

Agreement Between Quantiferon-TB Gold Test and Tuberculin Skin Test in the Identification of Latent Tuberculosis Infection in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT. Objective. To compare the Quantiferon-TB Gold test (QTF-G) with the tuberculin skin test (TST) for the detection of latent tuberculosis infection (LTBI) among patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), with reevaluation of the patients treated with tumor necrosis factor- α (TNF- α) antagonists in the followup.

Methods. The study involved 140 consecutive patients, 82 with RA and 58 with AS. Thirty patients were evaluated with QTF-G for detection of LTBI before and after 6 months of TNF- α antagonist treatment. QTF-G was also performed on 49 healthy controls. QTF-G results were recorded as positive, negative, or indeterminate. A positive TST was defined as ≥ 5 mm for RA and AS.

Results. The percentages of positive QTF-G were comparable in RA and AS (37% vs 32%). The rate of positive QTF-G in healthy controls (29%) was also similar to RA and AS. In contrast to QTF-G results, a high rate of TST positivity was observed in AS compared to RA (82% vs 55%; $p = 0.02$). The total agreement between QTF-G and TST was observed to be 61% ($\kappa = 0.29$) in the whole group, 70% ($\kappa = 0.42$) in RA, and 49% ($\kappa = 0.14$) in AS. After 6 months of treatment with TNF- α antagonists, a high rate of QTF-G change was observed in patients with indeterminate results (23% vs 3%; $p = 0.03$).

Conclusion. The comparable prevalence of LTBI among the study groups according to QTF-G supports the view that QTF-G is less susceptible to external factors than TST. Sequential testing for QTF-G in patients with indeterminate or negative results may also be helpful in discriminating LTBI better. (First Release Nov 15 2009; J Rheumatol 2009;36:2675–81; doi:10.3899/jrheum.090268)

Key Indexing Terms:

QUANTIFERON TB GOLD TEST
RHEUMATOID ARTHRITIS

TUBERCULIN SKIN TEST
ANKYLOSING SPONDYLITIS

Patients with inflammatory diseases are at increased risk of developing serious infections, mainly tuberculosis (TB). The higher risk observed in autoimmune diseases could be related to immune dysregulation caused by the disease itself or to the immunosuppressive drugs used for the treatment¹. It has been observed that patients diagnosed with RA were 4 times more likely to develop TB². A higher incidence of *Mycobacterium tuberculosis* infection with the use of tumor

necrosis factor- α (TNF- α) antagonist treatments has also been recorded in postmarketing reports^{3,4}. The diagnosis and treatment of latent TB infection (LTBI) in chronic inflammatory diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) have appeared as a priority before treatment with TNF- α antagonists, and it was suggested that patients should be screened for LTBI before the initiation of treatment with TNF- α antagonists⁵⁻⁷.

In recommendations for assessing the risk of LTBI and managing it in patients due to start TNF- α antagonist treatments, tuberculin skin test (TST) is one of the major ways to determine LTBI^{8,9}. Unfortunately, TST has serious shortcomings for the screening of LTBI. The induration threshold values for positive TST results appear diverse (5 to 10 mm induration)^{2,9}. As well, there have been some concerns about an impaired delayed-type hypersensitivity reaction to tuberculin in patients with RA, owing either to the deficient cell-mediated immunity of the disease itself or to treatment with disease-modifying antirheumatic drugs (DMARD)¹⁰. Some of the guidelines recommend a second step or a TST

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booster 14 days later⁷. Another problem in countries where TB is prevalent and bacillus Calmette-Guerin (BCG) vaccination is routine might be false-positive TST results. Environmental mycobacterial exposure may also lead to false positivity^{11,12}. Impaired TST response may cause false-negative results, increasing the risk of TB reactivation in candidates for TNF- α antagonist treatments, while false-positive tests can lead to unnecessary treatment with isoniazid, with a possibility of drug toxicity¹³.

