Clin Rheumatol (2008) 27:1083–1086
DOI 10.1007/s10067-008-0867-3

ORIGINAL ARTICLE

The evaluation of latent tuberculosis in rheumatologic diseases for anti-TNF therapy: experience with 192 patients

Ismail Hanta · Suleyman Ozbek · Sedat Kuleci · Ali Kocabas

Received: 25 January 2008 / Revised: 6 February 2008 / Accepted: 12 February 2008 / Published online: 5 March 2008

Abstract It is recommended to evaluate the presence of latent tuberculosis infection (LTBI) before initiating antitumor necrosis factor α (anti-TNF) therapy for rheumatologic diseases. We aimed to present the follow-up results of 192 patients with rheumatologic diseases before anti-TNF therapy for LTBI. We enrolled 192 patients who were given anti-TNF therapy for their rheumatologic diseases between April 2005 and January 2008. The demographic characteristics of the patients were recorded. Chest X-ray was obtained and tuberculin skin test (TST) was performed in all patients before anti-TNF therapy. LTBI was assessed by detailed history of close contact with infectious cases within the last year, abnormal chest radiography, and positive TST (≥5 mm) before initiating anti-TNF therapy. Patients with anti-TNF therapy were followed with 2-month intervals for active tuberculosis by pulmonary and extrapulmonary symptoms, physical examination, and chest X-ray. Of 192 patients, 104 (54.2%) patients were women, age (mean±SD) 43.1±12.7 years and 88 (45.8%) patients were men, age (mean±SD) 39.3± 11.2 years. Ninety-one (47.4%) of them had rheumatoid arthritis (RA); 92 (47.9%) had ankylosing spondylitis (AS), and nine (4.7%) had psoriatic arthritis. Isoniazid treatment was started in 129 (67.2%) patients in whom LTBI was detected. No significant difference was observed for TST positivity (TST≥5 mm) between the patients with RA and AS (p=0.101). Similarly, no significant difference was also observed for TST positivity between the patients who received immunosuppressive therapy and those who did not (p=0.154). Only three (1.6%) patients developed active tuberculosis at the study period. We suggested that in despite of the presence of rheumatologic disease and/or immunosuppressive therapy, TST is an acceptable and available diagnostic test for detecting LTBI before anti-TNF therapy.

Keywords Anti-TNF therapy · Latent tuberculosis infection · Tuberculin skin test

I. Hanta (✉) · S. Kuleci · A. Kocabas
School of Medicine,
Department of Chest Diseases, Çukurova University,
01330 Balcali,
Adana, Turkey
e-mail: ihanta@cu.edu.tr

S. Ozbek
School of Medicine,
Department of Rheumatology, Çukurova University,
Adana, Turkey

Introduction

Antitumor necrosis factor (anti-TNF) therapies are now widely used for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis [1]. The side effects of these biologic agents include the potential for an increased risk of serious infections especially reactivation of latent tuberculosis infection (LTBI) [2, 3]. Screening of these patients should include history of close contacts with infectious cases with tuberculosis, tuberculin skin test (TST), and chest radiography [4].

Although TST is a widely used diagnostic method for LTBI, the presence of rheumatologic diseases and immunosuppressive therapy, and Bacille–Calmette Guerin (BCG) vaccination may lead false positive and false negative results [5]. However, several guidelines recommended 6 or 9 months of isoniazid (INH) prophylaxis for the treatment of latent tuberculosis infection [6, 7] because it is reported that, by using anti-TNF therapy, the risk of development of tuberculosis may increase fourfold to tenfold [4].

How active tuberculosis will be suspected, which diagnostic methods may be used for detecting tuberculosis

in routine evaluation, and how frequently these patients will be followed has not been adequately elucidated yet.

In this study, we aimed to present the follow-up results of 192 patients with rheumatologic diseases before anti-TNF therapy for LTBI.

Materials and methods

One hundred ninety-two patients who administered anti-TNF treatment for their rheumatologic diseases were included in the study at both Departments of Chest Diseases and Rheumatology Outpatient Clinics from April 2005 to January 2008. The diagnosis and anti-TNF therapy indications were assessed and administered by an experienced specialist on rheumatology. The demographic characteristics of the patients were recorded (Table 1). Chest X-ray was obtained and TST was performed in all patients.

