Positive Conversion of Tuberculin Skin Test and Performance of Interferon Release Assay to Detect Hidden Tuberculosis Infection During Anti-Tumor Necrosis Factor Agent Trial

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ABSTRACT. ***Objectives.*** To evaluate tuberculin skin tests (TST) and interferon-γ (IFN-γ) assay in the detection of latent tuberculosis (TB) infection during tumor necrosis factor (TNF) antagonist treatment in Korean patients with initial negative TST result.

Methods. Eighty-six patients with rheumatic diseases who had received anti-TNF agents for over one year were investigated. Clinical data were obtained from medical records. All patients received followup TST, and IFN-γ assay was performed in 64.

Results. The study population consisted of 40 rheumatoid arthritis (RA), 34 ankylosing spondylitis (AS), 9 juvenile rheumatoid arthritis (JRA), and 3 other patients. The TST converted to positive in 28 (32.6%) patients. There was no significant variation between TST conversion rate and all risk factors. Although there was no statistical significance, the odds of the TST conversion rate tended to increase with the duration of TNF antagonist administration. Nine (14.1%) of 64 patients who performed an IFN-γ assay had positive results. Among 28 TST positive conversion cases, 4 patients with AS and 1 with psoriatic arthritis had positive IFN-γ assay results, and one of them developed miliary TB. However, none of the 4 RA patients with positive IFN-γ assay showed TST conversion. There was 68.6% agreement (kappa = 0.29, p = 0.02) between TST and IFN-γ assay results.

Conclusion. Serial TST with IFN-γ assay may be useful to identify false-negative response to cases of latent *Mycobacterium tuberculosis* infection and new TB infections in patients with immune mediated inflammatory diseases during longterm anti-TNF therapy, especially in areas with intermediate TB burden. (J Rheumatol First Release Sept 1 2009; doi:10.3899/jrheum.090150)

Key Indexing Terms:
TUBERCULIN SKIN TEST CONVERSION
TUBERCULOSIS TUMOR NECROSIS FACTOR

Anti-tumor necrosis factor (TNF) agents have emerged as effective treatments in immune mediated inflammatory diseases (IMID) such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and Crohn's disease. Patients receiving anti-TNF agents are at increased risk of developing serious infections. In particular, the incidence of life threatening extrapulmonary and disseminated tuberculosis (TB), resulting from reactivated latent *Mycobacterium tuberculosis* infection (LTBI), is increased in patients treated with anti-TNF agents[1-3]. Therefore, LTBI screening and prophylaxis are recommended prior to TNF antagonist trial. Tuberculin skin test (TST) has been used to screen for TB infection in general and high-risk populations. The TST positive rate was reported to be much lower in RA patients than the normal population. Anergy to delayed-type hypersensitivity (DTH) tests owing to active disease or immunosuppressive agents might be responsible for the lower rate of positive TST in patients with RA[4]. The TST may present a false negative result to detect LTBI in patients with IMID, placing the patient at increased risk. Also, new TB infections may occur during longterm anti-TNF treatment in patients initially negative for TST. Although many countries have established guidelines to prevent TB infections prior to anti-TNF trials, guidelines to monitor TB infection during anti-TNF agent treatment have not been established.

New *in vitro* IFN-γ assays have been introduced to compensate for the drawbacks of TST in detecting LTBI. These assays detect cell-mediated immune responses to TB infection by quantifying IFN-γ in the presence of specific mycobacterial antigens such as early secretory target-6

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(EAST-6) and culture filtrate protein-10 (CFP-10). The IFN-γ assays, QuantiFERON TB Gold (QFT-G; Cellestis, Carnegie, Australia) and T-SPOT TB (Oxford Immunotec, Abingdon, UK) diagnose active TB or LTBI more specifically. Several studies demonstrated that these tests are more accurate than TST in the general population[5,6]. Nevertheless, the utility of IFN-γ assay in detecting LTBI in patients with IMID receiving immunosuppressive drugs, including TNF antagonists, has not been demonstrated sufficiently.

We evaluated whether patients with a negative TST result before anti-TNF therapy convert to a positive TST or IFN-γ result. We analyzed the TST positive conversion rate, IFN-γ assay value, and factors influencing our data during TNF antagonist treatment in Korean patients with rheumatic diseases with an initial negative TST result.

