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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

TST, QuantiFERON-TB Gold test and T-SPOT.TB test for detecting latent tuberculosis infection in patients with rheumatic disease prior to anti-TNF therapy

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SUMMARY

TST, QuantiFERON-TB Gold test and T-SPOT.TB test for detecting latent tuberculosis infection in patients with rheumatic disease prior to anti-TNF therapy

Introduction: *Before starting tumour necrosis factor (TNF)-α blocking agents, standard tests should be used for the diagnosis of tuberculosis infection. The specificity of traditional tuberculin skin test (TST) is low in immunosuppressed patients due to prior Bacille Calmette Guérin (BCG) vaccination, non-tuberculous mycobacteria infections, false positive and negative results. In this study, we aimed to compare TST and Interferon-Gamma Release Assay (IGRA) tests for detecting latent tuberculosis infection in patients with rheumatic disease planned to receive TNF-α blocking agents.*

Materials and Methods: *One hundred and nine patients (45 male, 64 female) with the diagnosis of rheumatoid arthritis (RA) (n= 70) and ankylosing spondylitis (AS) (n= 39) were included in the study. Age, sex, number of BCG scar, results of TST (using the Mantoux method), QuantiFERON-TB Gold test and T-SPOT.TB test were recorded for all patients. Correlation between the tests was assessed by Pearson correlation coefficient.*

Results: *The mean age of RA and AS patients were 50 ± 13 (19-78 years). The prevalence of latent tuberculosis was 43.1% for TST, 39.4% for QuantiFERON-TB Gold test and 13.8% for T-SPOT.TB test, compared with the evaluation using the composite criteria such as close contact with active tuberculosis infection and/or suspicious fibrotic/calcific lesions on chest X-Ray without active tuberculosis infection. There was a moderate correlation between BCG scar number and TST (p< 0.001, r= 0.495), T-SPOT.TB test*

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and QuantiFERON-TB Gold test (p= 0.007, r= 0.406), T-SPOT.TB test and composite criteria (p= 0.024, r= 0.343). The specificity of QuantiFERON-TB Gold test was 85.7%, and sensitivity was 73.9% for all patients with rheumatic disease. It was 73.5% and 66.7% for T-SPOT.TB test, respectively. The specificity of TST was 60.3% and sensitivity was 47.8% for TST.

Conclusion: *IGRA tests are not affected prior vaccination and useful for detecting latent tuberculosis infection in patients treated with corticosteroid due to lack of correlation between test negativity and corticosteroid therapy. Also, they are useful tests for diagnosis of latent tuberculosis infection as an alternative to TST due to their specificity and sensitivity.*

Key words: *Tumor necrosis factor-α blocking agents; latent tuberculosis infection; tuberculin skin test; QuantiFERON-TB Gold test; T-SPOT.TB test*

ÖZET

Anti-TNF tedavisi öncesinde romatizmal hastalarda latent tüberküloz infeksiyonu saptanmasında TDT, QuantiFERON-TB Gold test ve T-SPOT.TB testi

Giriş: *Tümör nekroz faktör (TNF)-α bloke edici ajanlara başlamadan önce, tüberküloz infeksiyonu tanısı için standart testler kullanılmalıdır. Bağışıklığı baskılanmış hastalarda, Bacillus Calmette-Guérin (BCG) aşısı, non-tüberküloz mikobakteri infeksiyonları, yalancı pozitif ve negatif sonuçlar nedeniyle geleneksel tüberkülin deri testinin (TDT) özgüllüğü düşüktür. Biz bu çalışmada, TNF-α bloke edici ajan tedavisi alması planlanan romatizmal hastalığı bulunan hastalarda latent tüberküloz infeksiyonu tespitinde TDT ve Interferon-Gamma Release Assay (IGRA) testlerini karşılaştırmayı amaçladık.*

