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Original Research

Performance of LTBI Screening in Patients with Rheumatic Diseases Using Two Different Interferon-Gamma Releasing Assays

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Abstract

Background: To evaluate the concordance between QuantiFERON-TB Gold in-tube test (QFT-GIT) and T-SPOT.TB test (T-SPOT) for the screening of latent tuberculosis infection (LTBI) in patients with rheumatic diseases (RDs). **Methods**: Patients diagnosed as rheumatic diseases (RDs) with clinical indications for test of interferon gamma release test (IGRA) were prospectively recruited from 2019 to 2020. The consistency of QFT-GIT and T-SPOT was assessed by Kappa analysis and the factors associated with the indeterminate results were explored by multivariable logistic analysis. **Results**: A total of 108 patients with RDs were enrolled, including 64 patients with systemic lupus erythematosus (SLE) and 44 with inflammatory arthritis (26 with rheumatoid arthritis (RA) and 18 with ankylosing spondylitis (AS)). Poor concordance was confirmed between QFT-GIT and T-SPOT results in patients with SLE (K = 0.175, 95% confidence interval [95% CI] [–0.06, 0.40], $p < 0.001$), whereas concordance was moderate in patients with inflammatory arthritis (K = 0.539, 95% CI [0.11, 0.88], $p < 0.001$). Among SLE patients, the ratio of indeterminate results in detecting LTBI was significantly higher by QFT-GIT than by T-SPOT (18.8% vs. 4.7%, $p = 0.013$), while the statistical difference was not achieved in patients with inflammatory arthritis. The multivariable logistic analysis identified that the presence of lower lymphocyte counts (odds ratio [OR] = 0.81, 95% CI [0.68, 0.97], $p = 0.020$) was the independent predictor of an indeterminate result of the QFT-GIT in SLE patients. **Conclusions**: In patients with RDs, the result of screening of LTBI was more definitive by T-SPOT test than QFT, and the concordance was poor especially in the setting of SLE.

Keywords: latent tuberculosis infection (LTBI); T-SPOT.TB test (T-SPOT); QuantiFERON-TB Gold in-tube test (QFT-GIT); rheumatic diseases (RDs)

1. Introduction

Mycobacterium tuberculosis (MTB) infection could be a lethal complication in patients with rheumatic diseases (RDs), e.g., systemic lupus erythematosus (SLE) and inflammatory arthritis, due to autoimmune disorder and the treatment with glucocorticoid and immunosuppressants [1–3]. SLE patients are 5–15 times more likely to develop tuberculosis infection than the general population [3,4], while patients with inflammatory arthritis had a 4 to 8-fold increased risk of tuberculosis compared to the general population [2]. Early recognition of latent tuberculosis infection (LTBI) and prophylaxis in patients at high risk is fundamental in order to improve the prognosis and life quality of patients, as well as to reduce the costs associated with the disease. Therefore, the screening of LTBI and tuberculosis prophylaxis prior to immunosuppressive treatment are of a central importance in these population.

Latent tuberculosis infection is "a state of persistent immune response to stimulation by MTB antigens without evidence of clinically manifested active tuberculosis" [5]. Both of tuberculin test (TST) and interferon gamma release test (IGRA) are used in the screening of LTBI. IGRA is an interferon-gamma (IFN-γ) release assay which assesses responses to specific MTB proteins, like early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). It has been proved that IGRA has higher sensitivity and specificity than TST in detecting immunosuppressed population and Bacillus Calmette Guerin (BCG) vaccinated population [6–10]. IGRA consists of tuberculosis infection T-SPOT.TB test (T-SPOT) and QuantiFERON TB-GOLD in-tube test (QFT-GIT) [11]. Both IGRA tests are commonly used for the diagnosis of LTBI, and QFT-GIT is advantageous over T-SPOT for its operational convenience and low cost. However, despite the two IGRAs tests being an effective tool, the screening of LTBI in SLE patients need to be clarified. Our study was the first to investigate the concordance between T-SPOT and QFT-GIT in patients with SLE and inflammatory arthritis, and to assess factors associated with indeterminate outcomes of QFT-GIT in patients with SLE.