MATERIALS AND METHODS

Patients. Eighty-six patients treated for rheumatic diseases at the Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea were enrolled in the study between January 2007 and July 2008. All patients were treated with anti-TNF agents (infliximab, etanercept) for over one year and had a negative initial TST result. An IFN-γ assay and followup TST were performed simultaneously during the period. Clinical data were obtained from medical records and classified according to treatment with systemic corticosteroids, conventional disease modifying antirheumatic drugs (DMARD), and TNF antagonists, including type and start date. No patient had a condition with anergy or false-negative initial TST for presence of viral infections, bacterial infections, metabolic derangements, or diseases affecting lymphoid organs. No patient had household TB contact or a medically confirmed history of active TB infection on followup tests. Written informed consent was obtained from each participant, and the study was approved by the institutional review board of Hanyang University Medical Center.

Interferon-γ assay and TST. TST was performed on the volar side of the forearm according to the Mantoux method by trained technicians. A 2-TU dose of tuberculin purified protein derivative (PPD RT23; Staten Serum Institut, Copenhagen, Denmark) was injected intradermally and read after 48 to 72 hours. A trained reader measured any induration in millimeters using the ballpoint method[7]; a TST conversion result was defined as an erythematous induration larger than 10 mm after one or more baseline negative TST results in accordance with current guideline for LTBI in anti-TNF agents user in Korea[8,9]. None of our patients had 2-step TST at both baseline screening and followup.

An IFN-γ assay, the QFT-G in-tube test, was performed in 2 stages, according to the manufacturer's instructions. First, we directly collected peripheral venous blood in three 1-ml heparin containing tubes. One tube contained the *M. tuberculosis* specific peptides EAST-6, CFP-10, and TB7.7 antigens; a positive control tube contained the T cell mitogen phytohemagglutinin; and a negative control tube contained only heparin. The test tubes were incubated at 37°C in a carbon dioxide incubator for 16 to 24 hours. After overnight incubation, 200 μl plasma was removed from each tube and the IFN-γ concentration was measured using the assay kit according to manufacturer's instructions. A positive result was defined as an IFN-γ concentration ≥ 0.35 IU/ml, and ≥ 25% of the negative control[10]. The experienced investigator performing the IFN-γ assay was blinded to the status of all participants.

Statistical analysis. We performed tests for trend across individual risk factors for TST conversion or IFN-γ assays. Group data were compared using the t-test for quantitative variables and chi-square test for qualitative variables. The final multivariate logistic regression models were adjusted for sex, age, underlying disease, concomitant corticosteroid use, and treatment duration. Concordance between the tests was quantified using kappa statistics. All reported p values were 2-sided and those < 0.05 were considered statistically significant. All analyses were performed with SPSS (SPSS, version 12.0, Inc in Chicago, IL, USA).

RESULTS

Characterstics of participants. The 86 patients in our study consisted of 40 RA (46.5%), 34 AS (39.5%), 9 JRA (10.5%), and 3 (3.5%) patients with other rheumatic disease. There were 38 (44.2%) male and 48 (55.8%) female patients, with a mean age of 39.2 ± 15.8 years, and median TST followup duration of 33.3 mo (range 12-76.7). Sixty-six (76.7%) patients received etanercept, and 20 (23.3%) received infliximab. Table 1 shows clinical characteristics and TST conversion rate of each patient.

TST conversion results. During the study period, the negative TST result converted to positive in 28 (32.6%) of 86 enrolled patients (overall rate, 15.1 per 100 person-years). The conversion rate was significantly higher in AS (50%) than RA (17.5%) patients, and was negatively associated with steroid use in univariable analysis. The duration of receiving TNF antagonists was also associated with increased risk of TST conversion in the univariable analysis. A history of bacillus Calmette-Guérin (BCG) vaccination as well as age, and type of TNF antagonists were not associated TST conversion rate. After correcting for confounding factors such as age, sex and concomitant immunosuppressant use, including steroids, there was no statistically significant variation. Although there was no statistical significance in multivariate analysis, the odds of the TST conversion rate tended to increase with increasing duration of TNF antagonist administration (duration of anti-TNF 2-3 years, OR 2.78, p = 0.16; duration ≥ 3 yrs, OR 3.44, p = 0.09). There were 23 patients who underwent 3 or more TST in the past. Seven of 28 TST converted patients had had consecutive negative TST results in the past; 6 patients converted at 3rd TST and 1 patient converted at 4th TST. The median duration of TST conversion was 33.3 mo (range 12-76.7) after anti-TNF agent trial. Sixteen patients had more than 3 consecutive negative TST results.

