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Concordance between the Tuberculin Skin Test and Interferon Gamma Release Assays for Diagnosing Latent Tuberculosis Infection in Patients with Chronic Inflammatory Arthritis

Kronik İnflamatuar Artritli Hastalarda Latent Tüberkülozun Belirlenmesinde Tüberkülin Deri Testi ve İnterferon Gama Salınım Testleri Arasındaki Uyum

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ABSTRACT

Objectives: After the discovery of benefits of biologic agents in the management of rheumatologic diseases, with increased use, we are witnessing an increase in side effects also. As the reactivation of latent tuberculosis infection (LTBI) is one of the main concerns, screening for infection is an essential step before treatment with biologic agents. Investigation of the diagnostic agreement between tuberculin skin test (TST) and interferon gamma release assay (IGRA) in chronic inflammatory arthritis diagnosed persons who were screened for LTBI before treatment with biologic agents is the main objective of this study.

Methods: Clinical and demographic information, TST, and IGRA results of patients with chronic inflammatory arthritis who are candidates for biologic therapy were collected for evaluation. The TST and IGRA methods were compared through Kappa coefficient.

Results: A total of 47 included patients, 32 (68.1%) had a positive TST, and 12 (25.5%) had a positive IGRA. Of the 32 TST positive patients, 23 (48.9%) were IGRA negative. Of the 15 TST negative patients, 3 (6.4%) were IGRA positive. For both tests, 9 (19.1%) patients were positive and 12 (25.5%) were negative. The McNemar test between the two methods was significant ($p<0.001$), and concordance between two tests with kappa was 0.060 (standard error = 0.097), both indicating discordance between the two methods.

Conclusion: The results of our study suggest that IGRA is a better choice over TST for the screening of LTBI in chronic inflammatory arthritis diagnosed patients before starting the biologic agent treatment, especially in Bacillus Calmette-Guerin vaccination recipients in endemic populations.

Keywords: Biologic agents; latent tuberculosis; rheumatic diseases; tuberculin test.

ÖZET

Amaç: Romatolojik hastalıkların tedavisinde biyolojik ajanların faydalarının keşfedilmesinden sonra, kullanımlarının artmasıyla yan etkilerde de artış ortaya çıkmıştır. Latent tüberküloz enfeksiyonunun (LTBE) reaktivasyonu ana sorunlardan biri olduğundan, enfeksiyon taraması biyolojik ajan tedavisinden önce önemli bir adımdır. Bu çalışmanın temel amacı, kronik inflamatuar artrit tanısı alan ve biyolojik ajan tedavisinden önce LTBE için tarama yapılan kişilerde tüberkülin deri testi (TDT) ve interferon gamma salınım testleri (IGST) arasındaki uyumun araştırılmasıdır.

Yöntem: Biyolojik tedavi adayı olan kronik inflamatuar artrit tanılı hastaların demografik ve klinik bilgileri, TDT ve IGST sonuçları kaydedildi. TDT ve IGST yöntemleri arasındaki uyumluluk kappa katsayısı kullanılarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen toplam 47 hastadan 32'si (%68.1) TDT pozitif, 12'si (%25.5) IGST pozitifti. TDT pozitif olan 32 hastanın 23'ünde (%48.9) IGST negatif saptanırken, TDT negatif olan 15 hastanın 3'ünde (%6.4) IGST pozitif bulundu. Her iki testin sonucu 9 (%19.1) hastada pozitifken, 12 (%25.5) hastada negatif bulundu. IGST ve TDT yöntemlerinin istatistiksel olarak uyumsuz olduğu görüldü (McNemar test: p<0.001), (kappa: 0.060).

Sonuç: Çalışmamızın sonuçları, IGST'nin kronik inflamatuar artritli hastalarda, özellikle de endemik popülasyonlardaki Bacillus Calmette-Guerin aşılı bireylerde, biyolojik ajan tedavisine başlamadan önce LTBE taraması için TDT'ne göre daha iyi bir seçim olduğunu göstermektedir.

Anahtar sözcükler: Biyolojik ajanlar; latent tüberküloz; romatolojik hastalıklar; tüberkülin testi.

