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Research Article

Comparison of PPD and IGST Sensitivity in Latent Tuberculosis Assessment (Cross-sectional Study)

Fuat Erel[1], Nurhan Sarıoğlu[1], Nilay Şahin[2], Mustafa Çolak[1*], Kazım Batıhan Büyükzengin[3], Hikmet Çoban[1]

[1] Balıkesir University Faculty of Medicine Department of Pulmonary Diseases, Balıkesir, Türkiye, fuatereldr@hotmail.com, nurhangencer@hotmail.com, drmclk@yahoo.com, hikmetcoban04@gmail.com, ror.org/02tv7db43

[2] Balıkesir University Faculty of Medicine Department of Physical Medicine and Rehabilitation, Balıkesir, Türkiye, dincernilay@yahoo.com, ror.org/02tv7db43

[3] Osmaniye State Hospital Medical Microbiology Clinic, Osmaniye, Türkiye, baturka10@hotmail.com

[*] Corresponding Author

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Objective: Purified Protein Derivative (PPD) and Interferon Gamma Release Assay (IGRA) were performed on patients with ankylosing spondylitis and rheumatoid arthritis who were planned to initiate immunosuppressive treatment. The aim was to determine which test would be more appropriate for diagnosing latent tuberculosis (TB) and to evaluate the sensitivity and specificity of PPD and IGRA tests in latent TB diagnosis.

Materials and Methods: Forty-seven patients with rheumatoid arthritis and 27 patients with ankylosing spondylitis were included in the study. All patients underwent both PPD and QuantiFERON-TB Gold Plus testing. Latent TB was defined as close contact with active tuberculosis infection and/or presence of suspicious fibrotic/calcified lesions on chest radiography without active tuberculosis infection.

Results: The QuantiFERON-TB Gold Plus test demonstrated a specificity of 96.6% and sensitivity of 73.3%, while the tuberculin skin test (TST) showed a specificity of 25.4% and sensitivity of 93.3%. A significant correlation was found between the QuantiFERON-TB Gold Plus test and latent tuberculosis criteria ($p<0.001$, $r=0.562$), whereas no statistically significant correlation existed between TST and latent tuberculosis criteria ($p=0.309$, $r=0.120$).

Conclusion: The IGRA test demonstrated higher specificity and sensitivity compared to TST. Given the lower specificity of TST observed in our study compared to other studies, the IGRA test may be recommended for patients planned to receive prophylactic treatment.

Keywords: PPD, BCG, IGRA, Latent tuberculosis, Prophylaxis

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M.tuberculosis*) that can manifest at any stage of life. While it predominantly affects the pulmonary system, it has the potential to involve all bodily organs and systems. The World Health Organization (WHO) has documented tuberculosis incidence and prevalence rates in Türkiye as 18 per 100,000 and 22 per 100,000 individuals, respectively.[1]

Tumor necrosis factor-alpha (TNF-α) serves as a critical proinflammatory cytokine that significantly contributes to the immunological response against *Mycobacterium tuberculosis*, maintaining the structural integrity of granulomas following infection.[2] Disease-modifying antirheumatic drugs (DMARDs) such as infliximab, etanercept, and adalimumab function as TNF-α antagonists used in the therapeutic management of rheumatic diseases.[3] The administration of anti-TNF agents may precipitate active tuberculosis following organism invasion or incite reactivation of latent bacilli within granulomas.[4] Similarly, conventional DMARDs used in rheumatic conditions, including methotrexate, sulfasalazine, and leflunomide, can also induce tuberculosis reactivation.[5]

The tuberculin skin test (TST/PPD) has served as an established immunological diagnostic approach for many years. It measures the diameter of induration resulting from a delayed-type hypersensitivity response to mycobacterial protein derivatives in subjects previously exposed to the bacillus. This test is administered on the inner forearm and evaluated after 72 hours. PPD is widely used globally due to its ease of application and low cost. Mycobacteria

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are potent inducers of interferon-gamma secretion from Th1 cells. The interferon-gamma release assay (IGRA), which has emerged as a pivotal diagnostic instrument in contemporary practice, quantifies interferon-gamma specifically secreted in response to *M. tuberculosis* antigens in vitro. Unlike PPD, IGRA employs ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) antigens.[6–8]

PPD may cross-react with the Bacillus Calmette-Guérin (BCG) vaccine and is affected by non-tuberculous mycobacteria, producing false-positive results that diminish diagnostic specificity.[2] IGRA can largely differentiate true tuberculosis infection from vaccine effects in BCG-vaccinated individuals and non-tuberculous mycobacterial infections.