Comparison between TST and IFN-γ assays. TST and IFN-γ assays showed 68.6% agreement (kappa = 0.29, p = 0.02) of the time. Nine (14.1%) of the 64 patients who received an IFN-γ assay had positive results. There was no association between IFN-γ assay result and BCG scarring, concomitant steroid or DMARD use, underlying disease, or anti-TNF agent type, in either univariable or multivariable analysis.

Of the 28 TST positive converted cases, 16 patients received IFN-γ assay, only 5 of which were positive and 1 indeterminate. Four AS and 1 psoriatic arthritis (PsA) patient had positive results in both TST and IFN-γ assay. Four RA patients with positive IFN-γ assay did not have TST positive conversion. Five spondyloarthropathy (SpA) patients who had positive TST and IFN-γ assay results showed a strong TST reaction (> 15 mm). One of those AS patients who was treated with infliximab for 16 months developed miliary TB.

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Table 1. Patients characteristics and tuberculin skin test (TST) conversion rate.

Characteristics	All Participants (%), n = 86	TST Conversion No. (%)	Multivariate OR (95% CI)
Age, yrs, mean (SD)	39.3 (15.8)		
≤ 29	29 (33.7)	7 (24)	1.00
30–39	17 (19.8)	10 (58.8)*	3.93 (0.82–18.86)
40–49	14 (16.3)	7 (50)	4.39 (0.68–28.27)
≥ 50	26 (30.2)	4 (15.4)	0.78 (0.09–6.71)
Women, no. (%)	48 (55.8)	10 (20.8)	0.35 (0.08–1.62)
Diagnosis			
RA	40 (46.5)	7 (17.5)	1.00
AS	34 (39.5)	17 (50)	1.01 (0.12–8.75)
JRA	9 (10.5)	1 (11.1)	0.44 (0.02–9.67)
Other	3 (3.5)	3 (100)	—
Tuberculin skin tested in the past	23 (26.7)	7 (30.4)	
BCG vaccination	77 (89.5)	23 (29.9)	0.34 (0.08–1.39)
Duration of TNF inhibitor therapy			
1–2 yrs	35 (40.7)	7 (20)	1.00
2–3 yrs	26 (30.2)	10 (38.5)	2.78 (0.68–11.38)
≥ 3 yrs	25 (29.1)	11 (44)*	3.44 (0.83–14.22)
TNF antagonists			
Etanercept	66 (76.7)	20 (30.3)	1.00
Infliximab	20 (23.3)	8 (40)	1.53 (0.54–4.33)
DMARD, no. (%)	49 (57)	13 (26.5)	0.53 (0.21–1.32)
Corticosteroids, no. (%)	35 (40.7)	5 (14.3)	0.35 (0.08–1.62)

RA: rheumatoid arthritis; AS: ankylosing spondylitis; JRA: juvenile rheumatoid arthritis; BCG: bacillus Calmette-Guérin; TNF: tumor necrosis factor; DMARD: disease modifying antirheumatic drugs; OR: odds ratio; CI: confidence interval, * $p < 0.10$.

Comparison results of TST and QFT-G between RA and AS patients. TST conversion rate was significantly different between RA (17.5%) and AS (50%) patients. RA patients were older and used DMARD and steroids more often than AS patients. There were more BCG vaccinated subjects among RA (97.5%) patients than AS (79.4%) patients. Thus prior BCG vaccination did not affect TST positive conversion, and a continuous negative reaction to PPD was higher in RA patients. Twenty-eight RA patients and 28 AS patients received IFN-γ assay with TST. Regardless of different participant characteristics, including diagnosis, QFT-G was positive in 4 RA (14.3%) and 4 AS (14.3%) patients. Twenty-three (82.1%) patients showed negative QFT-G results and 1 (3.6%) patient in each disease group showed an indeterminate result (Table 2).

Table 2. Comparison of characteristics of RA and AS patients.