In this rapid development era of medicine and all other fields of science, with the integration of new methods into daily life, we need to be careful and find ways to avoid the possible side effects accompanied by these new applications. With the increased benefit of biologic therapies in the management of rheumatologic diseases, there has seen an increase in some side effects such as reactivation of latent tuberculosis infection (LTBI).[1] Hence, it is essential to screen patients for LTBI before initiating biologic agents.[2,3] According to The American College of Rheumatology, tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) should be performed on patients diagnosed with rheumatoid arthritis (RA) before initiating biologic agent treatment for the screening of LTBI.[4]

Although there is no standard guideline, currently TST and IGRA are commonly used screening methods for LTBI. The main component of TST which has been used for many years as the diagnostic test is a derivative of Mycobacterium tuberculosis (Mtb) which initiates a delayed-type hypersensitivity response. The high rate of false positive results is the main disadvantage of this method, especially seen in Bacillus Calmette-Guerin (BCG) vaccination and non-tuberculosis Mycobacterium (NTMB) infections.[5] IGRA measures the interferon-gamma originated from T cells, synthesized against Mtb complex specific antigens. As IGRA targeted interferon-gamma is absent in BCG vaccinated and/or some NTMB infected persons, by avoiding antigenic cross-reactivity this method is more valuable in countries where BCG vaccination is mandatory.[6]

Despite the presence of several works investigating the diagnostic value of TST and IGRA for LTBI screening, we observed discrepancy in studies, some of which can be explained by differences in the studied population from different countries.[7] This study was conducted to investigate the diagnostic agreement between TST and IGRA in patients with chronic inflammatory arthritis in a population where BCG vaccination is mandatory.

Methods

Clinical and laboratory results of chronic inflammatory arthritis diagnosed patients who are candidates for biologic therapy and screened for LTBI with TST and IGRA between 2015 and 2018 were retrospectively evaluated in this single center study. Exclusion criteria was having a history of active tuberculosis. A written informed consent was obtained from each participant. The Institutional Ethics Committee approved this project (No: 2018/6) and every step of this study was performed in accordance with the Helsinki Declaration.

Mantoux method was performed by intradermal injection to the ventral surface of the forearm of tuberculin-purified protein derivative (manufactured by BB-NCIP, Bulgaria) for TST screening. To detect a booster effect, all patients with <5 mm induration in the first TST were given a second TST, 14 days later. It was accepted as positive if the size of the induration exceeded 5 mm after 72 h from the injection.[8] Within 10th and 15th days period after TST, IGRA was performed on the same patients using The QuantiFERON-TB Gold In-Tube (QFT-GIT) test (Cellestis Ltd., Carnegie, Australia) in accordance with the manufacturer's protocols.

Statistical Analysis

Continuous variables were reported as the mean±standard deviation (Mean±SD), while categorical variables were reported as numbers and percentages (n [%]). Kappa coefficient (κ) test for concordance between TST and IGRA, and McNemar test for comparison of test results were performed on IBM SPSS Statistics for Windows, Version 24.0 software.

Kappa values interpreted as weak (≤0.40), moderate (0.41–0.60), strong (0.61–0.80), or excellent (>0.80) agreement. p<0.05 values were considered as significant.

Results

From 47 included patients, 34 (72.3%) were diagnosed with ankylosing spondylitis (AS), 12 (25.5%) with RA, and 1 (2.1%) with psoriatic arthritis. All patients had BCG vaccination scarring. Patient characteristics are shown in Table 1.

Overall, TST results were positive for 32 (68.1%) and IGRA were positive for 12 (25.5%) subjects. TST and IGRA comparison results are described in Table 2. Twenty-three (48.9%) patients from 32 TST positive were IGRA negative and 3 (6.4%) patients from 15 TST negative were IGRA positive. For both tests, 9 (19.1%) were positive and 12 (25.5%) were negative. The McNemar test between the two methods was significant (p<0.001), and concordance between two tests with kappa was 0.060 (standard error = 0.097), both indicating discordance between these two methods.

Table 1. Patients' characteristics and LTBI screening results

	Mean±SD
Age	43.53±12.99
Duration of disease (year)	7.23±5.54
	n (%)
Gender	
Male	20 (42.6)
Female	27 (57.4)
Underlying disease	
AS	34 (72.3)
RA	12 (25.5)
PsA	1 (2.1)
TST	
Negative	15 (31.9)
Positive	32 (68.1)
IGRA	
Negative	35 (74.5)
Positive	12 (25.5)

LTBI: Latent tuberculosis infection; TST: Tuberculin skin test; IGRA: Interferon gamma release assays; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; PsA: Psoriatic arthritis.

