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

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Background: TNF-α plays a key role in host defense against mycobacterial infection, and patients receiving TNF-α 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-α 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-α 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. Patients with psoriasis have more physical and mental disabilities than those with many major diseases. 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)-α was elevated in sera and overexpressed in skin tissue of psoriatic lesions in patients with psoriasis. 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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Eine spezifische Bindung an TNF-α und Lymphotoxin, inhibierend ihre Interaktion mit Zell-surface-Rezeptoren. Etanercept hat gezeigt Efficacy in der Behandlung von Erwachsenen mit Psoriasis.5,6 Allerdings, TNF-α spielt eine zentrale Rolle in der Abwehr gegen mykobakterielle Infektion, Patienten, die solche Behandlung erhalten haben, haben eine erhöhte Empfindlichkeit für Infektionen, einschließlich Tuberkulose (TB).7,8 Allerdings, zu diesem Zeitpunkt, werden die Ergebnisse von Tuberkulose Latenz (LTBI) von Psoriasis-Patienten mit Etanercept in der Volksrepublik China nicht veröffentlicht wurden. Ein solch ein Studium kann uns dabei helfen, den LTBI-Risiko von Chinesischen Patienten zu verstehen.

LTBI wird definiert als eine anhaltende immunologische Reaktion auf Stimulation durch Mycobacterium tuberculosis Antigene ohne Anzeichen von klinisch manifestem aktiven TB.9 Allerdings, das Risiko, Tuberkulose nach Infektion zu entwickeln, hängt von mehreren Faktoren, der wichtigste davon ist die Immunologische Stellung des Wirts. Ein direkter Messmittel-Tool für M. tuberculosisis Infektion in Menschen ist derzeit nicht verfügbar. Systematische Untersuchung und Therapie des LTBI sollte in Patienten initiiert werden, die Anti-TNF Behandlung erhalten. Einer interferon-gamma-Releasenassay oder Mantoux Tuberkulin Hauttest (TST) sollte für die LTBI gemessen werden.10 Gemäß einer nationalen epidemiologischen Umfrage in 2000, die jährliche Incidence von LTBI ist 0.72% in der Volksrepublik China.11

Patienten und Methoden

Patienten

Wir retrospektiv analysierten Psoriasis-Patienten, die mit Etanercept behandelt wurden zwischen 2009 und 2013. Sie waren Patienten und Inpatienten. Vor und nach der Behandlung mit Etanercept, alle Patienten wurden getestet werden muss, um die TB zurückzulassen. Patienten, die aktive TB oder einen positiven TST oder radiologische Evidenz fokalen tuberkulösen Lungenläsionen im oberen Lungfeld wurden von der Untersuchung ausgeschlossen werden. Als TB könnte es in den ersten drei Monaten nach der Therapie mit TNF Blocker kommt, die Patienten mit Etanercept für weniger als drei Monaten wurden aus der Analyse ausgeschlossen werden.

Alle Patienten signierten einen formalen Eingriff. Die Untersuchung wurde in Übereinstimmung mit den Prinzipien der Deklaration von Helsinki und wurde von unserer lokalen Ethik-Kommission, das Ethik-Gericht der Peking Union Medical College genehmigt.

TST und T-SPOT®-TB Test für LTBI

Der TST wurde durch eine intradermale Injektion von zwei Tuberkulinskiton-Einheiten von gereinigter Proteinabkömmling RT-23 (Statens Serum Institut, Kopenhagen, Dänemark) in die ventrale Oberfläche des Unterarms, gemäß der Mantoux-Methode. In der Volksrepublik China, wird ein TST Erfahrungscutoff ≥5 mm als positiv gewertet. Der T-SPOT®-TB Test (Oxford Immunotec, Abingdon, UK), ein interferon-gamma-Releasenassay für TB Infektion, weist nicht gegen Bacille Calmette-Guérin oder gegen non-tuberkulöse Mycobacterium spp. und basierend auf interferon-gamma Responses auf M. tuberculosisispezifische Antigene. Der T-SPOT®-TB Test wurde bei Patienten, die TST sich positiv erweckt, nach der Etanercept-Behandlung für TB Infektion. Der T-SPOT®-TB Test, ein 10 mL Blut-Sample wurde entnommen und analysiert gemäß des Herstelleranweisung.

Diagnose und prophylaktische Behandlung von LTBI

Nach der Etanercept-Behandlung wurde LTBI bestätigt, wenn der Patient’s TST Test sich zu einem positiven Resultat veränderte, aber sie nicht haben eine klinische, radiologische oder mikrobiologische Evidenz von aktiver TB. Es gibt ein Manko im Bezirk LTBI-Behandlung. Ein 3-Monats-Regime von Isoniazid 300 mg tgl. plus Rifampicin 450 mg tgl. wurde empfohlen, aber nicht verpflichtend für die LTBI-Patienten. Nach anti-TB Behandlung für 3 Monate, der TST und T-SPOT®-TB Test wurden erneut durchgeführt.

Ergebnisse

Patienten behandelte mit Etanercept

Demografische und klinische Merkmale der Studienpopulation sind in Tabelle 1 berichtet. Wir retrospektiv analysierten 192 Patienten mit Psoriasis mit mittelstark bis schwer chronisch Plaques Psoriasis, die TST und Brust-Röntgenaufnahmen waren negativ und die Patienten, die mit Etanercept 25 mg pro Woche behandelt wurden. Sie waren 192 Patienten mit mittelstark bis schwer chronisch Plaques Psoriasis, die TST und Brust-Röntgenaufnahmen waren negativ und die Patienten, die mit Etanercept 25 mg pro Woche behandelt wurden. Sie waren 141 Mann und 51 weibliche Patienten, davon haben folgende Charakteristika: Mittel 40.8 ± 12.4 (Range 16–67) Jahresalter; Mittel 167,5 ± 7,2 (Range 150–185) cm; Mittel 67,1 ± 10,4 (Range 45–87) kg; Psoriasis Area and Severity Index (PASI) Score 21,4 ± 10,3 (Range 10–53); und Mittel Krankheitsdauer 12,2 ± 9,8 (Range 0,5–40) Jahre. Keiner der Patienten wurden ausgeschlossen werden.

Tabelle 1 Demografische und klinische Merkmale der Studienpopulation

| Zahl der Patienten mit Psoriasis | 192 |
|---------------------------------|-----|
| Mann (%)/weiblich (%)            | 141 (73,4)/51 (26,6) |
| Mittleres Alter (Jahre)          | 40,8 ± 12,4 (Range 16–67) |
| Mittlerer Körpergröße (cm)       | 167,5 ± 7,2 (Range 150–185) |
| Mittleres Gewicht (kg)           | 67,1 ± 10,4 (Range 45–87) |
| Mittleres PASI-Score             | 21,4 ± 10,3 (Range 10–53) |
| Mittleres Krankheitsdauer (Jahre)| 12,2 ± 9,8 (Range 0,5–40) |

Abkürzung: 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. The prevalence of LTBI in the People’s Republic of China is still more than 44.5%, 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. 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.

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 bacteriologic 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. The probability of developing active TB is reportedly up to seven times higher when early detection and treatment of LTBI are not followed. There may be several regimens of prophylactic therapy available within a single country. Nine months of isoniazid treatment is recommended by the US Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS). 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.

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%), 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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