In vitro interferon- γ (IFN- γ) assays that use proteins specific for *M. tuberculosis* have become available to detect LTBI. One of the IFN- γ -based *in vitro* diagnostic tests, which measure responses to specifically expressed ESAT-6, CFP-10, and TB7.7 proteins by pathogenic *M. tuberculosis* complex strains, is the Quantiferon TB Gold test (QTF-G; Cellestis, South Melbourne, Victoria, Australia). It was suggested that QTF-G is more accurate than TST for the diagnosis of active and LTBI in the general population¹². The performance of the QTF-G and other commercial assays based on similar assay principles has been investigated in a group of patients with inflammatory diseases and in RA¹⁴⁻¹⁷. However, it is still not clear from these studies if the use of IFN- γ -based tests instead of relying only on TST has additional benefit in reducing the rate of LTBI reactivation.

We compared a whole-blood IFN- γ assay with TST for LTBI testing in a high-incidence country with prevalent BCG vaccination in patients with RA and AS. The IFN- γ responses of patients who were treated with TNF- α antagonists for 6 months were also reevaluated.

MATERIALS AND METHODS

Patients with RA and AS who had both QTF-G and TST were enrolled consecutively for the study. Eighty-two patients with RA fulfilling the 1987 American College of Rheumatology RA criteria¹⁸ and 58 patients with AS fulfilling the modified New York criteria¹⁹ between March 2007 and June 2008 from the outpatient rheumatology clinic were recruited for the study (Figure 1). We also included 49 healthy volunteers as control subjects for

the study. Exclusion criteria for healthy volunteers were being on the hospital staff, being a patient in the hospital, and having chronic diseases and/or immunosuppressive drug treatments. All patients in the study were taking DMARD. Thirty of them who fulfilled recognized national criteria for TNF- α antagonist therapy were reevaluated for latent TB with QTF-G after taking TNF- α antagonists for 6 months. Patients were excluded from the study if they had treatment incompliance, had acute infections, or did not return for a TST reading at baseline and for the second control of QTF-G at 6 months. The study was approved by the Ethical Committee of Marmara University Medical School, and all patients gave their informed consent.

All patients and controls were interviewed for a personal and family history of TB. BCG vaccinations were examined and recorded. Chest radiographs were performed and evaluated by a specialist in pulmonology for the presence of any signs of TB infection (Table 1). All study participants underwent TST after a blood sample was taken for a QTF-G test. The Mendel-Mantoux skin test using an intradermal injection of 0.1 ml of purified protein derivative (PPD) was given, and the induration was measured in millimeters by an experienced examiner after 72 hours of inoculation. Boosters were performed in all patients with no response to TST. According to the national guideline developed by the Society for Research and Education in Rheumatology (RAED), an induration of 5 mm was considered positive for TNF- α antagonist-eligible patients. LTBI treatment was given as necessary according to the results of the TST before TNF- α antagonists were introduced.

We performed the QTF-G test, which measures responses to ESAT-6, CFP-10, and TB7.7 proteins, on all participants in the study. QTF-G results were considered positive, negative, or indeterminate according to manufacturer's recommendations.

The concordance between TST and QTF-G was evaluated using agreement and the kappa analysis. The test results were evaluated using Cohen's kappa (κ), with κ value > 0.75 representing good agreement, 0.4–0.75 fair to good agreement, and < 0.40 poor agreement. The Mann-Whitney U test was used to compare the quantitative variables in the group's data, and the chi-square test was performed to compare the qualitative variables. The paired sample t test was used for the comparison of sequential test results in the same group. Statistical analysis was performed using SPSS version 11.5.

RESULTS

Whole-group analysis. In the evaluation of the whole group for whom both tests were available, indeterminate QTF-G