Characteristics	RA, n = 40	AS, n = 34
Mean age ± SD, yrs**	50.98 ± 12.31	30.12 ± 9.44
Female (%)**	34 (85)	6 (17.6)
Treatment duration ± SD, mo	31.73 ± 18.66	35.26 ± 20.89
Treatment		
Steroid**	30 (75)	2 (5.9)
MTX**	32 (80)	9 (26.5)
TNF antagonist		
Infliximab	12 (30)	6 (17.6)
Etanercept	28 (70)	28 (82.4)
BCG vaccination (%)*	39 (97.5)	27 (79.4)
TST conversion (%)*	7 (17.5)	17 (50)
QuantiFERON	28	28
Positive	4 (14.3)	4 (14.3)
Negative	23 (82.1)	23 (82.1)
Indeterminate	1 (36)	1 (3.6)

RA: rheumatoid arthritis; AS: ankylosing spondylitis; SD: standard deviation; MTX: methotrexate; TNF: tumor necrosis factor; BCG: bacillus Calmette-Guérin; * $p < 0.05$, ** $p < 0.01$.

DISCUSSION

Our study shows that TST positive conversion occurs frequently in patients receiving longterm anti-TNF treatment and supports that an initial negative TST result does not conclusively indicate the absence of LTBI. It has been reported that RA patients have anergy to DTH tests owing to active disease or immunosuppressive treatments[4]. To overcome the known limitations of TST in detecting LTBI, a 2-step TST or IFN-γ assay was suggested. Despite an attenuated PPD response, TST positive conversion was noted in 17.5% of RA patients receiving anti-TNF agents in this study. In some countries, patients develop TB despite initial negative TST result[11]. A positive TST conversion might be interpreted as a new TB infection or an existing LTBI, even though the patients were not diagnosed with LTBI initially. Non-tuberculous mycobacteria (NTM) is not a clinically important cause of false-positive TST, except in populations with a

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high prevalence of NTM sensitization and very low prevalence of TB infection[12].

Both BCG vaccination and the booster phenomenon are suspected causes of false positive TST results. Boosting is maximal when the interval between the first and second tests is between 1 and 5 weeks, and is much less frequent if the interval is more than 60 days[9]. The median TST followup duration was 33.3 mo (range 12–76.7) in this study. Although a Spanish study suggested a 2-step TST for LTBI, only 8% of patients receiving a 2-step TST displayed a positive result in a second TST following an initial negative result. Moreover, a 2-step TST was the major cause of failure in complying with Spanish recommendations[13]. Until 1996, Korean children performed a 2nd TST at age 12 or 13 years, and some children who showed negative TST results took BCG vaccination again. The conversion rate was significantly higher in AS (50%) than RA (17.5%) patients in this study. The different TST conversion rates agreed with a previous Korean report[14]. As well as their different cellular immune function, a significant age difference between AS and RA patients may partially explain different TST conversion results. Relatively young AS patients might be more affected by previous BCG vaccination than RA patients. However, in order to minimize previous BCG vaccination influence on TST conversion and to increase specificity, a high cut-off (10 mm) to define a conversion reaction should be used instead of an increment > 6 mm induration. Wang, *et al* reported that even in BCG vaccination given after infancy, TST more than 15 years after vaccination did not result in a significant reaction[15]. If TST is performed more than 15 years after BCG vaccination, the influence of BCG vaccination could be disregarded as a cause of a positive TST, especially when a patient has a strong positive TST result.

Our team previously reported that the TB infection risk is 8.9-fold higher in Korean patients with RA and 30.1-fold higher in RA patients receiving TNF antagonists, compared with the Korean general population. Several studies conducted in the US, Spain, France, and Sweden have also shown that TNF antagonists increase the risk of TB infection. Additionally, they show that the TB incidence is higher in RA patients than in the general population with or without TNF antagonists[2,16-18]. The rate of TB infection is very low in the general US population, and not increased in RA patients compared to the general US population[19]. Although the risk of TB infection could not be ignored in all patients with IMID, especially when the patients were treated with TNF blocking agents[20], serial screening for LTBI is not recommended in the US. Because the prevalence of *M. tuberculosis* infection is intermediate, and the TB risk is much higher in Korean RA patients taking anti-TNF agents, physicians should be concerned about preventing or detecting TB infection in patients receiving anti-TNF agents. Conversion can be stated to occur following significant exposure to TB, such as close contact with a highly contagious case or living in a country with a high or intermediate TB burden.

