

# Acquired latent tuberculosis infection in psoriasis patients treated with etanercept in the People's Republic of China

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**Background:** TNF- $\alpha$  plays a key role in host defense against mycobacterial infection, and patients receiving TNF- $\alpha$  blocker treatment have increased susceptibility to tuberculosis disease. In the People's Republic of China, an intermediate tuberculosis-burden country, the latent tuberculosis infection (LTBI) risk in patients with psoriasis who are treated with etanercept, the safest kind of TNF- $\alpha$  blocker, is unknown.

**Objectives:** This study reports the LTBI risk in patients with psoriasis after etanercept treatment and aims to answer the question of how often rescreening for LTBI should be done in order to reduce active tuberculosis infection of patients and further reduce the incidence of active tuberculosis disease.

**Patients and methods:** This retrospective review evaluated patients with moderate-to-severe chronic plaque psoriasis between 2009 and 2013. All patients were excluded tuberculosis infection and received etanercept 25 mg twice weekly, then the patients were checked for LTBI 3 months after etanercept treatment to observe the incidence of LTBI and assess the need for rescreening for LTBI every 3 months.

**Results:** We retrospectively analyzed 192 patients with psoriasis with moderate-to-severe chronic plaque whose tuberculin skin test and chest X-rays were negative and who received etanercept 25 mg twice weekly. Eighteen of them were excluded because they received less than 3 months of etanercept therapy. After treatment with etanercept, four patients were found to have LTBI.

**Conclusion:** In this study, the incidence of LTBI after 3 months was four in 192 (2.1%), which is higher than the annual incidence of LTBI in the People's Republic of China (0.72%), so LTBI could be expected to occur within 3 months in psoriasis patients on etanercept. Periodic screening for LTBI in the therapy course, as well as before initiating treatment, is necessary in those patients who use a TNF- $\alpha$  blocker. We recommend rescreening for LTBI every 3 months.

**Keywords:** TNF receptor, TNFR, fusion protein, treatment, LTBI, TB screening

## Introduction

Psoriasis is a chronic, inflammatory, systemic disease that affects approximately 2% of the world's population.<sup>1</sup> Patients with psoriasis have more physical and mental disabilities than those with many major diseases.<sup>2</sup> Patients with severe chronic plaque psoriasis are not satisfied with the treatment effect, because cumulative toxicity of the therapies limits their usefulness in this chronic disease. Early reports by different investigators demonstrated that tumor necrosis factor (TNF)- $\alpha$  was elevated in sera and overexpressed in skin tissue of psoriatic lesions in patients with psoriasis.<sup>3,4</sup> Etanercept is a bioengineered human TNF receptor (TNFR) fusion protein incorporating soluble TNFR p75 and the Fc component of IgG 1. This recombinant product

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binds specifically to TNF- $\alpha$  and lymphotoxin, inhibiting their interaction with cell-surface receptors. Etanercept has shown efficacy in the treatment of adults with psoriasis.<sup>5,6</sup> However, as TNF- $\alpha$  plays a key role in host defense against mycobacterial infection, patients receiving such treatment have increased susceptibility to serious infections, including tuberculosis (TB).<sup>7,8</sup> However, to date, studies of acquired latent TB infection (LTBI) of psoriasis patients treated with etanercept in the People's Republic of China has not been published. Such a study can help us to understand the LTBI risk of etanercept in Chinese patients.

LTBI is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB.<sup>9</sup> However, the risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the host. A direct measurement tool for *M. tuberculosis* infection in humans is currently unavailable. Systematic testing and treatment of LTBI should be performed in patients initiating anti-TNF treatment. Either interferon-gamma release assays or the Mantoux tuberculin skin test (TST) should be used to test for LTBI.<sup>10</sup> According to a national epidemiological survey of TB in 2000, the annual incidence of LTBI is 0.72% in the People's Republic of China.<sup>11</sup>

## Patients and methods

### Patients

We retrospectively reviewed psoriasis patients treated with etanercept between 2009 and 2013. They were outpatients and inpatients. Before and after treatment with etanercept, all patients needed to be examined to rule out TB. Patients who had clinically active TB or a positive TST or showed radiographic evidence of fibrocalcified lesions in the upper lung fields were excluded from using etanercept. As TB usually appears several months after treatment with TNF blockers, patients who used etanercept for less than 3 months were excluded from the analysis.

All patients signed written informed consents. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by our local ethics committee, the Institutional Ethical Review Board of Peking Union Medical College.

### TST and T-SPOT<sup>®</sup>.TB test for LTBI

The TST was performed with an intradermal injection of two tuberculin units of purified protein derivative RT-23 (Statens Serum Institut, Copenhagen, Denmark) into the ventral surface of the forearm, according to the Mantoux

method. In the People's Republic of China, a TST induration cutoff  $\geq 5$  mm is considered positive. The T-SPOT<sup>®</sup>.TB test (Oxford Immunotec, Abingdon, UK), an interferon-gamma release assay for TB infection, does not cross-react with bacille Calmette-Guérin or most non-tuberculosis *Mycobacterium* spp. and is based on interferon-gamma responses to *M. tuberculosis*-specific antigens. The T-SPOT<sup>®</sup>.TB test was conducted in patients whose TST changed to a positive result after etanercept treatment. For the T-SPOT<sup>®</sup>.TB, a 10 mL blood sample was taken and analyzed according to the manufacturer's instructions.<sup>12,13</sup>

## Diagnosis and prophylactic treatment of LTBI

After etanercept treatment, LTBI was confirmed when a patient's TST test changed to a positive result but they did not have any clinical, radiological, or microbiological evidence of active TB. There is a lack of consensus regarding LTBI treatment. A 3-month regimen of isoniazid 300 mg daily plus rifampicin 450 mg daily was recommended but not mandatory for the LTBI patients. After anti-TB treatment for 3 months, the TST and T-SPOT<sup>®</sup>.TB test were conducted again.