Table 1 Patients characteristics

Features	Study group (n=192), n (%)
Female	104 (54.2)
Male	88 (45.8)
Age (years)[a]	
Female	43.1±12.7
Male	39.3±11.2
Primary disease	
RA	91 (47.4)
AS	92 (47.9)
PsA	9 (4.7)
Immunosuppressive therapy	
Yes	108 (56.2)
No	84 (43.8)
Anti-TNF therapy	
Infliximab	72 (37.5)
Etanercept	93 (48.4)
Adalimumab	27 (14.1)
Abnormal chest X-ray	
Yes	6 (3.1)
No	186 (96.9)
Close contact	
Yes	4 (2.1)
No	188 (97.9)
BCG scarring	
Yes	172 (89.6)
No	20 (10.4)
TST results	
0 mm	43 (22.4)
1–4 mm	30 (15.6)
5–9 mm	36 (18.8)
≥10 mm	83 (43.2)
INH therapy	
Yes	129 (67.2)
No	63 (32.8)

[a] Mean±standard deviation

Table 2 TST status in patients with RA and AS

TST status	RA (n=71), n (%)	AS (n=83), n (%)	p
TST≥5 mm	48 (67.6)	66 (79.5)	0.101
TST=0 mm	23 (32.4)	17 (20.5)	

The presence of LTBI was assessed by detailed history of close contact with infectious cases within the last year, abnormal chest radiography, and positive TST (≥5 mm) before initiating anti-TNF therapy. Because Turkey is a high-frequency area for tuberculosis, we preferred TST of ≥5 mm for detecting LTBI.

Tuberculin skin test Five tuberculin units of purified protein derivative were injected intradermally into the volar surface of the forearm (Mantoux method). Reaction was read at 48 to 72 h as the transverse diameter in millimeters of induration. The cutoff value for a positive skin test was accepted as an area of induration of ≥5 mm in diameter.

INH tablet 300 mg/day and pyridoxine tablet 10 mg/day were administered for 9 months in patients with LTBI. Anti-TNF treatment was administrated after starting INH prophylaxis 1 month later.

Patients with anti-TNF therapy were followed by 2-month intervals for active tuberculosis by pulmonary and extrapulmonary symptoms, physical examination, and chest X-ray.

Statistical analysis Statistical analyses were performed by using the SPSS version 15.0 statistical package program. Fisher exact test was used for comparing categorical data. Continuous variables were listed in the form of mean± standard deviation, and all categorical variables were shown as the number and percent of cases.

Results

The patients characteristics are summarized on Table 1. Of 192 patients, 104 (54.2%) were women, age (mean±SD) 43.1±12.7 years and 88 (45.8%) were men, age (mean±SD) 39.3±11.2 years. Ninety-one (47.4%) of them had RA; 92 (47.9%) had AS, and nine (4.7%) had psoriatic arthritis (PsA). Of 192 patients, 108 (56.2%) patients were using at

Table 3 TST status according to usage of immunosuppressive agent

TST status	Immunosuppressive therapy (+; n=85), n (%)	Immunosuppressive therapy (−; n=77), n (%)	p
TST≥5 mm	58 (68.2)	61 (79.2)	0.154
TST=0 mm	27 (31.8)	16 (20.8)	

Table 4 Patients characteristics of active tuberculosis receiving anti-TNF therapy during the study

Features	Patient 1	Patient 2	Patient 3
Age, gender	48, F	44, F	57, F
Primary disease	AS	RA	AS
Anti-TNF agent	Infliximab	Etanercept	Infliximab
Immunosuppressive agent	None	Yes	None
TST (mm)	0	14	0
INH therapy	None	None, refused to use	None
Symptoms	Swelling on the neck	Nonspecific	Ileus
Clinical manifestation of tuberculosis	Lymphadenopathy	Only cavitary lesion	Only extrapulmonary lesion (small intestine)
Time from first dose of anti-TNF agent (months)	2	8	30
Diagnostic method	Histopathology	Positive *M. tuberculosis* culture (bronchoalveolar lavage)	Positive *M. tuberculosis* culture + histopathology

least one immunosuppressive agent (corticosteroids and/or methotrexate) for their rheumatologic disease. Of 192 patients, 93 (48.4%) were using etanercept; 72 (37.5%) were using infliximab, and 27 (14.1%) were using adalimumab.