Table 2. Agreement between IGRA and TST results

IGRA	TST		Total, n (%)	p
	Negative n (%)	Positive n (%)		
Negative	12 (25.5)	23 (48.9)	35 (74.5)	0.0001
Positive	3 (6.4)	9 (19.1)	12 (25.5)	
Total	15 (31.9)	32 (68.1)		

Kappa coefficient: 0.060, p=0.552; TST: tuberculin skin test; IGRA: interferon gamma release assays.

Discussion

LTBI is a state of the persistent immune response to stimulation by Mtb antigens without clinical signs or symptoms of active disease.[5] Patients with chronic inflammatory arthritis treated with biologic agents are under the risk of activation of LTBI and susceptible to more severe forms of tuberculosis.[9] Chemoprophylaxis against LTBI is an effective way against this side event of treatment with biologic agents.[10] When considered the constant increase in the number of patients treated with biologic agents, accurate diagnosis of LTBI is crucial in daily practice. The aim of this work is the evaluation of diagnostic agreement between TST and IGRA in patients with chronic inflammatory arthritis who were screened for LTBI before initiating biologic agents.

The TST is a long-established screening test for LTBI because of its simplicity and efficiency. Unfortunately, false-positive results are common in this test due to cross-reaction with the BCG vaccine and environmental non-tuberculous mycobacteria.[11]

With this study, we confirm that in a population with mandatory BCG vaccination, there is a poor agreement between TST and IGRA results.[11,12] In our study, only 19.1% patients with positive TST result were also positively tested with IGRA, this discrepancy between tests which also observed in several other studies can be explained BCG vaccination.[11-14] Therefore, considering the false positive result possibility, positive TST result must not be used as the only indicator for isoniazid treatment, since too many patients would be exposed to an unnecessary toxic therapy.

A recent prospective cohort study of Abubakar et al.[15] compared the prognostic value of IGRA and TST in predicting the development of active tuberculosis among high-risk groups who were not undergoing chemoprophylaxis against LTBI. This study reported that IGRA was significantly better predictor of progression than the TST thresholds of 5 and 10 mm. In addition, a low threshold for TST (5 mm) identified more individuals who progressed to active tuberculosis

than a high threshold (10 or 15 mm), however classified large groups of participants as infected who then did not progress to active tuberculosis.

There also observed discordance between tests due to false negative TST results. The cause of a false-negative TST is thought to be immunosuppressive treatment or anergy in patients with inflammatory diseases.[10,16] Previous studies have shown that IGRA is also more sensitive method than the TST regarding LTBI detection in immunocompromised patients, as it was observed in these studies that there was not significant discrepancy in the IGRA results between control groups and immunocompromised patient groups, while TST could not detect LTBI in a number of immunocompromised patients.[17-19] Without proper prophylaxis, LTBI patients on biological treatment who were false negatively diagnosed with TST will develop active tuberculosis, this is the worst-case scenario which could be prevented through more accurate screening methods.

We detected 12 (25.5%) LTBI positive patients using IGRA and 32 (68.1%) patients using TST. Results from the previous study from Turkey conducted on rheumatic patients by Cobanoglu et al.[14], showed the almost similar difference between methods, as IGRA positive rate was 10.3% while TST positive rate was 50.5% according to their results. A similar difference between tests was also reported in another study performed on RA and AS patients from Turkey, where IGRA positive percent reported to be 35%, while this number for TST was 66%.[20] Because of the higher discordance rate in reports from countries with endemic tuberculosis, it was concluded that the main cause of the false positive results of TST while IGRA is negative, is BCG vaccination.[21]

Due to the lack of a gold standard diagnosis method of LTBI, it is impossible to completely prove which screening test is more reliable. This is the main limitation of this work.

According to our results, IGRA is a better choice over TST for the screening of LTBI in chronic inflammatory arthritis diagnosed patients before starting the biologic agent treatment. Being more accurate IGRA can be the main role player in preventing unneeded chemoprophylaxis in cases with false positives and vice versa in false negatively diagnosed cases by other tests. Further prospective studies required for evaluation of both tests regarding usefulness and cost-effectiveness.

Disclosures

Ethics Committee Approval: Institutional Ethics Committee approved this project (No: 2018/6) and every step of this study were performed in accordance with the Helsinki Declaration.

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Conflict of Interest: None declared.

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