## Results

### Patients treated with etanercept

Demographic and clinical characteristics of the study population are reported in Table 1. We retrospectively analyzed 192 patients with psoriasis with moderate-to-severe chronic plaque psoriasis whose TST and chest X-rays were negative and who received etanercept 25 mg twice weekly. Eighteen of them were excluded because they received less than 3 months of etanercept therapy. The patients, including a total of 141 male patients and 51 female patients, had the following characteristics: mean age 40.8 $\pm$ 12.4 (range 16–67) years; mean height 167.5 $\pm$ 7.2 (range 150–185) cm; mean weight 67.1 $\pm$ 10.4 (range 45–87) kg; mean Psoriasis Area and Severity Index (PASI) score 21.4 $\pm$ 10.3 (range 10–53); and mean course of disease 12.2 $\pm$ 9.8 (range 0.5–40) years. None of the

**Table 1** Demographic and clinical characteristics of the study population

Number of patients with psoriasis	192
Male (%) / female (%)	141 (73.4) / 51 (26.6)
Mean age (years)	40.8 $\pm$ 12.4 (range 16–67)
Mean height (cm)	167.5 $\pm$ 7.2 (range 150–185)
Mean weight (kg)	67.1 $\pm$ 10.4 (range 45–87)
Mean PASI score	21.4 $\pm$ 10.3 (range 10–53)
Mean course of disease (years)	12.2 $\pm$ 9.8 (range 0.5–40)

**Abbreviation:** PASI, Psoriasis Area and Severity Index.

psoriasis patients systematically used immunosuppressive agents such as methotrexate, cyclosporin, and glucocorticoids, and none of them had malnutrition, immunosuppression, HIV, or a definite history of contact with patients with TB, etc.

## TST and T-SPOT®.TB test results after more than 3 months of continuous etanercept therapy

After treatment with etanercept for 3 months, TSTs were performed again, and we found four patients' TSTs had become positive. TSTs were done 0–3 days after the last dose of etanercept. Three of the four patients also had a positive T-SPOT®.TB test. No patients with a positive TST had any clinical, radiological, or microbiological evidence of active TB, and LTBI was confirmed.

## Prophylactic treatment of LTBI and patient outcomes

Three of the LTBI patients received therapy with isoniazid 300 mg daily and rifampicin 450 mg daily. After 3 months of anti-TB treatment, they were given the TST and T-SPOT®.TB test again. One patient's screening test converted to negative and those of another two patients were improved. We suggested the two patients whose tests did not convert to negative should retest for LTBI after 6 months, but they failed to retest for LTBI for some reason. One of the LTBI patients did not receive any anti-TB treatment but stopped etanercept. This patient repeated the T-SPOT®.TB test 8 months later and had a negative result.

## Discussion

In 2013, the largest number of new TB cases occurred in the South East of Asia and Western Pacific regions, accounting for 56% of new cases globally.<sup>14,15</sup> The prevalence of LTBI in the People's Republic of China is still more than 44.5%,<sup>11</sup> although it has shown a sustained decline over the past decade.

It is a well-established finding that use of a TNF blocker increases the risk for TB disease. Published data from registries suggest that etanercept was associated with TB, but the incidence was lower and associated with a longer time to TB onset when compared to infliximab and adalimumab.<sup>16,17</sup> The British Society for Rheumatology Biologics Register (BSRBR) confirms that the relative risk of TB is three to four times higher with the monoclonal antibodies than with etanercept.<sup>17</sup>

In the present study, we found that four patients acquired LTBI after 3 months of treatment with etanercept, which

implies that one should recheck for TB every 3 months. LTBI is the presence of *M. tuberculosis* in the body with neither signs and symptoms nor radiographic or bacteriological evidence of TB disease. It is estimated that around 10% of LTBI carriers are potentially at risk of developing an active infection, which is both symptomatic and contagious. Early detection and treatment of LTBI while on TNF-inhibitor therapy may result in better outcomes for the patient.<sup>18</sup> The probability of developing active TB is reportedly up to seven times higher when early detection and treatment of LTBI are not followed.<sup>19</sup> There may be several regimens of prophylactic therapy available within a single country.<sup>20,21</sup> Nine months of isoniazid treatment is recommended by the US Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS).<sup>22</sup> Given the high incidence and the high multidrug resistance of TB in the People's Republic of China, LTBI patients are typically given therapy with isoniazid 300 mg daily and rifampicin 450 mg daily.<sup>23,24</sup>

A limitation of the present study was lack of a control group, because it was a retrospective study. In the absence of a placebo arm, conclusions about acquired LTBI are less reliable; however, the TST results of four patients in this article became positive after 3 months of treatment with etanercept. In our study, the incidence of LTBI in 3 months was four in 192 (2.1%), which is higher than the annual incidence of LTBI in the People's Republic of China (0.72%),<sup>11</sup> so acquired LTBI is a plausible result of using etanercept.

## Conclusion

We have reported LTBI induced by mid-dose and short-course etanercept treatment in the People's Republic of China. Although etanercept is the safest TNF blocker, periodic screening for LTBI in the therapy course, as well as before initiating treatment, is necessary. We recommend rescreening for LTBI every 3 months. However, in order to better answer how often rescreening for LTBI should be done, we expect other authors will design further scientific prospective studies that will involve expanding the sample size; rescreening for LTBI every 1, 2, 3, 4, or 5 months; rescreening for LTBI 1–3 weeks after the last dose of etanercept; and so on.

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## Disclosure

The authors report no conflicts of interest in this work.

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