Latent TB screening should be performed in patients for whom DMARD therapy is planned. No universally accepted gold standard test exists for identifying latent TB. PPD and IGRA are used to determine whether patients should receive TB prophylaxis (isoniazid 300 mg for 9 months) based on test results. However, it remains unclear which test provides better prediction for latent TB. While some studies have shown no significant difference, others have demonstrated that IGRA detects latent TB better than TST in psoriasis patients.[9,10]

This research assessed the sensitivity and specificity of PPD and IGRA for detecting latent TB in ankylosing spondylitis and rheumatoid arthritis patients to determine which test would be more appropriate for these diseases where DMARD therapy is planned.

2. MATERIALS AND METHODS

Forty-seven patients with rheumatoid arthritis and 27 patients with ankylosing spondylitis for whom DMARD therapy was planned were included in the study. Routine posteroanterior (PA) chest X-rays and PPD tests were performed on all patients. Additionally, IGRA was conducted in the laboratory environment for this study. Age, gender, number of BCG scars, documented history of contact with active tuberculosis infection, presence of suspicious fibrotic or calcified lesions on chest radiography, TST results, and IGRA results were recorded for all patients.

Exclusion criteria included age parameters (individuals younger than 18 years or older than 70 years), pregnancy, active tuberculosis infection, and history of prior anti-tuberculosis treatment. Written informed consent was obtained, and the research protocol received approval from the Ethics Committee of the Faculty of Medicine at Balıkesir University (2017/67).

Latent tuberculosis was defined as a history of close contact with individuals exhibiting active tuberculosis infection and/or presence of fibrotic or calcified lesions on chest X-ray indicative of prior infection, without signs of active tuberculosis. The identification of at least one of these criteria was considered positive.

For the Tuberculin Skin Test (TST), purified protein derivative (0.1 mL) was administered using the Mantoux technique. Induration measurement at the TST site was conducted 72 hours post-administration. An induration measurement of ≥5 mm was classified as positive.[11]

The QuantiFERON-TB Gold Plus Test was employed as the IGRA. This test utilized 4 tubes with 1 mL of blood drawn into each: Nil tube (gray cap, white ring), TB1 tube (green cap, white ring), TB2 tube (yellow cap, white ring), and Mitogen tube (purple cap, white ring). All tubes underwent incubation at 37°C for 16-24 hours. Following incubation, samples were centrifuged at 2000-3000 Relative Centrifuge Force (RCF) for 15 minutes. Optical density values were computed using a primary wavelength of 450 nm and reference wavelength of 620-650 nm to determine Interferon Gamma (IFN-γ) concentrations. Results were considered positive (M. tuberculosis infection likely) when IFN-γ level was ≥0.35 IU/mL, and negative when IFN-γ level was <0.35 IU/mL based on the Mitogen-Nil difference value. The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki.

Ethical Approval in the conducted research, informed consent was acquired from all participants involved in the study, adhering to the

principles articulated in the Declaration of Helsinki. Authorization from the Ethics Committee was secured from the Clinical Research Ethics Committee of Balıkesir University Medical Faculty, with the resolution dated 26.07.2017 and assigned the number 67.

2.1. Statistical analysis

Data were analyzed using SPSS version 23.0. Normal distribution assessment was conducted using the Kolmogorov-Smirnov test. Chi-square and Pearson correlation tests were implemented for statistical evaluation. Interrelationships among tests were assessed using Pearson correlation coefficient. Sensitivity and specificity for both IGRA test and TST were computed. Categorical variables were represented as percentages with total patient numbers (n). A p-value <0.05 was considered statistically significant.

3. RESULTS

A total of 47 cases with rheumatoid arthritis and 27 patients with ankylosing spondylitis were included in the study. Twenty-one patients (28.4%) were male and 53 (71.6%) were female, with a mean age of 49.82±13.16 years.

The demographic attributes of the patient cohort are delineated in Table 1. A weak positive relationship was detected between BCG scar number and TST results (p=0.02, r=0.271). The Quantiferon-TB Gold Plus assay was positive in 9 of 44 patients (20.5%) with 1 BCG scar and in 3 of 18 patients (16.6%) with 2 BCG scars. Conversely, it returned negative results for all 9 individuals with 3 BCG scars. No statistically significant association was identified between BCG scar number and Quantiferon-TB Gold assay results (p=0.128). The results of the testing are presented in Table 2.

Table 1.

Demographic characteristics of the patients included in the study

Demographic characteristics	n (%)
Gender, Male/Female	21 (28.4) / 53 (71.6)
Age, mean years	49.82±13.16
Rheumatoid Arthritis	47 (63.5)
Ankylosing Spondylitis	27 (36.5)
BCG Scar	
Present	71 (96)
Absent	3 (4)
Latent Tb¶	15(20.3)
Non-Latent Tb	59(79.7)

¶Patient diagnosed with latent Tb according to clinical criteria.

Table 2.