At the time of evaluation before anti-TNF therapy, fiberoptic bronchoscopy was performed in six (3.1%) patients due to abnormal chest X-ray graph. However, no active tuberculosis was detected in any of the patients. TST was found positive for 119 (62.0%) patients and INH therapy was administered in 129 (67.2%) patients.

Patients with TST≥5 mm and TST=0 mm were included for statistical evaluation in subgroup analysis. No significant difference was found between patients with RA and AS according to frequency of TST positivity (p=0.101; Table 2). Although 108 patients had used immunosuppressive agent due to rheumatologic diseases, we excluded 23 patients in whom TST was between 1 and 4 mm or had PsA from statistical analysis. Finally, 85 patients had been evaluated for statistical analysis. According to frequency of TST positivity, no significant difference was observed between the patients who were using immunosuppressive agent and those who were not (p=0.154; Table 3).

During the follow-up period, active tuberculosis has developed only three (1.6%) patients. The demographics characteristics of these patients was shown on Table 4.

Discussion

TNFα is important to the host's immune response against *Mycobacterium tuberculosis*. In addition, production of TNFα is required to contain *M. tuberculosis* via granuloma formation that sequesters bacilli and prevents their dissemination. Furthermore, TNFα elicits macrophage apoptosis, a prominent feature of tuberculous granulomas promoting their integrity [4, 8].

Several guidelines suggest evaluating LTBI before anti-TNF therapy. Screening of LTBI includes a careful analysis regarding the history of exposure to tuberculosis, TST, and chest radiograph [1, 3, 6, 7]. INH tablet 300 mg/day were administered for 6 or 9 months for the treatment of LTBI [6, 7].

Although TST is a widely used diagnostic method for detecting LTBI, there are some limitations like possible effect of BCG on result of TST, and the interpretation of negative tests is complicated by the effect of immunosuppressants precluding effective testing. Moreover, patients with RA might not produce an adequate delayed-type hypersensitivity reaction to tuberculin because of their deficient cell-mediated immunity [9, 10]. Therefore, a false negative TST makes it unreliable for determining the risk of tuberculosis [11]. Hence, expensive and advanced technological in vitro tests have recently been developed and it is reported that these tests are superior than TST for detecting LTBI [12, 13]. In our country, BCG vaccination is widely and routinely performed; we are unable to detect false positive TST results. Hence, we lack adequate data on which cutoff TST value can be used to determine LTBI in our country.

In our study, we determined no significant difference between the patients using and not using immunosuppressive agent according to the frequencies of TST positivity or anergy. Similarly, the presence of rheumatologic disease (RA and AS) did not significantly effect the frequencies of TST positivity or anergy.

Diagnosis and treatment of LTBI is an important issue to be considered for anti-TNF therapy. Sichletidis et al. [14] have reported that active tuberculosis had developed in 1/3 of patients despite of INH prophylaxis (patients with TST≥10 mm had received INH tablets for 6 months) in 3-year follow-up. In contrast, in a separate study, it is reported that none of the 86 patients had developed active tuberculosis

regardless of usage of INH prophylaxis in 18 months, although it is a short follow-up period [15]. Similarly, Manadan et al. [16] have reported that no active tuberculosis had developed in 48 patients during 17 months of follow-up period. In our study, only three (1.6%) of our patients had developed active tuberculosis in nearly 3 years of follow-up period and none of them had used INH prophylaxis. Because Turkey is a highly prevalent country for tuberculosis, we had administrated INH prophylaxis for 9 months to our all patients with TST≥5 mm; this might be a possible cause of encountering less frequent active tuberculosis in our study.

It is reported that active tuberculosis may develop after 2–8 months for infliximab, 2–3 months for etanercept, and 12 months for adalimumab [17]. Active tuberculosis related to infliximab and etanercept may have same clinical manifestation, and nonspecific symptoms are generally predominant [18]. Similarly, principal pulmonary symptoms such as cough and phlegm were not prominent in our active tuberculosis patients. In several studies, it is reported that disseminated or extrapulmonary tuberculosis might developed more frequently in patients who were using anti-TNF agent [18–21].

