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SERIAL QUANTIFERON-TB TEST SCREENING IN RHEUMATOLOGY PATIENTS DURING TUMOR NECROSIS FACTOR ALPHA INHIBITORS TREATMENT

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Abstract

Aim: Screening for latent tuberculosis infection (LTBI) prior to biological therapy are recommended. Although our country is in the moderate risk category for tuberculosis infection, our national data regarding the seroconversion rate of the tuberculosis test during the use of these drugs remains unclear. The aim of this study was to evaluate the risk of emerging LTBI in our patients during treatment with tumor necrosis factor-alpha inhibitors.

Material and Methods: This study included 81 patients with rheumatic diseases who had negative baseline QuantiFERON-TB test. All patients were evaluated by a serial QuantiFERON-TB test during their treatments. The primary endpoint was to reveal the LTBI risk by serial testing, while secondary endpoints were to determine the factors associated with seroconversion.

Results: A total of 81 patients were evaluated with serial QuantiFERON-TB testing for an average of 28.3 months. During the follow-up, positive conversion of QuantiFERON-TB was detected in 6 (7.4%) of 81 patients. In multivariate analysis, aging was found to be the only independent risk factor for positive seroconversion rate (p=0.01).

Conclusion: In this study, which we conducted in a population where tuberculosis infection is relatively common, QuantiFERON-TB test seroconversion rate was found to be 7.4% during treatment with inhibitors. Five out of six patients who developed seroconversion were in the ankylosing spondylitis group. These results emphasize the importance of annual LTBI screening in both rheumatoid arthritis and spondyloarthritis patients receiving biological therapy.

Keywords: Latent tuberculosis, quantiferon-plus, rheumatic diseases, tumor necrosis factor-alpha inhibitors

INTRODUCTION

Tuberculosis (TB) infection, which has a geographically heterogeneous distribution, is especially common in developing countries (1-3). According to epidemiological data, Türkiye is in the moderate-risk category for TB, with an annual incidence of 14.6 per 100,000 and latent TB infection (LTBI) prevalence of ~25% (4). Although the immune system is generally effective in keeping the infection in the latent stage, approximately 5-10% of people are at risk of developing active TB over time. Rheumatic diseases are among the high-risk group for the development of active TB due to both immune dysfunction and the use of immunosuppressive therapies. Tumor necrosis factor-alpha

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(TNF-α) inhibitors, which are widely and effectively used in the treatment of rheumatic diseases, are among the leading drugs that cause LTBI reactivation. Therefore, the guidelines recommend that patients be evaluated for both active and latent TB before treatment with these agents (5,6).

De novo TB infection is another significant problem that occurs during the use of immunosuppressive agents, especially in areas with high TB prevalence. It is reported in the literature that the seroconversion rate of LTBI tests is 4-14% after starting TNF-α treatment (7-11). Although the clinical significance of LTBI screening tests' seroconversion is not clear, data from countries with moderate-high TB incidence suggest that a positive test conversion may precede development of clinical TB activation. Therefore, according to the 2012 American College of Rheumatology recommendations, annual LTBI screening is recommended for rheumatoid arthritis (RA) patients who are at high risk of encountering TB while using biological therapy (5). However, clear recommendations for other rheumatic diseases are not available, and the optimal screening strategy for LTBI is still questioned due to the uncertainty regarding the performance of tests in immunosuppressed patients.

Tuberculin skin tests (TST) or interferon-gamma (IFN-γ) release assays (IGRAs) are used in LTBI screening. It is known that the specificity of TST decreases, especially in individuals vaccinated with Bacillus Calmette-Guérin (BCG), patients using immunosuppressive therapy, or with non-TB mycobacterial infections. Since TST lacks sensitivity and specificity, novel screening tools, the IGRAs, have been introduced. IGRAs are a method of detecting and quantifying IFN-γ response of T lymphocytes to specific antigens for mycobacterium TB, without directly detecting the presence of the bacterium. In this way, the reliability of determining whether the individual has been exposed to bacteria before is improved. The 4th generation IGRA, QuantiFERON-TB Gold Plus (QFT-plus) test, contains the antigens early-secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) that are not encoded by non-tuberculous mycobacteria, and is approved by the Food and Drug Administration and is currently in use (12,13).

In our country, which is in the moderate to high-risk category for TB infection and where national BCG vaccination is carried out, the Ministry of Health recommends annual testing. However, our national data on the IGRAs conversion rate in individuals using biological drugs are unclear. Therefore, in this study, we aimed to assess the risk of LTBI development and to determine the factors associated with seroconversion rates under TNF-α treatments.