Materyal ve Metod: *Çalışmaya, romatoid artrit (RA) (n= 70) ve ankilozan spondilit (AS) (n= 39) tanısı olan 109 hasta (45 erkek, 64 kadın) dahil edildi. Yaş, cinsiyet, BCG skar sayısı, TST (Mantoux yöntemini kullanılarak), QuantiFERON-TB Gold test ve T-SPOT.TB test sonuçları tüm hastalar için kaydedildi. Testler arasındaki korelasyon Pearson korelasyon katsayısı ile değerlendirildi.*

Bulgular: *RA ve AS hastalarının yaş ortalaması 50 ± 13 (19-78 yıl) idi. Geçmişte aktif tüberküloz infeksiyonu ile yakın teması ve/veya aktif tüberküloz infeksiyonu olmadan akciğer grafisinde şüpheli fibrotik/kalsifik lezyonlar gibi kompozit kriterler kullanılarak yapılan değerlendirme ile karşılaştırıldığında, latent tüberkülozun prevalansı TST için %43.1, QuantiFERON-TB Gold testi için %39.4 ve T-SPOT.TB testi için %13.8 idi. BCG skar sayısı ile TST (p< 0.001, r= 0.495), T-SPOT.TB testi ile QuantiFERON-TB Gold testi (p= 0.007, r= 0.406), T-SPOT.TB testi ile kompozit kriterler arasında orta düzeyde korelasyon (p= 0.024, r= 0.343) vardı. Romatizmal hastalığı olan tüm hastalar için QuantiFERON-TB Gold testinin spesifitesi %85.7 ve sensitivitesi %73.9 idi. Bunlar T-SPOT.TB testi için sırasıyla %73.5 ve %66.7 idi. TDT'nin spesifitesi %60.3 ve TDT için sensitivite %47.8 idi.*

Sonuç: *IGRA testleri önceki aşılamalardan etkilenmez ve kortikosteroid tedavisi ile test negatifliği arasında korelasyon olmaması nedeniyle kortikosteroid ile tedavi alan hastalarda latent tüberküloz infeksiyonunun tespitinde yararlıdır. Ayrıca spesifite ve sensitiviteleri nedeniyle latent tüberküloz infeksiyonunun tanısında TDT'ye alternatif olarak yararlı testlerdir.*

Anahtar kelimeler: *Tümör nekroz faktör-α bloke edici ajanlar; latent tüberküloz infeksiyonu; tüberkülin deri testi; Quantiferon TB-Gold test; T-SPOT.TB test*

INTRODUCTION

Tumor necrosis factor (TNF)-α blocking agents such as infliximab, etanercept, adalimumab, golimumab and certolizumab have been used for the treatment of rheumatic diseases. Increased infection risk such as tuberculosis has been reported with anti-TNF agents. The incidence and prevalence rate of tuberculosis in Turkey were reported as 18/100.000 and 22/100.000 according to world health organization 2014 (1). Tuberculosis incidence was reported as 24/100.000 with infliximab (2). Before starting TNF-α blocking agents, standard tests should be used for the diagnosis of tuberculosis infection. Tuberculin skin test (TST) is routinely used in clinical practice and useful for diagnosis of latent tuberculosis infection. But, the specificity of traditional TST is low in immunosuppressed patients due to false positive or negative results, because of prior Bacille Calmette Guérin (BCG) vaccination and non-tuberculous mycobacteria infections (3-5). Mycobacterium tuberculosis-specific antigens such as early secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) are absent in BCG and most non-tuberculosis mycobacterium. QuantiFERON-TB Gold test and T-SPOT.TB test measure interferon gamma (IFN-γ) production by sensitized T-cells in response to ESAT-6 and CFP-10 (6-8). So, these tests may be useful to distinguish Mycobacterium tuberculosis from non-tuberculous mycobacteria infections and prior BCG vaccination.

Many studies about specificity and sensitivity of TST and IFN-γ release assay (IGRA) tests have been reported. Also, the relationship between IGRA tests and TST was reported (9-13). In this study, we aimed to compare correlation, specificity and sensitivity between TST, QuantiFERON-TB Gold test and T-SPOT.

