Ethanscept therapy in patients with a positive tuberculin skin test

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ABSTRACT

Introduction. Etanercept (Enbrel™), a tumor necrosis factor-α (TNF-α) antagonist, is commonly used for the treatment of a variety of rheumatic diseases. Tuberculosis (TB) infections have been associated with chronic TNF-α blocking therapy, and there is concern that such therapy may predispose patients to TB reactivation. In this study, we attempted to evaluate the frequency of latent TB reactivation among patients treated with etanercept.

Methods. All patients with either a positive purified protein derivative (PPD) for TB or a previous history of therapy for latent TB infection (LTBI) who were prescribed etanercept in the division of rheumatology at John H. Stroger Jr Hospital of Cook County prior to November 2005 were enrolled in this study. A retrospective chart review was performed looking for evidence of active TB infection during etanercept treatment.

Results. Forty-eight patients with a positive PPD were treated with etanercept, and followed for an aggregate of 818 patient-months of etanercept exposure, with a mean follow-up period of 17 months (range 5 to 48 months); all patients had at least one follow-up visit. Forty-four patients (92%) were fully or partially treated with LTBI therapy prior to initiation of etanercept. Chest roentgenograms were available for review in 43 patients, ten of which had evidence of old granulomatous disease. No cases of active TB were described during the study period.

Conclusions. In this small retrospective analysis, none of the 48 patients with positive PPDs who were treated with etanercept for average of 17 months developed active TB.

Introduction

Etanercept (Enbrel™) has been approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), ankylosing spondylitis, psoriatic arthritis (PsA), and psoriasis (1). Etanercept is a fusion protein consisting of two soluble p75 Tumor Necrosis Factor (TNF)-α receptors linked to a human immunoglobulin Fc fragment. It functions as a soluble receptor of TNF-α, competing with TNF-α cell membrane receptors and blocking the biological activity of the cytokine (1). Other currently available TNF-α antagonists include infliximab (Remicade™) and adalimumab (Humira™). TNF-α blockade has become a standard treatment for a variety of rheumatic diseases. Despite dramatic clinical benefit provided for some patients by these drugs, there has been significant concern regarding the potential susceptibility to serious infections during treatment. TNF-α is a cytokine that has been shown to be essential for an effective immune response to mycobacterial infection in animal models (2). Tuberculosis (TB) infections have been linked to all of the currently available TNF-α blockers (3-7). In a previous report, we described 25 cases of tuberculosis cases associated with etanercept (4, 5). The estimated incidence of TB in this study was found to be 10 cases/100,000 patient-years of etanercept exposure. The median time from the first dose of etanercept to diagnosis of TB was 11.5 months (4, 5). Many of these patients suffered serious health consequences including disseminated extrapulmonary infection and/or death. As the status of their purified protein derivative (PPD) test prior to etanercept therapy was not available, it was unclear if these 25 cases represented primary TB infection or reactivation of latent TB in the presence of etanercept. Similarly, there is no evidence in the literature regarding the risk of reactivation of TB during etanercept therapy, with or without concomitant anti-TB medication. Here, we assessed the frequency of reactivation of latent TB in PPD positive patients receiving etanercept with concomitant anti-TB chemotherapy, in the context of a large public county-run hospital in a major metropolitan area.

Methods

All patients between January 2001 and November 2005 with a positive single stage PPD test or previous history of therapy for latent TB infection (LTBI) who were prescribed etanercept 25 mg subcutaneously (SQ) twice a week in the division of rheumatology at John H. Stroger Jr Hospital of Cook County.
hospital (Chicago, Illinois, USA) were enrolled in this study. Some patients were switched to etanercept 50 mg SQ in May of 2005. Etanercept was the only TNF-α antagonist on formulary during most of the study period. This study represents the prescribing practices of five academic attending rheumatologists. A positive PPD was defined as ≥ 15 mm palpable induration or ≥ 10 mm in individuals born in countries with a high prevalence of TB. PPDs were evaluated between 48-72 hours after inoculation. After obtaining approval of the Human Investigations Review Board, all outpatient records, culture results, and hospital discharge summaries of the patients were retrospectively reviewed for the following information: demographic data, rheumatologic diagnosis, PPD status, chest roentgenogram results, evidence of active tuberculosis infection, and type of therapy prescribed for LTBI. The primary endpoint was the development of active TB during or after etanercept therapy.