2. Materials and Methods

2.1 Study Design and Settings

This prospective cohort study was conducted from 1 January 2019 to 31 December 2020 at Renji Hospital, Shanghai, China. The research protocol was approved by Shanghai Jiao Tong University, School of Medicine, Renji Hospital Ethics Committee (No. 2016-Clinical-Res-011). All participating patients provided written informed consent. Eligible patients were recruited when the following inclusion criteria were met: (1) they fulfilled the American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) criteria for SLE, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) [12–14]; (2) they had clinical indications for the test of IGRA. Exclusion criteria were: presence of active tuberculosis, patients undergoing anti-tuberculosis treatment, incomplete medical history, or patients who refused QFT-GIT and T-SPOT testing.

2.2 The QFT-GIT and T-SPOT Test

QFT-GIT was used for testing LTBI in the study. Peripheral blood samples were collected and processed following the instructions of manufacturer, Cellestis/Qiagen, Carnegie, VIC, Australia. While performing QFT-GIT test, patients' whole blood was collected into three QFT-GIT collection tubes, including blank control (Nil) tubes, mitogen (M) tubes and tuberculosis antigen (TB) tubes with an enzyme-linked immunosorbent assay to detect interferon values. The Nil tube was a negative control, and IFN-γ in Nil $\leq 8 \times 10^3$ international units (IU)/mL was regarded as explicable. If the level of IFN-γ in TB tube minus the level in Nil tube value (T-N value) was $\geq$0.35 IU/mL, the test was considered positive. If the T-N value was $<$0.35 IU/mL and the level of IFN-γ in M tube minus the level in Nil tube value (M-N value) was $\geq$0.5 IU/mL, the test was judged as negative. If the T-N value was $<$0.35 IU/mL and M-N value was $<$0.5 IU/ mL, the result was interpreted as indeterminate.

T-SPOT was preformed simultaneously. Specifically, the peripheral blood mononuclear cell (PBMC) samples were stimulated with Panel A with ESAT-6, Panel B with CFP-10, negative control and positive control. IFN-γ producing T-cells were detected by enzyme-linked immunospot assay (ELISPOT). Results were assessed by counting visible points through a microscope. The assay was positive if Panel A tube and/or Panel B tube were $\geq$6 points and negative control were $\leq$5 points. Assays were considered weakly positive if the points in the positive control were $<$20, or points in the negative control were $>$10, and points in both Panel A and Panel B had less than twice points in the negative control. The assay was negative if Panel A tube and/or Panel B tube were $<$6 points and negative control were $\leq$5 points.

2.3 Study Covariates and Outcomes

We recorded demographic data (age, gender), laboratory indicators, including C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and CD4+ lymphocyte count, which were operated on the same day with IGRAs. For SLE patients, neutrophil counts, lymphocyte counts, hemoglobin, platelet counts, and complement 3/4 (C3/4) and anti-double-stranded DNA (anti-dsDNA) antibody were assessed additionally. Medication was reviewed, including the treatment with glucocorticoids and immunosuppressive agents. SLE disease activity was assessed with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2000) [15]. The concordance between QFT-GIT and T-SPOT were calculated and factors associated with indeterminate results were also analyzed in the SLE patients.

2.4 Statistics

The data were analyzed using IBM SPSS version 20.0 (Chicago, IL, USA). The quantified variables were expressed as mean $\pm$ standard deviation or median (interquartile range) based on the distributions. Group comparisons for categorical variables were analyzed with Chi-square test. The agreement between T-SPOT and QFT-GIT was assessed by the Kappa statistics [16]. Factors associated with QFT-GIT indeterminate values were identified by multiple logistic regression analysis and expressed with Odds ratio (OR) and 95% confidential intervals (CI). Variables with a p-value of 0.05 or less were included in logistic regression analyses to quantify the strength of the multivariate association. A two-sided p values less than 0.05 was considered statistically significant.