MATERIAL AND METHODS

In this study, 113 patients treated with TNF-α inhibitors for rheumatic disease at a rheumatology clinic at a tertiary university hospital between January 2017 and June 2022 were included. A written informed consent was obtained from each patient. All patients enrolled were diagnosed with RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and Behçet's disease based on standard criteria (14-17). Data regarding the patients' demographic information, concomitant medications, biologic treatment types, and disease duration were retrieved from patients' medical files.

IGRA test, which is recommended by Centers for Disease Control and Prevention guidelines to increase diagnostic sensitivity in those who received BCG vaccination, was preferred to reveal LTBI in this study (18). We performed the QFT-plus (Cellestis, Australia) test, which measures the responses to ESAT-6, CFP-10, and TB 7.7 proteins in all the participants of the study. QFT-plus results were considered positive, negative, or indeterminate according to manufacturer's recommendations. Chest X-rays were assessed by two radiologists for the presence of any signs of active TB infection.

The QFT-plus test results of a total of 113 patients at the beginning of the biological therapy were retrospectively scanned from patient files, and 28 (24.7%) cases thought to have LTBI because the test results were positive were identified. Four cases whose results were indeterminate were excluded. The patients who had a negative baseline QFT-plus test (n=81), were followed prospectively, and control QFT tests were requested at intervals of 13.8-30 months at outpatient clinic admissions. Eighty-one patients (>18 years of age) with more than 1 year of follow-up who had at least 2 QFT-plus test results were included in the study. The primary endpoints included investigating the positive seroconversion rate of serial QFT-plus testing. The secondary endpoints included revealing factors affecting this outcome and rates of treatment-associated active TB infection.

Ethical Statement

This study was approved by the Demiroğlu Science University Clinical Research Ethics Committee (approval number: 2022-15-04, date: 02.08.2022) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Parametric variables were expressed as mean ± standard deviation, and non-parametric variables as median [interquartile range (IQR)]. Discontinuous variables were given as percentages. The Fisher exact test, univariate regression, and multivariate

logistic regression analyses were used to reveal independent risk factors (age, gender, underlying disease, etc.) associated with the positive conversion of QFT-plus test outcome. The Mann-Whitney U test was used to compare non-normally distributed continuous variables between groups with and without positive seroconversion according to the QFT-plus test. We considered a p-value less than 0.05 to be statistically significant. Statistical analyses were performed using the SPSS version 21.0 (IBM Corp. Armonk, NY, USA).

RESULTS

In this study, a total of 113 patients were evaluated, and the LTBI rate was identified in 24.7%, based on the QFT-plus test. A total of 81 patients (67-spondyloarthritis, 11-RA, 3-Behçet's disease) were treated with TNF-α inhibitors with a negative baseline QFT-plus result were serially screened using the QFT-plus test. Of these patients, the median age was 42 (IQR=34-54.5) years and the median TNF-α inhibitors therapy duration was 44 (IQR=24.5-63.5) months. The most frequently used agent among biological treatments was etanercept (n=25). Overall, 23 patients were treated with adalimumab, 6 with infliximab, 12 with certolizumab, 15 with golimumab, and 18 patients were also receiving concomitant immunosuppressant therapy. The demographics and clinical characteristics of the patients are summarized in Tables 1 and 2.

The QFT-plus test was repeated in all patients at intervals of at least 12 months after the initial measurement, and the patients were followed for an average of 28.3 (IQR=16.6-46.9) months. At the end point, all patients underwent a second QFT-plus test, and 37 of them, additionally, underwent a third test. The median time interval between the QFT-plus tests was 19 (IQR=13.8-30) months. Positive conversion was detected in 6 of 81 patients (7.4%): 5 with AS and 1 with RA, in the serial QFT-plus test, and all of this seroconversion was detected within the first

Table 1. The baseline demographic characteristics of the patients

	Total (n=81)	Converters (n=6)	Non-converters (n=75)	p-value
Age, median (IQR), years	42 (34-54.5)	59.5 (50.5-65)	40 (33-50)	<0.01
Female sex n (%)	35 (43.2)	4 (66.6)	31 (41.3)	NS
Diagnosis n (%) Ankylosing spondylitis Rheumatoid arthritis Psoriatic arthritis Behçet's disease	 54 (66.6) 11 (13.5) 13 (16) 3 (3.7)	 5 (83.3) 1 (16.7) 0 0	 49 (65.3) 10 (13.3) 13 (17.3) 3 (4)	 NS NS
Drugs administered, n (%) Adalimumab Etanercept Infliximab Golimumab Certolizumab	 23 (28.3) 25 (20.8) 6 (7.4) 15 (18.5) 12 (14.8)	 1 (16.6) 2 (33.3) 0 2 (33.3) 1 (16.6)	 22 (29.3) 23 (20.6) 6 (8) 13 (17.3) 11 (14.6)	
Concomitant csDMARD, n (%)	18 (22.2)	1 (16.6)	17 (22.6)	NS

csDMARD: Conventional synthetic disease-modifying antirheumatic drug, IQR: Interquartile range, NS: Not significant