TB test for the diagnosis of latent tuberculosis infection in patients with rheumatic disease planned to receive TNF blocking agents.

MATERIALS and METHODS

In total, 109 patients with the diagnosis of rheumatoid arthritis (RA) (n= 70) and ankylosing spondylitis (AS) (n= 39) were included in the present study. Age, sex, number of BCG scar, history of contact with active tuberculosis infection, suspicious fibrotic/calcific lesions on chest X-Ray, results of TST (using the Mantoux method), QuantiFERON-TB Gold test and T-SPOT.TB test were recorded for all patients. Exclusion criterias were age (younger than 18 years, older than 70 years), pregnancy, active tuberculosis infection and patients receiving prior anti-tuberculosis therapy. Written informed consent was obtained, and the study protocol was approved by the Ethics Board of Adnan Menderes University Medical School.

The sensitivity and specificity of IFN gamma assays was found to be comparable to the evaluation using composide criteria. The composite criteria were accepted as close contact with active tuberculosis infection and/or suspicious fibrotic/calcific lesions on chest X-Ray without active tuberculosis infection. The presence of at least one of these was considered as positive.

Purified protein derivative (0.1 Ml) was used to perform TST with Mantoux method. The induration at TST site was measured 72 hours later. TST reaction of ≥ 5 mm of induration is classified as positive in patients receiving corticosteroid (the equivalent of ≥ 15 mg/day of prednisone, ≥ 2-4 weeks) or patients with Acquired Immune Deficiency Syndrome, diabetes mellitus, lymphoma, and leukaemia (14).

For TB-Gold Test, 1 mL blood was collected into each of 3 tubes. There were 3 tubes: nil control (grey, without antigens or mitogen), positive control (purple, with the mitogen phytohaemagglutinin) and test tube (red, with ESAT-6 or CFP-10). All 3 tubes were incubated at 37^{o}C for 16-24 hours. After the incubation period, it was centrifuged at 2000 and 3000 RCF (Relative Centrifuge Force) for 15 minutes. 450 nanometers (nm) of main wavelength and 620-650 nm reference wavelengths were used to determine IFN-γ's concentrations, and optical density values were calculated. The result was considered positive when the IFN-γ level was ≥ 0.35 IU/mL and negative when IFN-γ level was < 0.35 IU/mL.

For T-SPOT.TB test, the 7 mL blood sample from each patient was collected in tubes with lithium heparin. Tubes were centrifuged, the supernatant was discharged and dispersed. T-cells were incubated with the negative control, positive control, Panel A with ESAT-6 and Panel B with CFP-10. IFN-γ producing T-cells were detected by ELISPOT. The result was considered positive when there was a positive response to panel A or B. Results were obtained by counting visible cells through a microscope. The test result is positive if Panel A-Nil and/or Panel B-Nil ≥ 6 spots.

The data obtained in the study were evaluated by using SPSS 17.0 (Statistical Package for the Social Science, version 17.0). Patients with positive (negative) result for reference and evaluated test were accepted as true positive (negative). If the reference test was negative (positive) and the evaluated test was positive (negative), it was considered as false positive. Sensitivity (sensitivity) was evaluated as the ratio of true positive (negative) to true positive (negative) and false negative (positive) according to the reference and evaluated test. The distribution of normality was examined with the Kolmogorov-Smirnov test. Chi-Square test, and Pearson correlation test were used for statistical analysis. Correlation between the tests was assessed by Pearson correlation coefficient. The value of $r < 0.30$ was accepted as weak, 0.30-0.50 as moderate, and > 0.50 as strong correlation. We have calculated sensitivity and specificity of IGRA tests and TST. The categorical data were expressed as percentages and number of patients (n). The data was examined at the confidence level of 95%, and the p value < 0.05 was accepted as statistically significant.