3. Results

3.1 Demographic and Clinical Characteristics

A total of 108 patients were enrolled in this study, including 64 with SLE and 44 with inflammatory arthritis (25 with RA and 19 with AS) (Fig. 1). Patients' characteristics, laboratory parameters and medications were summarized in Table 1. The mean age of SLE patients was 37.3 years old and 85.4% were female patients. The median disease duration for patients with SLE was 60 months with a median SLEDAI score of 6.0 (4.0–9.0). For patients with inflammatory arthritis, the mean age in years was 47.3 (16.4) and the proportion of women was 26 (59.1%).

3.2 Consistency Analysis

Among SLE patients, QFT-GIT was positive in 3 patients (4.7%), indeterminate in 12 (18.8%) and negative in 49 (76.6%). T-SPOT was positive in 2 (3.1%), indeterminate in 3 (4.7%) and negative in 59 (92.2%) (Tables 2,3). In patients with inflammatory arthritis, QFT-positive, -negative and -indeterminate results were 7 (15.9%), 36 (81.8%) and 1 (2.3%), respectively. Positive, negative and

Table 1. Patients' demographic and clinical characteristics (n = 108).

Characteristics	SLE (n = 64)	Inflammatory arthritis (n = 44)
Female, n (%)	54 (85.4%)	26 (59.1%)
Age, years, Mean ± SD	37.3 ± 14.8	47.3 ± 16.4
Disease Duration, Median (IQR), Months	60 (0–120)	3.5 (2–8.3)
SLEDAI, Median (IQR)	6.0 (4.0–9.0)	/
Previous Tuberculosis History, N (%)	1 (1.56%)	1 (2.27%)
Dose of Glucocorticoids, Median (IQR), mg/day	15 (0.25–33.75)	0 (0–6.9)
Lymphocyte Count, Mean ± SD, Per mm^3	1032.97 ± 758.22	1541.63 ± 701.39
Neutrophil Count, Mean ± SD, Per mm^3	4728.91 ± 2897.11	4729.05 ± 2174.41
CD4+ T Lymphocyte Count, Mean ± SD, Per mm^3	363.61 ± 265.53	619.82 ± 283.51
Complement 3, Mean ± SD, mg/dL	58.56 ± 27.60	/
Complement 4, Median (IQR), mg/dL	9.65 (5.43–14.75)	/
C-Reactive Protein, Median (IQR) mg/dL	0.07 (0–1.24)	0.95 (0.31–2.89)
Erythrocyte Sedimentation Rate, Median (IQR), mm/hour	30 (20–49)	25 (14–62)
Anti-dsDNA Antibody Median (IQR), IU/mL	42.8 (22.5–100)	/
Hydroxychloroquine, n (%)	40 (62.50%)	9 (20.5%)
Methotrexate, n (%)	5 (7.81%)	20 (45.5%)
Leflunomide, n (%)	4 (6.3%)	9 (20.5%)
Sulfasalazine, n (%)	0	9 (20.5%)
Azathioprine, n (%)	1 (1.56%)	0
Tacrolimus, n (%)	8 (12.50%)	0
Mycophenolate mofetil, n (%)	9 (14.06%)	0
Cyclophosphamide, n (%)	5 (7.81%)	0

SLEDAI, Systemic Lupus Erythematosus disease activity index; Anti-dsDNA, anti-double strand DNA antibody.