Results

Two hundred and sixty-six patients received etanercept during the study period. Fifty-one of those patients had a positive PPD skin test. Two of the PPD positive patients were excluded because of history of active pulmonary TB prior to etanercept therapy. One additional patient was excluded because she moved out of the region shortly after the first follow-up visit at 1.5 months. The remaining 48 patients represent the primary study cohort. All 48 PPD positive patients attended at least one follow-up visit. No evidence for active TB infection was found in outpatient records, hospital discharge summaries, and culture results. The mean follow-up after initiation of etanercept was 17 months (range 5 to 48 months). This series represents 818 patient-months of etanercept exposure. Indications for treatment included: RA, 32 (66%), ankylosing spondylitis, 7 (15%), psoriatic arthritis, 7 (15%), JRA 1 (2%), and psoriasis, 1 (2%). The cohort consisted of 27 females and 21 males. 36 (75%) of the patients were foreign born. The cohort included 28 Hispanics, 9 African Americans, 6 Caucasians, 4 Asians, and one Filipino. Forty-four patients were fully or partially treated for latent TB infection (LTBI) prior to initiation of etanercept: 42 (96%) received isoniazid (INH), 1 (2%) received rifampin, and 1 (2%) received rifampin and PZA. Only 42 patients were compliant with and completed LTBI therapy (an average of 9.6 months). LTBI therapy had been initiated a mean of 2.5 months prior to etanercept therapy (range 0 to 8 months). Chest roentgenograms were available for review in 43 patients: 32 were normal, 10 revealed old granulomatous disease and one had pulmonary fibrosis. Etanercept was temporarily discontinued in two patients due to serious infectious complications: one case of Staphylococcus aureus pneumonia and cellulitis. In the patient with Staphylococcus aureus pneumonia, mycobacterium gordoniae was simultaneously cultured from sputum, though Mycobacterium gordoniae is not considered to be a pathogen. In both cases, etanercept was restarted after resolution of the infections without further problems. Two patients self reported a prior history of bacilli Calmette-Guérin (BCG) vaccination. It is interesting to note that 4 of the patients with a positive PPD were not given LTBI therapy. In one patient, isoniazid was avoided because of active viral hepatitis, in one it was withheld due to alcoholism, and in one for abnormal liver function tests. It is unclear from medical records why the remaining patient did not receive LTBI therapy.

Discussion

The lifetime risk for the reactivation of latent TB in PPD positive individuals is estimated to be approximately 10% (8). LTBI therapy with isoniazid has a protective effect of up to 90% in the general population (9, 10). Specific data regarding the efficacy of LTBI therapy in patients with rheumatic diseases are not available, and the optimal duration of LTBI therapy prior to initiation of etanercept therapy has not been established. Intuitively, one would assume that it would be best to complete a full course (9 months) of LTBI therapy prior to TNF-α blockade, although this must be balanced against compelling evidence that structural articular changes occur early in the course of RA. In our cohort of 48 patients with a positive PPD, some patients were treated with etanercept and LTBI therapy simultaneously while others received several months of LTBI therapy prior to etanercept initiation. The prescribing physicians reported that a variety of factors affected their choices regarding the timing of etanercept initiation in patients with a positive PPD, such as the patient’s country of origin, chest roentgenogram findings, rheumatologic disease activity, probability of prior BCG vaccination, and patient/physician comfort level.