RESULTS

Seventy patients with the diagnosis of RA and 39 with the diagnosis of AS were enrolled in the study. Forty-five of patients were male (41.3%) and 64 were female (58.7%), the mean age of all patients was 50 ± 13 (19-78 years). There were 68 (62.4%) patients receiving corticosteroid and the mean dose was 9.7 ± 5.2 mg/day.

The demographic characteristics of patients are shown in Table 1.

There was a moderate correlation between BCG scar number and TST ($p< 0.001$, $r= 0.495$). QuantiFERON-TB Gold test was positive in 29 (36.7%) patients with 1 BCG scar, 13 (48.1%) patients with 2 BCG scars. And it was negative in 1 patient with 3 BCG scars.

Table 1. Demographic characteristics of patients included in the study

Demographic Characteristics	n (%)
Sex, Male/Female	45 (41.3%)/64 (58.7%)
Age, mean years	50 ± 13
Rheumatoid arthritis	70 (64.2%)
Ankylosing spondylitis	39 (35.8%)
BCG scarring	
• Present	48 (99.1%)
• Absent	1 (0.9%)
Corticosteroid therapy	68 (62.4%)
The mean steroid dose (daily), mg	9.7 ± 5.2

There was no statistically significant correlation between BCG scar number and QuantiFERON-TB Gold test (p= 0.223). T-SPOT.TB test was negative in 1 patient with no BCG scar. The test result was positive in 7 of 22 patients (31.8%) with 1 BCG scar, 7 of 18 patients (38.9%) with 2 BCG scars and negative in 1 of 2 patients with 3 BCG scars. Also, there was no statistically significant correlation between BCG scar number and T-SPOT.TB test (p= 0.403). The test results are shown in Table 2.

Quantiferon TB-Gold test was negative in 36 of 62 patients who had negative TST (< 5 mm), and it was positive in 17 of 43 patients with positive TST (≥ 5 mm) (Table 3). There was no correlation between TST and Quantiferon TB-Gold test. T-SPOT.TB test was positive in 8 of 15 patients with positive TST (≥ 5 mm), and negative in 9 of 28 patients with negative TST result (< 5 mm) (Table 4). There was no correlation between TST and T-SPOT.TB test. There was a moderate correlation between T-SPOT.TB test and QuantiFERON-TB Gold test (p= 0.007, r= 0.406), T-SPOT.TB test and composite criteria (p= 0.024, r= 0.343). Also, there was a strong correlation between QuantiFERON-TB Gold test and composite criteria (p< 0.001, r= 0.603).

The specificity of QuantiFERON-TB Gold test was 85.7%, and sensitivity was 73.9% for all patients with rheumatic disease. It was 73.5% and 66.7% for T-SPOT. TB test, respectively. The specificity of TST was 60.3 and sensitivity was 47.8% for TST. The specificity and sensitivity of TST, QuantiFERON-TB Gold test and T-SPOT.TB test in all patients is shown in Table 5. 62.4% of patients had a medical history of systemic steroid therapy, and the mean dose was 9.7 ± 5.2 mg/day. There was no statistically significant correlation between steroid therapy and all tests (TST, QuantiFERON-TB Gold test, and T-SPOT.TB test) (p> 0.05).

DISCUSSION

Screening of latent tuberculosis infection strategies varies according to different national guidelines. The guidelines of Portugal and Spain recommend only TST in the screening of latent tuberculosis infection.