Distribution of patients based on BCG scar count in IGRA and TST

		BCG Scar Count				
		Absent n (%)	1 n (%)	2 n (%)	3 n (%)	Total n (%)
TST	positive	2 (3.5)	30 (51.7)	17 (29.3)	9 (15.5)	58 (100)
	negative	1 (6.25)	14 (87.5)	1 (6.25)	0 (0)	16 (100)
IGRA	positive	1 (7.7)	9 (69.3)	3 (23)	0 (0)	13 (100)
	negative	2 (3.3)	35 (57.4)	15 (24.6)	9 (14.7)	61 (100)

The Quantiferon-TB Gold Plus assay yielded negative results in 12 of 16 subjects with negative TST results (<5 mm) and positive results in 9 of 58 individuals with positive TST results (≥5 mm) (refer to Table 3). Statistical analysis revealed no significant correlation between TST and Quantiferon-TB Gold Plus assay (p=0.547). Moreover, no significant correlation was established between TST and latent tuberculosis criteria (p=0.309, r=0.120). Conversely, a moderate correlation was identified between Quantiferon-TB Gold Plus assay and latent tuberculosis criteria (p<0.001, r=0.562).

Table 3.

Distribution of IGRA test and TST results in all patients

		IGRA		
		Positive	Negative	Total
TST, n (%)	Positive	9 (69.2)	49 (80.3)	58 (78.4)
	Negative	4 (30.8)	12 (19.7)	16 (21.6)
Total, n (%)		13 (100)	61 (100)	74 (100)

In our study, 15 (20.3%) patients had latent TB findings. In the present study, according to the latent tuberculosis criteria, the specificity of the Quantiferon-TB Gold Plus assay was determined to be 96.6%, while its sensitivity was recorded at 73.3%. In contrast, the specificity of the Tuberculin Skin Test (TST) was found to be 25.4%, with a sensitivity of 93.3%. The sensitivity and specificity metrics for both the TST and the Quantiferon-TB Gold Plus test across all patients are detailed in Table 4.

Table 4.

Specificity and sensitivity of the Quantiferon-TB Gold test and TST in all patients

		Latent TB Present	Latent TB Absent
TST	Positive	14	44
	Negative	1	15
		Sensitivity 93.3%	Specificity 25.4%
IGRA	Positive	11	2
	Negative	4	57
		Sensitivity 73.3%	Specificity 96.6%

Latent TB criteria: Patients without active tuberculosis infection, recent close contact with an active tuberculosis infection in the past year, or suspicious fibrotic/calcified lesions on chest X-ray. (The presence of at least one of these criteria was considered positive.)

4. DISCUSSION

TST specificity in our study was lower than in other studies. Consistent with other research, Quantiferon-TB Gold assay specificity and sensitivity were higher than TST. The Quantiferon-TB Gold assay may be recommended instead of TST for patients planned to start prophylactic treatment.

In Türkiye, IGRA is recommended for patients suspected of tuberculosis infection or those who are immunosuppressed or planning immunosuppressive therapy with negative TST (rapel).[12] A positive TST result may lead to misdiagnosis of latent tuberculosis infection, resulting in unwarranted treatment regimens. Consequently, in countries where BCG vaccine is routinely recommended, especially for low-risk pediatric populations, it is advisable to corroborate positive TST findings with interferon-gamma release assays (IGRA) to reduce false-positive results.[13]

IGRA test results may yield negative outcomes in individuals with positive TST. This can be attributed to exposure to non-tuberculous mycobacteria.[14] Lewinsohn et al. indicated that BCG vaccination does not influence IFN-gamma response.[15] Brock et al. determined that prior vaccination does not impact Quantiferon-TB Gold Plus test results.[10] In our study, no statistically significant correlation was identified between BCG scar quantity and Quantiferon-TB Plus test results. Consequently, we propose that Quantiferon-TB Gold Plus test can be employed confidently in rheumatic disease patients preparing to initiate TNF-alpha blocking agents, as no relationship exists between test outcomes and BCG scar number.

A cross-sectional study revealed poor concordance between Quantiferon-TB Gold Plus and TST.[16] Another study documented significant agreement between TST and Quantiferon-TB Gold Plus assay.[17] Among 150 individuals with rheumatic conditions, positive results for TST and

Quantiferon-TB Gold Plus assay were observed in 27 (18%) and 14 (9.8%) participants, respectively.[18] Chang et al. assessed Quantiferon-TB Gold Plus assay, TST, and chest radiography in 107 patients (61 with AS, 46 with RA) receiving TNF-α inhibitors for latent tuberculosis infection identification. Correlation was found between tests. Additionally, 34% of patients had positive TST results, while 66% had negative results.[19]

In our study, TST was positive in 58 patients and negative in 16 patients, while IGRA was positive in 13 patients and negative in 61 patients. No notable correlation was detected between TST and Quantiferon-TB Gold Plus assay. The lack of relationship between TST and Quantiferon-TB Gold Plus assay may be due to our small study population. Inconsistency between latent tuberculosis infection screening test results in rheumatic patients has been detected. The reason for this inconsistency varies depending on country endemic status and underlying disease.[20]