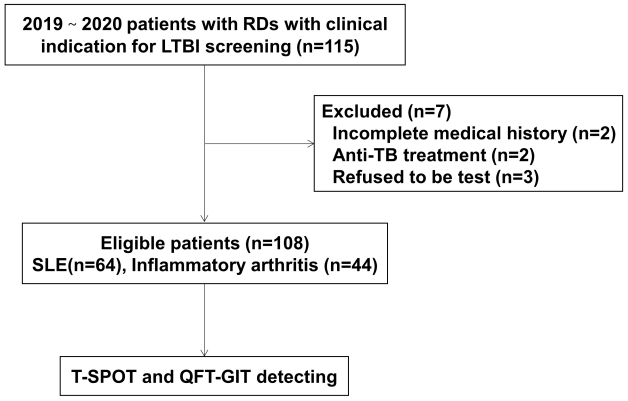

Fig. 1. Flow chart of the study. RDs, rheumatic diseases; LTBI, latent tuberculosis infection; SLE, systemic lupus erythematosus; T-SPOT, T-SPOT.TB test; QFT-GIT, QuantiFERON-TB Gold in-tube test.

indeterminate diagnosis of T-SPOT were, respectively, 4 (9.1%), 37 (84.1%) and 3 (6.8%). We found that QFT-GIT and T-SPOT have poor consistency in SLE (K = 0.179, $p < 0.001$), while the consistency in inflammatory arthritis patients is moderate (K = 0.539, $p < 0.001$) (Table 3).

The ratio of indeterminate values of QFT-GIT in SLE was higher than that in inflammatory arthritis patients (18.8% vs. 4.7%, $p = 0.013$) (Fig. 2A). Among the 12 patients with indeterminate results in SLE by QFT-GIT, one patient showed positive T-SPOT, one patient exhibited in-

Table 2. QFT-GIT and T-SPOT Result in patients with SLE and inflammatory arthritis.

Test	Disease	Indeterminate	Determinate	*p*-value
QFT-GIT	SLE	12 (18.8%)	52 (81.3%)	0.013
	Inflammatory arthritis	1 (2.3%)	43 (97.7%)	
T-SPOT	SLE	3 (4.7%)	61 (95.3%)	0.686
	Inflammatory arthritis	3 (6.8%)	41 (93.2%)	

RA, Rheumatoid Arthritis; AS, Ankylosing Spondylitis; SLE, Systemic Lupus Erythematosus.

determinate T-SPOT and 10 (83.3%) patients displayed a negative T-SPOT. In QFT-GIT, indeterminate results due to no response to phytohemagglutinin A (PHA) were more frequent in lupus patients (12.5%) compared to patients with inflammatory arthritis (1.56%) ($p = 0.046$) (Fig. 2B). Responses to PHA were lower in lupus patients compared to inflammatory arthritis ($p = 0.004$). During the follow-up, no patient received a treatment for LTBI or developed an active TB in the 12 patients with indeterminate results in SLE by QFT-GIT.

3.3 Risk Factors of Indeterminate QFT-GIT Results in SLE Patients

The indeterminate results in SLE patients were associate with neutrophil counts ($p = 0.041$), lymphocyte counts ($p = 0.004$), CD4+ T Lymphocyte counts ($p = 0.050$), C3 ($p = 0.011$) according to univariable analysis (Table 4). Lym-