Table 2. Distribution of TST, Quantiferon-TB Gold test, T-SPOT.TB test and BCG scar number in all patients

		Number of BCG Scar				
		Absent n (%)	One n (%)	Two n (%)	Three n (%)	Total n (%)
TST	positive	0 (0%)	25 (53.2%)	20 (42.6%)	2 (4.3%)	47 (100%)
	negative	1 (1.6%)	54 (87.1%)	7 (11.3%)	0 (0%)	62 (100%)
Quantiferon-TB Gold test	positive	0 (0%)	29 (67.4%)	13 (30.2%)	1 (2.3%)	43 (100%)
	negative	1 (1.5%)	50 (75.8%)	14 (21.2%)	1 (1.5%)	66 (100%)
T-SPOT.TB test	positive	0 (0%)	7 (46.7%)	7 (46.7%)	1 (6.7%)	15 (100%)
	negative	1 (2.3%)	15 (51.2%)	11 (41.9%)	1 (4.7%)	28 (100%)

Table 3. The distribution of QuantiFERON-TB Gold test and TST in all patients

		QuantiFERON-TB Gold Test		
		Positive n (%)	**Negative n (%)**	**Total n (%)**
TST	positive	17 (39.5%)	30 (45.5%)	47 (43.1%)
	negative	26 (60.5%)	36 (54.5%)	62 (56.9%)
Total n (%)		43 (100%)	66 (100%)	109 (100%)

Table 4. The distribution of T-SPOT.TB test and TST

		T-SPOT.TB Test		
		Positive n (%)	**Negative n (%)**	**Total n (%)**
TST	positive	8 (53.3%)	19 (67.9%)	27 (62.8%)
	negative	7 (46.7%)	9 (32.1%)	16 (37.2%)
Total n (%)		15 (100%)	28 (100%)	43 (100%)

Table 5. The specificity and sensitivity of QuantiFERON-TB Gold test, T-SPOT.TB test and TST in all patients

	Sensitivity	**Specificity**
TST	47.8%	60.3%
QuantiFERON-TB Gold test	73.9%	85.7%
T-SPOT.TB test	66.7%	73.5%

*Compared with composite criteria (patients without active tuberculosis infection, close contact with active tuberculosis infection in the past year, suspicious fibrotic/calcific lesions on chest X-Ray) (The presence of at least one of these was considered as positive).

German guidelines recommend using TST and IGRA to confirm a negative TST (15). Polish guidelines recommend using IGRA after TST (16). Canadian guidelines recommend starting with TST for laten tuberculosis infection screening, and IGRA in cases of negative TST or in cases with clinical suspicion for latent tuberculosis infection (17). European Respiratory Society proposes IGRA or one-step TST in individuals without a history of BCG vaccination (18). In France, medical history, physical examination, chest X-Ray and TST were used to determine latent tuberculosis infection (2). In Turkey, IGRA is recommended in patients with negative TST (with booster), who are strongly sucpected of having tuberculosis of having tuberculosis infection in immunocompromised patients or planned to receive immunosuppressive therapy (19). Positive TST result may lead to false-positive diagnosis of latent tuberculosis infection and thus unnecessary treatment and medication. So, it is suggested to confirm positive TST results with IGRA in countries where BCG vaccination is routinely recommended especially for low-risk children (20). In our study, TST, QuantiFERON-TB Gold test and T-SPOT.TB test were evaluated in all patients with rheumatic disease planned to receive TNF-α blocking agents.

IGRA test results may be negative in individuals with a positive TST. This situation is explained by exposure with non-tuberculosis mycobacterium (21). Lewinsohn et al. have reported that prior BCG vaccination did not affect IFN-gamma response (22). Brock et at. all evaluating the relationship between BCG scar and Quantiferon-TB test, found that this test was not influenced by prior vaccination (10). In a cross-sectional study, poor agreement was reported between QuantiFeron-TB Gold In-Tube test and TST (23). In our study, there was no statistically significant correlation between BCG scar and QuantiFERON-TB test. So, we

suggest that, Quantiferon-TB test can be safely used in patients with rheumatic disease planned to receive TNF blocking agents due to no correlation between test results and BCG scar number.

