ABSTRACT. Objective. The magnitude of the risk of reactivation of tuberculosis (TB) on use of etanercept, especially in patients with positive purified protein derivative (PPD) test, has not been assessed. We evaluated the risk of developing active TB among PPD-positive patients treated with etanercept.

Methods. All patients with a positive PPD test, as defined by American Thoracic Society guidelines, who received etanercept at Cook County Hospital from 2001 to 2008 were retrospectively reviewed. The primary endpoint was the development of active TB either while receiving or after completing etanercept therapy.

Results. Four hundred eighty-seven patients received etanercept, of whom 84 were PPD-positive and constituted the primary cohort. The cohort was composed largely of patients who were at high risk for development of active TB: born in endemic area (80%), ethnic/racial minorities (51 Hispanic, 16 African American, and 8 Asian), and low socioeconomic status (66, 78.57%). Overall etanercept exposure was a mean of 24.6 months (range 3 to 60 mo), with 196 patient-years of etanercept exposure in PPD-positive individuals. Indications for etanercept use included rheumatoid arthritis 58 (69%), ankylosing spondylitis 11 (13%), psoriatic arthritis 13 (15.5%), juvenile inflammatory arthritis 1 (1.2%), and vasculitis 1 (1.2%). Of the 80 subjects, 74 received treatment for latent TB infection (LTBI) prior to initiating etanercept. A comprehensive review of these patients’ medical records failed to reveal any active TB infection.

Conclusion. This systematic analysis suggests that the risk of reactivation of LTBI during etanercept therapy is low in appropriately treated individuals. (J Rheumatol First Release April 1 2009; doi:10.3899/jrheum.081041)

Key Indexing Terms:
ETANERCEPT
POSITIVE PURIFIED PROTEIN DERIVATIVE TUBERCULOSIS TUMOR NECROSIS FACTOR INHIBITORS

Tumor necrosis factor-α (TNF-α) blockade has become a standard treatment for a variety of rheumatic diseases; however, there has been significant concern regarding the potential susceptibility to serious infections, especially to tuberculosis (TB)1. TNF-α has been shown to be essential for an effective immune response to mycobacterial infection in animal models2, and an increased risk of active TB infection has been reported with all currently available TNF-α blockers3,4,5.

In a previous report we described 25 cases of TB associated with etanercept6, which is one of the 3 currently approved anti-TNF-α drugs in the US. We and others estimated the incidence of TB to be approximately 10/100,000 patient-years of etanercept exposure3,5. Many such patients develop disseminated TB and suffer serious complications; however, at the time it was not routine to assess for latent TB infection (LTBI) prior to initiating anti-TNF-α therapy. It has now become an accepted standard of care to screen for LTBI with purified protein derivative (PPD) and to initiate isoniazid (INH) therapy prior to instituting anti-TNF-α therapy6. As a result, the rate of active TB associated with TNF-α blockers has apparently been reduced6.

In developed nations generally, the majority of active TB results from reactivation of LTBI in foreign-born or immigrant populations7,9; in addition, in the US, active TB is associated with ethnic/racial minority populations and with lower socioeconomic status10,11. Hence, these patients may constitute a group at higher risk for the reactivation of TB during anti-TNF-α therapy. We recently reported the absence of TB activation in a short-term followup of 48 such patients with positive PPD who received INH prophylaxis prior to initiating etanercept12. The main limitations of that study and of other reports of TB risk in PPD-positive patients were small sample size and relatively brief followup periods. Here, we report the results of an extended followup...
of PPD-positive patients receiving etanercept therapy, to further define the longer term risk of reactivation of LTBI.

MATERIALS AND METHODS

All patients with a positive single-stage PPD test who were prescribed etanercept in the clinics staffed by the Division of Rheumatology at John H. Stroger Jr. Hospital of Cook County (Chicago, IL, USA) from January 2001 to June 2008 were evaluated. As per Centers for Disease Control (CDC) guidelines, a positive PPD was defined as ≥5 mm induration in patients with HIV, recent contact with TB, a chest radiograph consistent with TB, immunosuppressed, or who had organ transplantation. Since our patients had rheumatological disease and were receiving immunosuppression, 5 mm induration or more was considered to be positive.