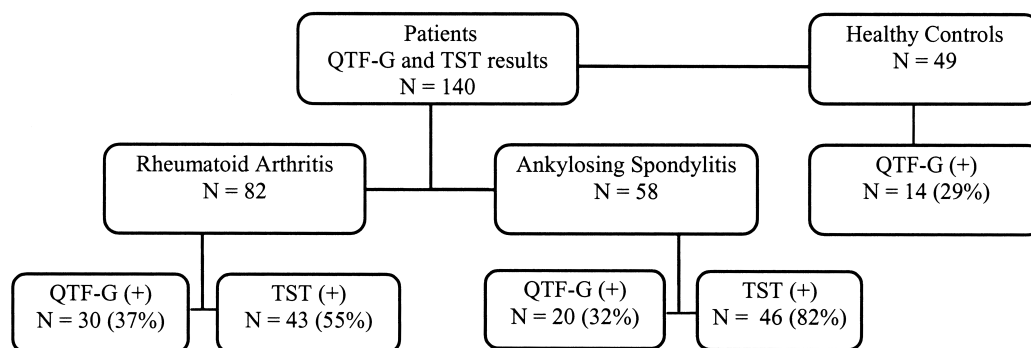


Figure 1. Breakdown of positive test results among patients with rheumatoid arthritis and ankylosing spondylitis and healthy controls. QTF-G: Quantiferon-TB Gold test; TST: tuberculin skin test.

Table 1. Demographic data, clinical characteristics, and individual risk factors for LTBI.

Characteristic	RA	AS
n	82	58
Age, mean, yrs (SD)	55.4 (11.2)	39.5 (11.2)
Sex (F/M)	73/9	22/36
BCG vaccinated, %	77	95
Disease related factors		
Disease duration, yrs, mean (SD)	13 ± 9	12 ± 8
RF-positive, %	65	NA
HLA-B27-positive, %	NA	78
DAS28 (mean ± SD)	4.8 ± 1.3	NA
BASDAI (mean ± SD)	NA	27 ± 14
Treatment at recruitment		
Prednisolone, %	60	5
Mean prednisolone at recruitment, mg/day	4.8 ± 5.2	0.3 ± 1.3
Mean duration of prednisolone, yrs	5.0 ± 5.4	2.4 ± 15.9
DMARD only, %	70	60
DMARD and TNF antagonist, %	7	2
TNF antagonist only, %	10	17
DMARD and TNF-naive, %	13	21
New treatment with TNF antagonists, %	21	22
Risk factors for LTBI, %		
History of TB infection, %	4	2
Chest radiograph suggestive of TB, %	8	6
History of TB in close relatives, %	15	11

LTBI: latent tuberculosis infection; RA: rheumatoid arthritis; AS: ankylosing spondylitis; BCG: bacillus Calmette-Guerin; SD: standard deviation; RF: rheumatoid factor; DAS28: Disease Activity Score 28-joint count; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; NA: not applicable.

results were observed in 8/140 (5.7%), and 4 of these patients had no reaction to TST. We excluded the results of these 8 patients from our analyses. Overall agreement between TST and QTF-G was low, with positive or negative concordance in 81/132 (61%) patients (κ value = 0.29). The proportion of patients with positive tests was higher in TST than QTF-G (66% vs 35%). A TST(+)/QTF-G(-) result was present in 35% (46/132) while a TST(-)/QTF-G(+) result was observed in only 4% (5/132).

When a booster was given to the patients with no response to PPD, 25% of TST results converted to positive. No improvement was observed in agreement between QTF-G and TST in RA, AS, and the whole group [κ values 0.259 ($p = 0.010$), 0.419 ($p = 0.052$), 0.149 ($p = 0.015$), respectively].

When we evaluated the presence of at least 1 of the risk factors for LTBI (history of TB personally or in close relatives, chest radiograph with findings of a previous TB exposure) and in relation to the BCG vaccination status, we observed fair to good agreement between TST and QTF-G in BCG-nonvaccinated (83%, $\kappa = 0.67$), which was higher than in the BCG-vaccinated patients (56%, $\kappa = 0.21$). The level of agreement between TST and QTF-G was also fair to good in the presence of one of the risk factors (82%, $\kappa = 0.65$) than in the absence of risk factors (57%, $\kappa = 0.22$).

QTF-G and TST in patients with RA. Five of 82 (6%) patients had indeterminate results. TST positivity was higher than QTF-G in RA (55% vs 37%) and QTF-G positive results of healthy controls (29%) were similar to those of RA (37%) (Figure 1). We observed that agreement between QTF-G and TST was moderate in RA, with negative or positive concordance in 54/77 (70%) and a κ value of 0.42 (Table 2).