Standard antituberculous drugs are recommended for the treatment of active tuberculosis in patients with anti-TNF therapy. But it is not clear to discontinue anti-TNF therapy during the tuberculous treatment period [6]. Our three patients with active tuberculosis were successfully treated with standard antituberculous therapy and anti-TNF therapy was discontinued during this period.

In conclusion, we observed that the presence of immunosuppressive agent or disease did not significantly affect TST results. Thus, TST is still reliable and an effective diagnostic method for the detection of LTBI in anti-TNF therapy. In addition, we suggested that INH prophylaxis seems to be a safe and efficient treatment modality for LTBI.

Conflict of Interest statement
Ismail HANTA: None
Süleyman OZBEK: None
Sedat KULECI: None
Ali KOCABAS: None

References

1. Ellerin T, Rubin RH, Weinblatt ME (2003) Infections and anti tumor necrosis factor a therapy. Arthritis Rheum 48:3013–3022
2. Kroesen S, Widmer AF, Tyndall A et al (2003) Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF alpha therapy. Rheumatology (Oxford) 42(5):617–621
3. Long R, Gardam M (2003) Tumour necrosis factor-α inhibitors and the reactivation of latent tuberculosis infection. CMAJ 168 (9):1153–1156
4. Mutlu G, Mutlu E, Bellmeyer A et al (2006) Pulmonary adverse events of anti tumour necrosis factor-a antibody therapy. Am J Med 119:639–646
5. Huebner RE, Schein MF, Bass JBJ (1993) The tuberculin skin test. Clin Infect Dis 17:968–975
6. American Thoracic Society (2000) Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 61:S221–S247
7. British Thoracic Society Standards of Care Committee (2005) BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF-α treatment. Thorax 60:800–805
8. Iliopoulos A, Psathakis K, Aslanidis S et al (2006) Tuberculosis and granuloma formation in patients receiving anti-TNF therapy. Int Tuberc Lung Dis 10(5):588–590
9. Nizam S, Emery P (2006) Attenuated response to purified protein derivative in patients with rheumatoid arthritis. Ann Rheum Dis 65:980
10. Emery P, Panayi G, Symmons D et al (1984) Mechanisms of depressed delayed-type hypersensitivity in rheumatoid arthritis: the role of protein energy malnutrition. Ann Rheum Dis 43:430–434
11. Ponce de Leon D, Acevedo-Vasquez E, Sanchez-Torres A et al (2005) Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. Ann Rheum Dis 64:1360–1361
12. Andersen P, Munk ME, Pollock JM et al (2000) Specific immune-based diagnosis of tuberculosis. Lancet 356:1099–1104
13. Kang YA, Lee HW, Yoon HI et al (2005) Discrepancy between the tuberculin skin test and the whole-blood interferon assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. JAMA 293:2756–2761
14. Sichletidis L, Settas L, Spyratos D et al (2006) Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 10(10):1127–1132
15. Hanta I, Ozbek S, Kuleci S et al (2007) Isoniazid intervention for latent tuberculosis among 86 patients with rheumatologic disease administered with anti-TNFα. Clin Rheumatol 26(11):1867–1870
16. Manadan AM, Joyce K, Sequeira W et al (2007) Etanercept therapy in patients with a positive tuberculin skin test. Clin Exp Rheumatol 25(5):743–745
17. Gomez-Reino JJ, Carmano L, Descalzo A, BIOBADASER GROUP (2007) Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 57(5):756–761
18. Mohan AK, Cote TR, Block JA et al (2004) Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 39:295–299
19. Dimakou K, Papaioannides D, Latsi P et al (2004) Disseminated tuberculosis complicating anti-TNF-α treatment. Int J Clin Pract 58(11):1052–1055
20. Stas P, D'Hoore A, Van Assche G et al (2006) Miliary tuberculosis following infliximab therapy for Crohn disease: a case report and review of the literature. Acta Gastroenterol Belg 69(29):217–220
21. Mayardomo L, Marenco JL, Gomez-Mateos J et al (2002) Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. Scand J Rheumatol 31(1):44–45