risk ratio for TNF-blockers is positive despite a small possibility of an increase in serious adverse events.

Ongoing surveillance is crucial to define accurately the incidences of adverse events, with a particular focus on lymphoma. Pharmaceutical companies, working with the FDA, have developed pharmacovigilance programs to collect data in clinical trials and registries for 3 to 10 years with projected enrollments of 600 to 5000 patients per program (70), in addition to efforts by rheumatologists such as the National Database for Rheumatic Diseases under leadership of Dr. Frederick Wolfe, and the Alberta Pharmacosurveillance Program under leadership of Dr. Walter Maksy

mowycz (71). Voluntary health care professional reporting is also making a key contribution to surveillance via the FDA MedWatch program. Anticipating and identifying complications early should decrease the frequency and severity of adverse events and improve the overall safety of these highly effective agents.

References