Patients with positive QTF-G had increased TST measurements (12.1 vs 5.1 mm; $p < 0.001$). Among 34 of 82 (41%) patients with no reaction to TST, QTF-G results were negative in 26 (76%), positive in 5 (15%), and indeterminate in 3 (11%).

Using 10 mm induration diameter as the TST cutoff value, the agreement between the 2 tests was 57/77 (74%) with a κ value of 0.47 (Table 3). Using 15 mm induration diameter as the TST cutoff value, the agreement between the tests was 51/77 (71%), with a κ value of 0.35. Comparisons of the corticosteroid dosage, the length of corticosteroid treatment at recruitment, and Disease Activity Score-28 joint (DAS28) score in patients with and without a false-negative (TST- but QTF+) result have also been performed. The dosage of corticosteroid at recruitment was higher in patients with false-negative results than in patients without false negatives (9.5 ± 6.2 vs 4.5 ± 5.0 ; $p = 0.03$). Although longer duration of corticosteroid treatment and higher DAS28 scores were also observed in the false-negative group, the differences were not significant.

QTF-G and TST in patients with AS. Three of 58 (5%) patients with AS had indeterminate results. In the analysis of patients with AS, the agreement between QTF-G and TST was low, with concordance in 27/55 (49%) and a κ value of 0.14 (Table 2). The number of patients with AS testing positive with the TST was higher than with QTF-G (82% vs 32%) (Figure 1).

Patients with positive QTF-G showed increased TST measurements (15.3 vs 8.9 mm; $p < 0.001$). Among 10 of 58 (17%) patients with no reaction to TST, QTF-G results were negative in 8 (80%), positive in 1 (10%), and indeterminate in 1 (10%). Using 10 mm induration diameter as the TST cutoff value, the agreement between 2 tests was 32/55 (58%) with a κ value of 0.26 ($p = 0.008$; Table 3). Using 15 mm induration diameter as the TST cutoff value, the agreement between the tests was 42/55 (76%) with a κ value of 0.47 ($p < 0.001$).

Only 1 patient with AS had a false-negative result, so the comparison with clinical characteristics was not done.

Comparison of QTF-G and TST results in patients with RA and AS. Positive results in patients with RA and AS were comparable for QTF-G (37% vs 32%) but significantly different with the TST (55% vs 82%; $p = 0.02$). The percentage of patients with TST(+)/QTF-G(-) results was higher in AS than RA (49% vs 25%; $p = 0.004$), while TST(-)/

Table 2. Agreement between QTF-G and TST in patients with rheumatoid arthritis and ankylosing spondylitis.

	Rheumatoid Arthritis			Ankylosing Spondylitis		
	TST (-)	TST (+)	Total	TST (-)	TST (+)	Total
QTF-G (-)	29	18	47	8	27	35
QTF-G (+)	5	25	30	1	19	20
Total	34	43	77	9	46	55
Kappa	0.42			0.14		

QTF-G: Quantiferon-TB Gold test; TST: tuberculin skin test.

Table 3. QTF-G positive test results according to different cutoffs for TST.

	TST Cut-off Values, mm	Agreement Between TST and QTF-G (%)	
		Kappa	p
Rheumatoid arthritis	≥ 5	54/77 (70)	0.42 NS
	≥ 10	57/77 (74)	0.47 NS
	≥ 15	51/77 (71)	0.35 NS
Ankylosing spondylitis	≥ 5	27/55 (49)	0.14 NS
	≥ 10	32/55 (58)	0.26 0.008
	≥ 15	42/55 (76)	0.47 <0.001

QTF-G: Quantiferon-TB Gold test; TST: tuberculin skin test; NS: not significant.

QTF-G(+) results were comparable. Forty-one percent of patients with RA showed no reaction to TST (0 mm), compared to 17% of patients with AS ($p = 0.001$). Indeterminate results of QTF-G tests were found to be comparable between patients with RA ($n = 5$) and patients with AS ($n = 3$; 5% vs 4%), while none of the healthy controls had indeterminate results.