Screening for LTBI before commencing anti-TNF therapy is important. Several countries have generated national guidelines to manage LTBI before TNF antagonist therapy; however, guidelines to monitor TB infection in patients receiving TNF antagonists have not been established. It is hard to directly determine the sensitivity and specificity of TST and QFT-G for detection of LTBI in our results. However, our data show 32.6% TST conversion rate in patients with IMID receiving TNF antagonists. Among these patients, there were 18 (20.8%) patients who had strong TST positive results. Several studies have demonstrated that TNF antagonists do not suppress TST results. A high TST positive conversion rate (37%) was observed among Taiwanese RA patients who received adalimumab for 12 months[21,22]. It is likely that anti-TNF agents can restore the diagnostic value of TST by improving the anergic status of IMID, although the precise mechanism is not known.

Hamdi and colleagues demonstrated that immediate IFN-γ release was affected by TNF antagonists. A decline in memory CD4+ T lymphocytes in patients with TNF antagonists results in decreased IFN-γ release. These data suggest that the *in vitro* IFN-γ assay should be performed before beginning anti-TNF treatment to detect LTBI[23]. Although IFN-γ assay showed better sensitivity and specificity for LTBI than TST in IMID, false negative results might be higher than suspected in patients receiving TNF antagonists. Further, it is well known that the capacity of active TB patients to produce IFN-γ as determined in blood stimulation assays is depressed. A recent study demonstrated that active TB patients had strongly depressed IFN-γ production in response to *M. tuberculosis* stimulation. The IFN-γ assay has high specificity and low sensitivity to diagnose active TB; therefore, these tests are suggested as supplementary tests for diagnostic exclusion of active TB in intermediate TB burden countries[24,25]. The QFT-G as a diagnostic method for active TB is likely to be limited in countries where LTBI is common, such as Korea.

We observed that the agreement between TST and IFN-γ assays was similar to previous Taiwanese data when using a 10 mm cutoff [21]. The discordance of TST and IFN-γ assays could be explained by several factors including false negative TST results caused by anergy, false positive TST results in BCG vaccinated subjects, and false negative IFN-γ assay results in patients receiving anti-TNF agents. All our enrolled patients were assessed carefully for a couple of days for presence of infection, serious metabolic diseases, or other conditions affecting the immune system before starting anti-TNF agents. We excluded those patients with suppressed immune systems transiently. Patients with active TB had depressed IFN-γ production. Also, anti-TNF agents might have affected negative IFN-γ assay results. In this study, 9 (14.1%) of 64 patients who received an IFN-γ assay

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had positive results. Four AS and 1 PsA patient who had a positive TST and IFN-γ results had an induration diameter of more than 15 mm. One of the 5 patients developed miliary TB at 16 months. Interestingly, none of the 4 RA patients with positive IFN-γ assay result had a TST positive conversion. In this study, patients who had a TST conversion or QFT-G positive result received prophylactic LTBI treatment during the TNF antagonist trial. IFN-γ assays such as the QFT-G in-tube method may be considered in addition to the TST for diagnostic screening and monitoring of LTBI in RA patients receiving TNF antagonists, because TST results as well as IFN-γ assays may give false negative results. If an initial screening fails to detect LTBI, serial TST with an IFN-γ assay may be useful to detect not only false-negative TST as hidden LTBI but also new TB infection in RA patients with longterm anti-TNF agent therapy, especially when patients live in a country of intermediate or high TB prevalence.

The cutoff should be low enough to increase sensitivity among patients with high risk of TB infection, such as children, close contacts, immunocompromised individuals, and patients with 2 or more prior negative TST results[9]. If several prior TST were negative, an increased induration size is more likely a cause of true conversion. In this study, 23 of the 86 enrolled patients received 2 or more TST, 7 (30.4%) of those patients had increased induration. It is important that investigators be always aware that patients undergoing longterm TNF antagonist therapy have susceptibility to new TB infection as well as reactivated LTBI. Currently, it is not clear what would be the best option: TST or IFN-γ assay among patients receiving anti-TNF agents. Further investigations are required to set up rational guidelines for performing IFN-γ assay and TST in patients receiving anti-TNF agents, depending upon TB burden in each country and type of anti-TNF agent (monoclonal antibody or soluble receptor blocker).

In conclusion, we have found that followup TST and IFN-γ assay are recommended to identify hidden LTBI cases or new TB infections in patients receiving TNF antagonists, especially in an intermediate TB burden area such as Korea. New TB monitoring guidelines should be established during anti-TNF agent trials according to the TB burden of each country.

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