Table 2. Clinical characteristics of 81 patients treated with TNF-α inhibitors

	Total (n=81)	Converters (n=6)	Non-converters (n=75)	p-value
Disease duration, median (IQR), months	96 (60-120)	78 (51-138)	96 (60-120)	NS
Cumulative exposure time to TNF-α inhibitors median (IQR), months	44 (24.5-63.5)	31 (15.7-53.2)	47 (26-64)	NS
Follow-up duration based on the QFT-plus test median (IQR), months	28.3 (16.6-46.9)	20 (13-30)	31.8 (17-47.3)	NS
Time interval between QFT tests, median (IQR), months	19 (13.8-30)	20 (13-30)	17.9 (13.5-30)	NS

IQR: Interquartile range, NS: Not significant, QFT: QuantiFERON, TNF-α: Tumor necrosis factor-alpha

24 months (mean 18.9±5.4). Isoniazid prophylaxis was started, and biological agent treatment was continued in these patients who had no signs of active TB. Table 3 shows the demographics and clinical characteristics of patients with QFT-plus positive conversion.

Chest radiographs of all patients were evaluated for active TB, such as cavitary lesions, consolidation, nodules, hilar lymphadenopathy, pleural effusion, and miliary TB. In both physical examinations and chest X-ray assessments, no evidence of active TB infection was found in the study patients during the follow-up.

Univariate analysis showed that age was significantly associated with the positive seroconversion rate of the QFT-plus test. All variables included in the univariate analysis were also entered into the multivariate analysis, and age was found to be a single independent factor in the multivariable analysis [odds ratio =1.1 (95% confidence interval =1.02-1.2), p=0.01] (Table 4).

DISCUSSION

TB continues to be a global health problem, although its incidence and mortality have been reported to be decreasing both in the world and in Türkiye. Immunosuppressive medications used in rheumatic diseases, especially TNF-α inhibitors, are known to increase the risk of active TB development. It has been reported that this risk is approximately 12 times higher in TNF-α inhibitor users than in the general population (19). Therefore, it is recommended to perform active and LTBI screening in all patients who will start TNF-α inhibitors and to repeat the test during treatment due to the risk of *de novo* infection in patients living in areas with a high incidence of TB. Although Türkiye is classified in the moderate risk category for TB, national data on LTBI during monitoring biological treatment is insufficiently available (4).

In our study, whose primary purpose was to evaluate new LTBI using serial IGRA in follow-up patients receiving TNF-α

Table 3. Clinical characteristics of six patients with QFT-plus positive conversion

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/gender	58/F	49/M	61/F	51/F	77/M	61/F
Diagnosis	AS	AS	AS	AS	AS	RA
Disease duration, (months)	60	264	24	84	96	72
Drugs administered	ETA	CER	GOL	ADA	GOL	ETA
TNF-α inhibitor therapy duration, (months)	38	60	12	24	51	17
Interval between OFT-plus tests, (months)	24	24	12.7	17	23	13
Time of QFT-plus conversion, (months)	24	24	12.7	17	23	13

ADA: Adalimumab, AS: Ankylosing spondylitis, CER: Certolizumab, ETA: Etanercept, F: Female, GOL: Golimumab, M: Male, QFT: QuantiFERON, RA: Rheumatoid arthritis, TNF-α: Tumor necrosis factor-alpha

Table 4. Factors affecting QFT-plus conversion during biologic treatment

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.112 (1.027-1.204)	0.009	1.1 (1.02-1.2)	0.01
Gender	1.41 (0.269-7.5)	0.68	-	
Diagnosis	0.47 (0.113-1.97)	0.3	-	
Drugs administered	1.06 (0.182-6.2)	0.94	-	
Concomitant csDMARDs	0.68 (0.075-6.24)	0.73	-	
Disease duration	0.99 (0.98-1.01)	0.86	-	
TNF-α inhibitors therapy duration	0.97 (0.93-1.01)	0.21	-	
Follow-up duration based on the QFT-plus test	0.96 (0.90-1.02)	0.17	-	