QTF-G results after TNF- α antagonist treatment. Thirty patients (17 RA, 13 AS) were investigated with QTF-G before and 6 months after treatment with TNF- α antagonists. After treatment, 30% of the QTF-G results changed. Five out of 7 indeterminate results changed to negative and 1 of them to positive. A statistically significant change of QTF-G was observed in patients with indeterminate results (23% vs 3%; $p = 0.03$). In 2 patients with RA, negative test results before TNF- α antagonists converted to positive at the sixth month. One of these patients had negative TST at the onset of treatment with TNF- α antagonists and had findings suggestive of TB in high-resolution computed tomography scans at the sixth month. Both patients had positive TST at the 6-month visit. Four patients with positive QTF-G had received LTBI treatment and only 1 reversion was detected after the sixth month.

DISCUSSION

Investigation of LTBI in patients with RA and AS is crucial, especially in those treated with TNF- α antagonists, because such patients are at increased risk of LTBI reactivation. In our study, we evaluated QTF-G, a widely investigated IFN- γ test and compared it to TST in patients with RA and AS. We determined a comparable presence of positive test results in patients with RA and AS with QTF-G, while a significant

difference was present with TST between the 2 diseases. The rate of positive QTF-G test results in healthy controls was similar in patients with RA and AS and was an encouraging observation for the use of QTF-G in LTBI evaluation.

In patients with RA, positive TST results using the 5 mm cutoff were higher than the rate of positive QTF-G results (55% vs 37%) and an overall agreement of 70% was found between the 2 tests (κ value 0.42). Our results were consistent with recent studies reporting an overall agreement of 60%–70% (Table 4). The level of agreement between QTF-G and TST was similar with the 10 mm cutoff but declines with the 15 mm cutoff (Table 3).

A higher number of patients with positive TST compared to QTF-G has been detected in patients with AS (82% vs 32%). To our knowledge, this is the first study evaluating the performance of QTF-G in comparison with TST in AS separately. We also observed that patients with positive QTF-G had significantly increased TST measurements in AS. Agreement between QTF-G and TST was increased from fair to moderate with the 15 mm cutoff, but this increase was less obvious with the 10 mm cutoff. The low level of agreement between TST and QTF-G might increase if the 15 mm cutoff, which is the standard value for healthy people in our country, is preferred (Table 3).

In our study, the percentage of patients who showed no reaction to TST was significantly higher in patients with RA than in patients with AS. Five of the patients with RA and 1 with AS had positive QTF-G results. A higher number of patients with RA showed no TST reaction compared to healthy controls in a previous study¹⁰, supporting the limitations of TST, especially in immunosuppressed patients.

We investigated the association between both tests and

Table 4. Characteristics of LTBI studies that use QTF-G as part of a screening program in RA and other chronic inflammatory diseases.

Study	Study Group	Positive QTF-G, %	Positive TST, %	Agreement, %	Kappa*	Patients, n
Matulis ¹⁶	RA, SpA, UA, other	NA	NA	64	0.17	109
Cobanoglu ²⁰	Chronic inflammatory diseases	18	73	NA	0.18	51
Takahashi ²¹	RA	28.5	28.5	NA	NA	14
Greenberg ¹⁷	RA	18	21.3	NA	NA	61
Chen ²²	RA	NA	NA	60	0.21	35
Ponce de Leon ¹⁰	RA	44.6	26.7	70.3	0.37	101
Bartalesi ²³	Autoimmune diseases	13	19	87.7	0.55	398
Bocchino ²⁴	RA, PsA, UC, CD	31.8	26	NA	0.26	69

RA: rheumatoid arthritis; SpA: spondyloarthropathies; UA: undifferentiated arthritis; PsA: psoriatic arthritis; UC: ulcerative colitis; CD: Crohn's disease; QTF-G: Quantiferon-TB Gold test; TST: tuberculin skin test. * For agreement between QTF-G and TST. NA: not available.