Another potentially confounding issue involves the definition of “positive PPD.” Based on the American Thoracic Society/Centers for Disease Control and Prevention (ATS/CDC) guidelines, a positive PPD is defined as 15 mm of palpable induration; but those individuals with ≥ 10 mm are considered to be positive in immigrants, intravenous drug users, residents of certain institutions (jails, homeless shelters, long term care facilities), children less than 4 years of age, and persons with certain predisposing conditions (silicosis, chronic renal failure, malignancies, weight loss > 10 percent of ideal body weight, gastrectomy, and jejunooileal bypass); those with induration ≥ 5mm are also considered to be positive in certain populations (HIV patients, recent contacts of tuberculosis patients, patients with chest radiographs consistent with prior TB, organ transplant patients and other immunosuppressed patients receiving ≥15 mg prednisone) (9). Some authors have recommended lowering the threshold to 10 mm in patients with rheumatic disease requiring anti-TNF therapy (11), while others have even suggested employing LTBI therapy prior to anti-TNF therapy in some patients with < 5mm induration, if significant epidemiological LTBI risk factors are present (12). This practice may be justified because of the relatively high prevalence of anergy among patients with chronic inflammatory diseases and among those who receive immunosuppressive medications. This study has several limitations. First, some patients may have been exposed to non-tuberculosis mycobacteria.

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which are capable of causing a positive PPD; and many of the patients were foreign born and may have received a BCG vaccination. This may result in a false positive PPD in the absence of prior TB exposure. However, from a public health perspective, it may be best to ignore the BCG issue when deciding upon treatment options, and assume that those patients have latent disease (13, 14). Second, cases of active TB infection have been described in PPD negative patients treated with TNF antagonists (15). This highlights the problem of using a PPD as a sole marker for latent TB infection. Third, routine follow-up chest roentgenograms or sputum examinations were not performed on these patients. Fourth, the follow-up period for many of the patients may have been insufficient; 16 subjects were followed less than 11.5 months, the previously described median period for the development of clinically apparent TB in etanercept treated patients (4, 5). Fifth, the lack of an untreated control group prevents any definitive conclusions. Sixth, our study is most likely under-powered. In our region (Illinois, USA), the incidence of active TB infection is 5.6 cases per 100,000 (16); but it is important to note that our cohort was largely foreign-born and Hispanic. The rate of TB in Hispanics in the USA is estimated to be 10.1 per 100,000 and the rate among foreign-born persons 22.5 per 100,000 (16). Despite our potentially high-risk cohort, it is still unlikely that this small study has adequate power to detect the low risk among these patients. Longer follow-up of this population, as well as larger studies may help determine an evidence-based algorithm for the management of PPD positive patients requiring etanercept.

Our results are similar to data published by Carmona et al. from the BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products) registry (17). This registry includes information on a cohort of patients treated with one or more of the TNF-α antagonists (infliximab, etanercept, and adalimumab). Thirty-four cases of active tuberculosis were reported since the registry’s inception in February 2000. All cases of active TB occurred in infliximab treated patients. In March 1, 2002, Spanish National Health Service and Spanish Society of Rheumatology made recommendations for management of patients with LTBI prior to TNF-α therapy. These recommendations called for INH therapy for individuals with a PPD>5 mm or chest radiograph findings suggestive of past TB. Thiry-two of the 34 cases of active TB occurred prior to these official recommendations for LTBI therapy. It seems that these recommendations resulted in a 88% reduction (p = 0.008) in the number of cases of active TB associated with infliximab therapy. No cases of active TB in etanercept treated patients were reported prior to or after the official recommendations. As in our study, the absence of cases of active TB associated with etanercept prevented calculations of incidence rates and risk reduction. Furthermore, the number of patients with a positive PPD treated with etanercept was not reported. Their etanercept data probably suffers from similar weaknesses as ours including inadequate power and/or inadequate follow-up.

Conclusions

In this retrospective analysis, none of the 48 patients with presumed latent TB infection who were treated with etanercept for an average of 17 months developed active TB infection. This represents the largest analysis of TB reactivation risk during etanercept therapy. Our data cannot be used to establish definitive guidelines, but in light of these findings, we currently advocate that patients who are PPD positive and who require etanercept therapy be treated with LTBI after clinically active TB has been excluded by history, physical examination, and chest roentgenography. No convincing evidence is available regarding the minimum size of PPD-induced induration that would predict a higher risk of reactivation of TB among patients initiating anti-TNF-α therapy, nor has the optimal duration of LTBI prophylaxis prior to etanercept therapy been established.

References


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