The results of the comparison of IGRA and TST are controversial. Good agreement was reported between TST and QuantiFERON-TB test (24). In a study of 150 patients with rheumatic disease, positive TST, T-SPOT.TB test and QuantiFERON-TB Gold test were detected in 27 (18%), 5 (7.1%), and 14 (9.8%) patients, respectively. There was reported 98.2% agreement between T-SPOT.TB test and QuantiFERON-TB Gold test in this study (25). Also, poor correlation was reported between TST and QuantiFERON-TB Gold, low agreement between QuantiFERON-TB test and ELISPOT (13,26,27). In our study, there were 15 patients (34.9%) with positive T-SPOT.TB test and 43 (39.4%) with positive QuantiFERON-TB Gold test. The concordance between QuantiFERON-TB test and ELISPOT was calculated as 74.4%, and a moderate correlation was found between these tests in our study.

In another study by Chang et al. the QuantiFERON-TB Gold In-Tube test, TST, and chest radiography were evaluated in 107 patients (61 with AS, 46 with RA) who received TNF-α blocking agents for the diagnosis of latent tuberculosis infection (28). The coherence between tests was found low in AS patients and moderate in patients with RA in this study (28). Also, 34% of patients had positive TST and 66% of patients had negative TST results. It was positive in 47 and negative in 62 patients in our study, respectively. We found no correlation between TST and QuantiFERON-TB Gold test, TST and T-SPOT.TB test.

There are different rates for specificity and sensitivity for TST in the literature. In a study by Mrozek et al. QuantiFERON and T-SPOT show a better sensitivity than TST (79%, 84%, 69%, respectively) (29). The specificity and sensitivity of QuantiFERON-TB Gold test were found as 98% and 90% for tuberculosis infection (9). In another prospective study, QuantiFERON-TB Gold and T-SPOT.TB test were evaluated. The specificity of QuantiFERON-TB Gold was higher than T-SPOT.TB (91.6 versus 84.7%) and TST (91.6 versus 78.6%) (30). Also, the sensitivity and specificity were higher with ELISPOT assays than TST for detecting latent tuberculosis in patients with RA, spondylarthropathy and Crohn's disease before anti-TNF therapy (31). The sensitivity and specificity for the diagnosis of latent tuberculosis infection are difficult due to the absence of a gold standard. In our study, the specificity of QuantiFERON-TB Gold test was 85.7%, and sensitivity was 73.9% for all patients with rheumatic disease. It was 73.5%, 66.7% for T-SPOT.TB test and 60.3%, 47.8% for TST (Table 5). Similar to Mrozek et al. we found higher sensitivity of QuantiFERON and T-SPOT than TST (29). Also, the QuantiFERON-TB Gold test showed a better specificity than T-SPOT test and TST in our study.

In our study, there were 47 patients (43.1%) with positive TST. It was reported that oral prednisolone suppressed the performance of QuantiFERON Gold In-Tube and TST (32). Kleinert et al. found significant correlation between QuantiFERON-TB Gold test and TST in patients receiving corticosteroid (33). Similarly, in our study, there was no significant correlation between steroid therapy and all tests (TST, QuantiFERON-TB Gold test, and T-SPOT.TB test). The sensitivity was found higher with QuantiFeron-TB Gold test than TST for the diagnosis of latent tuberculosis infection in immunosuppressed patients with RA (23). The limitation of our study is the lack of a gold standard test for the diagnosis of latent tuberculosis. So, we evaluated the sensitivity and specificity of IFN gamma assays by using composite criteria as previously mentioned.

The screening of tuberculosis infection is mandatory in patients with rheumatic diseases who were planned to receive TNF-α blocking agents. More specific and sensitive tests are required in which results are not affected by prior vaccination. IGRA tests are not affected by prior vaccination because they do not any common antigen with BCG. There was no correlation between QuantiFERON-TB Gold test, T-SPOT.TB test and steroid therapy. So, IGRA tests are useful in patients treated with corticosteroid due to lack of correlation between test results and corticosteroid therapy. Also, they are useful tests for diagnosis of latent tuberculosis infection as alternative tests to TST due to their specificity and sensitivity. Further studies are needed for different disease group and areas to assess the sensitivity and specificity of these tests.

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