In our study, TST was positive in 58 patients and negative in 16 patients, while IGRA was positive in 13 patients and negative in 61 patients. No notable correlation was detected between the Tuberculin Skin Test (TST) and the Quantiferon-TB Gold Plus assay. The lack of relationship between TST and Quantiferon-TB Gold Plus assay may be due to the small size of our study population. Inconsistency between the screening test results for latent tuberculosis infection in rheumatic patients has been detected. The reason for this inconsistency varies depending on country endemic status and underlying disease.[20]

Different sensitivity and specificity rates for TST have been reported in literature. Mrozek et al. demonstrated that Quantiferon-TB Gold Plus test had better sensitivity compared to TST (79% vs. 69%)[6]. Quantiferon-TB Gold Plus test specificity and sensitivity for tuberculosis infection were found to be 98% and 90%, respectively.[21] In a separate prospective investigation, Quantiferon-TB Gold Plus assay specificity was 91%, whereas TST specificity was 78.6%.[22]

Assessing sensitivity and specificity in latent tuberculosis infection diagnosis presents significant challenges due to the absence of a definitive gold standard. In another Turkish study on the same patient group, Quantiferon-TB Gold Plus specificity was 85.7% and sensitivity 73.9%, while TST specificity and sensitivity were 60.3% and 47.8%, respectively.[23] Similarly, Mrozek et al. demonstrated that the Quantiferon-TB Gold Plus assay showed superior sensitivity compared to the TST.[6] In a similar context, our investigation demonstrated that Quantiferon-TB Gold Plus assay displayed enhanced specificity compared to TST (96.6% vs. 25.4%). It has been emphasized that antigens used in IGRA tests are almost exclusively expressed by the *M. tuberculosis* complex, with exceptions of *Mycobacterium kansasii*, *Mycobacterium szulgai*, *Mycobacterium marinum*, and *Mycobacterium riyadhense*, making IGRA less likely to be confused with prior BCG vaccination and/or exposure to non-tuberculous mycobacteria (NTM).[24] For these reasons, TST test specificity in our study may have been low.

In a contemporary meta-analysis, IGRAs demonstrated superior specificity compared to TST. The negative predictive value (NPV) of IGRA tests in patients with active tuberculosis who had latent tuberculosis infection was high, and IGRA tests ability to predict that individuals with negative test results would not develop disease was better. Furthermore, IGRA assessments demonstrated superior predictive capability for progression to active disease compared to TST.[24]

In immunosuppressed RA patients, sensitivity for latent tuberculosis infection diagnosis was higher with Quantiferon-TB Gold Plus test compared to TST.[24]

A limitation of our research is the lack of a definitive gold standard assay for latent tuberculosis detection.

In this study, latent tuberculosis was defined as a history of close contact with individuals exhibiting active tuberculosis infection and/or the presence of fibrotic or calcified lesions on chest X-ray indicative of prior infection, without signs of active tuberculosis. This definition was made based on previous

studies.[23,25] To date, no test can directly identify viable *Mycobacterium tuberculosis* presence in humans. Latent tuberculosis infection diagnosis remains indirect and is based on detecting host immune responses to *Mycobacterium tuberculosis*-specific antigens, assuming such responses indicate prior bacterial exposure. The TST and IGRA tests are primary tools for LTBI diagnosis. However, both methods are immunological and do not provide direct evidence of *Mycobacterium tuberculosis* bacilli presence or viability. Therefore, latent tuberculosis evaluation should be performed together with clinical and radiological assessment.[25]

5. CONCLUSION

The implementation of tuberculosis screening is obligatory for individuals diagnosed with rheumatic disorders who are intending to undergo therapy involving TNF-α blockers. In our study, the IGRA test showed higher specificity and sensitivity compared to TST, consistent with other studies. As the specificity of the TST in our study was found to be lower than in other studies, despite the higher cost, we recommend the use of the IGRA test for patients in whom prophylactic treatment is planned. In Türkiye, prophylactic treatment is initiated based on TST results. Therefore, we believe that by reducing false positives, the number of patients receiving prophylaxis could also decrease. New prospective studies may show that prophylaxis is not necessary for patients with false-positive TST diagnoses.

Article Information Form

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Authors' Contribution

Concept (FE, NS, NŞ), Design (FE, NS), Data Collection and/or Processing (FE, NS, MÇ, HÇ, KBB), Analysis and/or Interpretation (FE, NS).

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

Ethics Committee permission (without specifying the institution from which it was obtained) was obtained from Balıkesir University Medical Faculty Clinical Research Ethics Committee with the decision number 67 on 26.07.2017.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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