The primary endpoint was the development of active TB, either while taking or after discontinuing etanercept therapy. Active TB infection was defined as a clinical diagnosis of active TB given by a physician, positive acid-fast bacillus stain or TB culture, pathology report of caseating granuloma in any tissue specimen, anyone receiving treatment for active TB as per pharmacy or clinical records, or chest imaging suggestive of new lesion(s) consistent with pulmonary TB.

All outpatient and inpatient medical records, pharmacy records, and microbiology and radiological results were retrospectively reviewed for the following information: demographic data including foreign-born status and country of origin, socioeconomic status, insurance status, duration of etanercept treatment, followup information, other immunosuppressive drugs, rheumatological diagnosis, millimeters of palpable induration in reaction to PPD, chest roentgenograms or chest computerized tomography (CT) scans, type of therapy for LTBI, and any evidence of active TB. Individuals from countries with a high risk of endemic TB were categorized as born in endemic area. Low socioeconomic status was defined as total income less than 200% of the poverty threshold established by the US government, which was also used as one of the criteria for receipt of free etanercept from the patient assistance program.

RESULTS

A total of 487 patients had past or current treatment with etanercept. Dosing conformed to the dosage instructions provided in the package insert, and was 25 mg subcutaneously (sc) twice weekly prior to May 2005 and 50 mg sc once weekly after that period. Etanercept was the only TNF-α antagonist available at Cook County Hospital during most of the study period. Eighty-five (17.45%) of the 487 patients had a positive PPD. One patient with a positive PPD was excluded from the analysis because of a lack of followup data: moved away from the region shortly after the first followup visit at 1.5 months. The primary study cohort of 84 patients included 33 men (39.28%) and 51 women (60.72%) of mean ± standard deviation (SD) age 48.9 ± 17.3 years. Indications for etanercept treatment included: rheumatoid arthritis (58/84, 69%), psoriatic arthritis (13/84, 15.5%), ankylosing spondylitis (11/84, 13%), juvenile idiopathic arthritis (1/84, 1.2%), and vasculitis (1/84, 1.2%).

Patient ethnicities included: Hispanic (51, 60.71%), African American (16, 19.04%), Asian (8, 9.5%), Caucasian (7, 8.33%), and Middle Eastern origin (2, 2.4%). Overall, 77 (91.66%) patients belonged to designated racial/ethnic minority populations. Most patients (64 of 80, 80%) were foreign-born, and all of them were from TB-endemic countries; these included Mexico (67.18%, 43/64), Guatemala (7.81%, 5/64), India (9.37%, 6/64), Puerto Rico (3.12%, 2/64), the Middle East (3.12%, 2/64), Vietnam (1/64), Philippines (1/64), South America (1/64), Jamaica (1/64), Russia (1/64), and Poland (1/64). The country of origin in 4 patients was not recorded.

Most of the cohort (66/84, 78.57%) were of low socioeconomic status and did not have medical insurance. They received etanercept without charge from the Encourage Foundation. Sixteen patients (19.04%) had Medicare and/or Medicaid and 2 (2.4%) had private insurance. Most of the patients (62.5%, 50/80) were foreign-born and low socioeconomic status, and members of a designated racial/ethnic minority population.

Most patients had severe PPD induration of ≥15 mm (56/84, 66.66%) with average PPD induration of 21.5 mm (range 6–50 mm), and most (78/84) were partially or fully treated for LTBI: 76 received INH and 1 each received rifampicin and a combination of rifampicin and pyrazinamide, respectively. Six patients did not receive any LTBI therapy due to various reasons: history of active TB with adequate treatment in the past (2), active viral hepatitis (1), therapy withheld due to alcoholism (1), abnormal liver enzymes (1), and not well documented (1). LTBI therapy had been initiated at a mean of 2.5 (SD 2.6, range 0–12) months prior to the initiation of etanercept therapy. Thirty-one patients began etanercept therapy simultaneously with LTBI. Only 52 of 78 patients completed 9 months of LTBI therapy, with an average duration of 9.9 months of INH, and 15 patients of these interrupted the 9-month course for at least some period due to noncompliance. Twenty-two patients (28.2%) were completely noncompliant with LTBI therapy and did not complete their course of INH; the noncompliant patients had an average of 6.3 months of interrupted INH therapy. Prednisone was prescribed to 46 of the 84 patients (54.76%) during the data collection period, with a mean dose of 6.4 mg (range 2.5–20 mg). Concomitant disease modifying antirheumatic drugs (DMARD) were used in 57/84 (67.85%) patients. Various DMARD used were methotrexate (44/84, 52.4%, median dose 18.75 mg weekly), leflunomide (16/84, 19.05%, median dose 20 mg daily), sulfasalazine (15/84, 17.85%, median dose 2 g daily), and hydroxychloroquine (23/84, 27.38%, median dose 400 mg daily).