CI: Confidence interval, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, NS: Not significant, QFT: QuantiFERON, TNF-α: Tumor necrosis factor-alpha

inhibitors, the positive conversion rate was found to be 7.4%. QFT test positivity and seroconversion risk vary according to regions, ethnicity, comorbidities, concomitant medications, and underlying diseases. Previous studies published in different populations reported that the seroconversion rate under TNF-α inhibitor treatment was 7.9% in AS patients and ranged from 3.7% to 13.6% in RA patients (9-11). Similarly, in studies including different rheumatic disease subsets, this rate varies between 6% and 14% (7,11,20,21). The variability of seroconversion rates in these studies is thought to be related to the use of different testing methods, follow-up times, host biological factors, and differences in TB risk rates between countries. As a matter of fact, it has been shown that the results vary depending on the method chosen, with the seroconversion rate 13-30% with TST, 10% with T-spot, and 4-14% with QFT-GIT (11,20-22). In addition, the low sensitivity of the QFT test in immunocompromised patients, and the potential suppression of IFN-γ release by immunosuppressive drugs may cause the variability seen in IGRA test results in these studies (23,24). Another important factor determining the LTBI seroconversion rate is the follow-up period. Although our study had a relatively short follow-up period of 28 months on average, all seroconversion cases were observed within the first 24 months. A similar study in RA patients in Italy reported TB test positivity in 13.6% of cases, with more than half of these cases occurring within the first two years (11). Although it is possible to add new LTBI cases as the follow-up period extends, the predominance of seroconversion in the first 2 years suggests the importance of close monitoring, especially in the initial 24 months of therapy.

The second aim of our study was to evaluate factors affecting QFT-plus seroconversion. Our results showed that the patient's age was the only independent factor and that the probability of QFT-plus conversion increased significantly with age. Similarly, in other previous studies, age was reported as the only factor determining seroconversion and increasing over the age of 50 (9,21). In only one study, Cuomo et al. (11) suggested that male sex is a second independent risk factor. In our study, no relationship could be determined with other possible factors such as disease subsets, type of biological drug, concomitantly used immunosuppressive agents, gender, disease duration and follow-up period. However, the limited number of patients with seroconversion is insufficient to draw conclusions on this issue.

Another important point is that most of the previous screening studies for LTBI were conducted in the RA group, as the risk of developing TB is thought to be higher due to both disease-related factors and the concomitant use of immunosuppressive drugs. Considering the high seroconversion rates of up to 13% in these data, it was predicted that disease subgroups might influence the results; however, no statistically significant differences were found in our multiple regression analyses (9,11,21). Five out of six patients who developed TB seroconversion were in the AS group in our study. This result may be related to the fact that the majority of our study population consists of AS patients. On the other hand, Kim et al. (8) have also shown that seroconversion occurs especially in AS patients, compared to other rheumatic diseases. Although the pathogenetic differences and the concomitant treatments (such as systemic steroids, immunosuppressive agents, etc.) between AS and RA can be confusing, these results suggest that patients with AS may also be at risk of TB seroconversion to at least the same extent as patients with RA (25-27). Therefore, monitoring for LTBI development in AS patients appears important, similar to the recommendations in RA guidelines.

Study Limitations

The main limitations of our study include a relatively small number of patients for subgroup analysis, variations in QFT re-test intervals, and a somewhat short follow-up period. However, considering that most LTBI cases occur in the first 2 years, the follow-up period can be considered sufficient.

CONCLUSION

In our study covering different rheumatological disease populations (AS, RA, PsA, and Behçet's disease) and treated with TNF-α inhibitors, the positive conversion rate in QFT-plus tests was found to be 7.4%, and age was determined as the only factor affecting this risk. The fact that most seroconversion was detected in AS patients emphasizes the importance of annual LTBI screening in all rheumatological diseases receiving biological therapy, and in RA as well. This situation emphasizes the need for personalized follow-up strategies not only among countries but also within different disease groups. However, larger studies with more extended follow-up periods are still needed to create clearer guidelines in this regard.

Ethics

Ethics Committee Approval: This study was approved by the Demiroğlu Science University Clinical Research Ethics Committee (approval number: 2022-15-04, date: 02.08.2022) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: A written informed consent was obtained from each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A., S.K.D., N.Y., Concept: C.A., N.Y., Design: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Data Collection or Processing: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Analysis or Interpretation: C.A., İ.H.S., S.K.D., C.Akm., N.Y., Literature Search: C.A., İ.H.S., C.Akm., N.Y., Writing: C.A., N.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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