the factors that could be related to a deficient cell-mediated immunity such as demographics, disease activity status, and drug regimens. It was determined that false-negative TST results in RA were affected by the corticosteroid dosage. This result may reflect the effect of corticosteroids on TST positivity and suggests that TST results might necessitate confirmation with QTF-G. We also observed a better agreement between the 2 tests in BCG-nonvaccinated than in BCG-vaccinated patients. The annual incidence of TB is 30/100,000 according to official reports in Turkey (www.saglik.gov.tr), and the latent TB rate is estimated to be 30%–50% of the adult population. According to Turkish Ministry of Health guidelines for BCG vaccination, all children should be BCG-vaccinated at 2–3 months of age and a booster vaccination given at 6–7 years of age. However, a repeated BCG vaccination schedule with 3 or 4 vaccinations had been used until the last decade in Turkey. Still, studies from different regions of Turkey have indicated that the rate of BCG scar was only 34.6%–64.5%²⁵. It was shown that BCG vaccination increases the likelihood of false-positive TST results for up to 15 years. A study by Cobanoglu, *et al* showed that when comparing subjects under 25 years of age to subjects aged older than 25 years, repeated BCG vaccinations were related to high discordance between the TST and QTF-G in subjects older than 25 years²⁰.

A higher rate of positive TST in comparison to QTF-G in patients with chronic inflammatory diseases was observed in a study from Turkey²⁰. It was reported also that false-positive results are common in BCG-vaccinated subjects, or due to a booster effect^{26,27}. In contrast, Ponce de Leon, *et al* did not find a relationship between BCG, TST, and QTF-G¹⁰. Several factors influencing TST response including BCG strain used, dosage, number of vaccinations, age, and time elapsed since vaccination have been reported.

In one study, it was observed that the performance of QTF-G was related to the presence of risk factors for LTBI (history of TB personally or in close relatives, chest radiograph with findings of previous TB exposure). The performance of QTF-G seems to be better than TST for the detection of LTBI in patients receiving immunosuppressive drugs for systemic autoimmune diseases¹⁶. We observed a better agreement between TST and QTF-G in the presence of at least 1 of the risk factors for LTBI. TST may perform better in patients with risk factors, but in patients without any risk for LTBI, QTF-G should be preferred.

In our study, a total of 30 patients with RA and AS were evaluated after treatment with TNF- α antagonists for 6 months. We observed that 30% of the QTF-G results changed. This high rate of QTF-G change was especially prominent among patients with pretreatment indeterminate results. Among 17 patients with negative QTF-G in the beginning, 2 converted to positive. It might be beneficial to evaluate patients with indeterminate and negative test results after TNF- α antagonist treatments. In this circumstance, anti-TB treatment should be considered for the cases of QTF-G conversion in patients with RA receiving treatment with TNF- α antagonists. T cell reactivity, as measured by IFN- γ production to PPD, influenza, and collagen type II, was shown to be increased after treatment with TNF- α antagonists²⁸ and this might explain the change in immune response in our negative patients. However, a high QTF-G cutoff value can also cause a problem, because a lower cutoff value for QTF-G increased the sensitivity of the assay in a comparative study involving patients with untreated, culture-confirmed cavitary pulmonary TB and healthy subjects²⁹.

There are some limitations in our study. The sample size was not calculated before the study but all the consecutive patients between March 2007 and June 2008 were enrolled.

There is no gold standard for the progression of TB in patients with positive test results and it is unethical to follow up patients with positive test results without LTBI treatment. We could not determine active TB in our group so we could not evaluate the value of the results according to the outcome. On the other hand, our results confirmed the reliability of current guidelines for the evaluation of these patients. We observed a higher prevalence of LTBI with TST than QTF-G in patients with RA and AS, with the probability of overtreatment according to TST results. As an encouraging result for the QTF-G test, the percentage of positive results was comparable between 2 different diseases and healthy controls. Additionally, QTF-G may be more useful in patients without LTBI risk factors. The possibility of conversion of the test results with QTF-G also necessitates the repeated evaluation of patients.

In a country with a high incidence of TB and BCG vaccination, the QTF-G test might help to differentiate false-positive TST tests from latent TB infections and might prevent overtreatment.

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