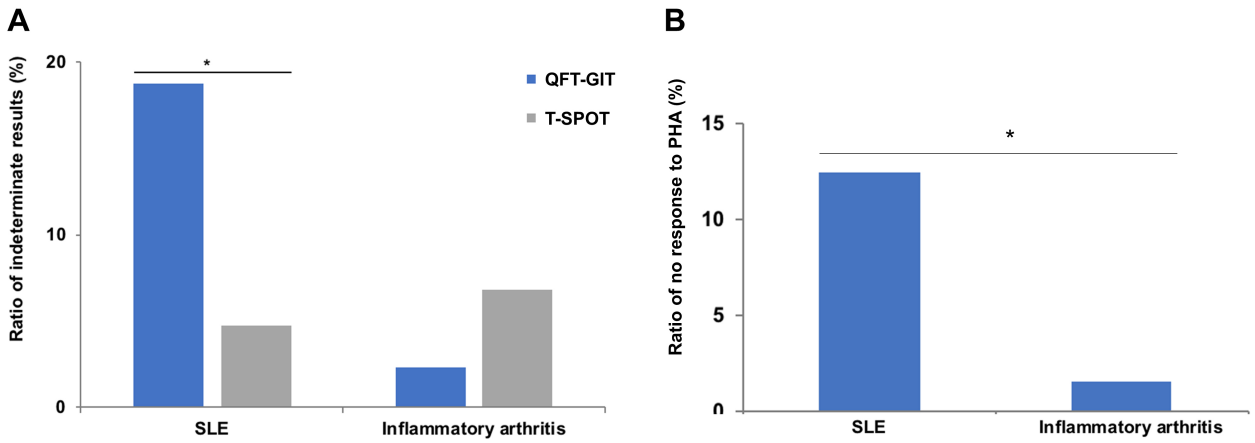

Fig. 2. Ratios of the indeterminate results in QFT-GIT and T-SPOT IGRA tests in patients with SLE and inflammatory arthritis. (*p = 0.013) (A); due to no response to PHA in patients with SLE and inflammatory arthritis by QFT-GIT (*p = 0.046) (B). SLE, systemic lupus erythematosus; QFT, QuantiFERON-TB Gold in-tube test; T-SPOT, T-SPOT.TB test; PHA, phytohaemagglutinin A.

Table 3. Results of IGRA in patients with SLE and inflammatory arthritis.

		SLE				Inflammatory arthritis			
		QFT-GIT							
		Positive	Negative	Indeterminate	Total	Positive	Negative	Indeterminate	Total
T-SPOT	Positive	1	0	1	2	4	0	0	4
	Negative	2	47	10	59	2	34	1	37
	Indeterminate	0	2	1	3	1	2	0	3
	Total	3	49	12	64	7	36	1	44
	Kappa	†K = 0.175 (95% CI [–0.06, 0.40])				‡K = 0.539 (95% CI [0.11, 0.88])			

†K: the concordance between QFT-GIT and T-SPOT in SLE ($p < 0.001$).

‡K: the concordance between QFT-GIT and T-SPOT in RA and AS ($p < 0.001$).

SLE, Systemic Lupus Erythematosus.

QFT-GIT, QuantiFERON® TB Gold In-Tube; T-SPOT, T-SPOT®.TB.

phocyte counts (OR [95% CI] 0.81 [0.68, 0.97], p = 0.020) was an independent predictor of QFT-GIT indeterminate results according to multivariable logistic analysis.

4. Discussion

This was the first study designed to compare the consistency of T-SPOT and QFT-GIT in patients with rheumatic diseases, including SLE, RA and AS. It was found that the consistency was particularly lower in patients with SLE. Low lymphocyte count was found to be associated with QFT-GIT indeterminate assay results. In addition, there was a fair-to-good agreement between QFT-GIT and T-SPOT in patients with inflammatory arthritis including RA and AS. The importance of this study lies in the comparison of efficacy between QFT-GIT and T-SPOT while screening LTBI in patients with SLE. Our data provided new evidence supporting T-SPOT could be a more suitable test for LTBI screening in SLE patients, for using T-SPOT yielded a significantly lower rate of indeterminate rates in this population.

Patients with rheumatic diseases are reported to have increased risk of tuberculosis infection due to the pathogenesis and medication [17]. A meta-analysis drew a conclusion that the method of T-SPOT was more sensitive than QFT-GIT in people who received immunosuppressive agents [18]. In several studies, the QFT-indeterminate ratio in SLE population has been reported to be higher than other rheumatic diseases or immunosuppressed patients [7,19,20]. In line with these results, QFT-GIT may be insufficient in detecting LTBI owing to higher rate of indeterminate results and T-SPOT could have a potential advantage in this aspect. At the same time, our findings are indicating that diminished response to PHA is a major reason for indeterminate results in SLE patients by QFT-GIT.