The mean followup after initiation of etanercept was 24.6 months (SD 16.2; range 3 to 60 mo). This represents 196 patient-years of etanercept exposure. A thorough search of inpatient, outpatient, and pharmacy records did not reveal a single active TB case in the cohort. All patients had at least 1 followup visit. At the time of data collection 66 patients were continuing etanercept treatment and 18 patients had discontinued. Common reasons for discontinuation of etanercept included lack of efficacy in 8, noncompliance in 5, surgery in 1, transfer of care in 2, and moved out of region in 2. Followup was considered adequate with 80.95%
fered reactivation of TB, although many physicians decided that active TB would have been present in the $77.33 \%$ of patients were normal, 15 revealed old granulomatous disease, and 2 had pulmonary fibrosis and 1 pleural thickening.

**DISCUSSION**

TNF-α inhibitors clearly predispose patients to reactivation of TB; however, the risk of TB activation in etanercept-treated PPD-positive patients who are otherwise at high risk of active TB (e.g., foreign-born, racial/ethnic minorities, and low socioeconomic status) remains poorly understood. Our study was intended to address that issue, and although relatively small, it represents one of the largest cohorts of high-risk PPD-positive patients who have been followed for reactivation of TB during etanercept treatment in the US. Further, this high-risk cohort had low compliance rates with their prophylactic regimen; as such, it may be expected that they would have had the highest risk of active TB, and the absence of such cases argues for the relative low risk of reactivation.

The TB rate among foreign-born people in the US is 9.5 times that of US-born individuals; among different ethnic groups, the TB rates in African Americans, Asians, and Hispanics are 8.4, 21.2, and 7.6 times higher than rates among Caucasians, respectively. Lower socioeconomic status and poor compliance are also associated with high risk of TB.

People with LTBI have an estimated lifetime risk of 10% for developing active TB. LTBI therapy with INH has a protective effect of up to 90% in the general population. Carmona, et al reported that routine screening and treatment of LTBI resulted in 78% reduction ($p = 0.008$) in the number of cases of active TB associated with infliximab therapy. However, there are marked variations in clinical practice in terms of the optimum duration of LTBI therapy prior to TNF-α antagonist, and there is no clear evidence to guide the decision. In our cohort, 36.9% of patients initiated etanercept and LTBI therapy simultaneously, and none suffered reactivation of TB, although many physicians decided to wait until LTBI treatment was completed before initiating TNF-α blockers.

Our results on safety of etanercept in terms of reactivation of LTBI are supported by other studies that also found a low rate of TB in PPD-positive patients treated with etanercept. However, most of these studies were not done on inner-city US populations in patients with other high-risk factors such as those seen in our study, and some of these studies did not report the PPD status.

The limitations of our study include that the identification of LTBI was based exclusively on PPD, which may have false-positive reactions in patients previously vaccinated with bacillus Calmette-Guerin (BCG) or who are infected with nontuberculous mycobacterium. However, the positive PPD identified in our cohort most likely represented LTBI, as the effect of BCG vaccination wanes in adults older than 30 years of age. Second, the PPD is not extremely sensitive; thus false-negative PPD results are not uncommon due to anergy in patients with chronic inflammatory disease or in immunosuppressed patients, and cases of active TB have been described in PPD-negative patients treated with TNF-α blockers. Most importantly, this study was most likely underpowered to detect a very low TB risk. The generalizability of the study was limited by the retrospective study design and selected population studied. Lastly, although we did not review public health department records for cases of TB among our study cohort, we do not expect missed TB cases because most of the study patients had followup visits within 3 months of data collection.

In this retrospective analysis, none of the 84 patients with latent TB infection who were at high risk of active TB and who were treated with etanercept for an average of 24.6 months (196 patient-yrs) developed active TB infection. This represents one of the largest analyses of TB reactivation risk in PPD-positive patients during etanercept therapy in the US. The absence of active TB during the followup period suggests that INH prophylaxis during etanercept therapy may effectively inhibit TB activation. The optimal duration of TB prophylaxis remains undetermined.

**REFERENCES**

13. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 2000;161:S221-47.