On the other hand, our study showed a fair-to-good agreement between QFT-GIT and T-SPOT in patients with RA and AS, which featured with chronic inflammation in joints. A study reports that no significant differences were found between QFT-GIT and T-SPOT according to the proportions of positive and indeterminate in patients with RA [21]. Kappa values were 0.6 (95% CI [0.39–0.80]) and 0.39 (95% CI [0.21–0.57]) for positive or negatives result. Another study showed that the QFT-GIT indeterminate results in RA patients were approximately 9.9% [22]. Both of the

Table 4. Factors associated with indeterminate results of QFT-GIT in univariable and multivariable analysis in SLE patients (n = 64).

Explanatory variables	OR (95% CI)	*p*-value
Univariable analysis		
Age	1.01 (0.97, 1.05)	0.743
Male	1.10 (0.20, 5.99)	0.912
Neutrophil count	0.98 (0.97, 1.00)	0.041
Lymphocyte count	0.80 (0.68, 0.93)	0.004
CD4+ T Lymphocyte count	0.84 (0.70, 1.00)	0.050
Neutrophil/lymphocyte counts	1.02 (0.89, 1.17)	0.762
Hemoglobin	0.98 (0.96, 1.01)	0.192
Platelet counts	0.99 (0.98, 1.00)	0.088
ESR	0.99 (0.96, 1.02)	0.477
C3	0.40 (0.20, 0.81)	0.011
C4	0.85 (0.68, 1.06)	0.140
Anti-dsDNA antibody	1.01 (0.99, 1.03)	0.375
SLEDAI	1.00 (0.85, 1.18)	0.987
Immunosuppressive agents	2.88 (0.57, 14.54)	0.201
Doses of glucocorticoids	0.99 (0.96, 1.02)	0.567
Multivariable analysis		
Age	1.02 (0.96, 1.09)	0.482
Male	1.05 (0.09, 11.96)	0.974
Neutrophil count	1.00 (0.98, 1.03)	0.853
Lymphocyte count	0.81 (0.68, 0.97)	0.020
C3	0.42 (0.15, 1.14)	0.094

QFT, QuantiFERON-TB Gold in-tube test; SLE, Systemic Lupus Erythematosus; SLEDAI, systemic lupus erythematous disease activity index.

two tests were applicable while diagnosing LTBI in patients with chronic inflammatory arthritis.

Furthermore, our study discovered that low lymphocyte count was associated with QFT-GIT indeterminate results. However, high SLEDAI scores seemed not related with a high proportion of indeterminate results, and this differs from some studies [20–24]. Other previous researches showed that CD4+ T cell count, lymphocyte count, and lymphocyte percentage were influencing factors for the indeterminate results of QFT-GIT in HIV and immunosuppressive people [25,26]. Glucocorticoid therapy is also another reason for the indeterminate outcome of QFT [20,27,28]. It was suggested that patients with indeterminate results were more likely to be aged over 70 years, females, suffering from SLE, lymphopenia, Anemia, thrombocytopenia, and hypoalbuminemia [29]. QFT-GIT results were affected by various factors and might have a limitation in LTBI screening based on the clinical settings, and further investigations were needed. The poor agreement between QFT-GIT and T-SPOT in lupus patients in this study might be due to the following two reasons. First, there was a large amount of IFN-γ in highly active SLE patients' serum, which appears to be demonstrated as an increased IFN-r level in the negative control tube. Second, the low number or activity of lymphocytes in lupus patients might be attributed to the decreased IFN-r production in the positive control tube.

The results of the study suggested that T-SPOT might have an advantage as a LTBI screening test in terms of having lesser indeterminate results, especially in patients with SLE. However, there were some limitations in the study. First, a general population was not included as a control in this single-center cohort study, due to practical constraints. Second, a bias might exist due to the limited number of patients with RA and AS. In addition, the influence of the inclusion of a heterogeneous population, the differences in testing indications, disease duration, and the different medications administrated on the results could not be ruled out.

5. Conclusions

Based on the results of the study, the T-SPOT assay might be more advantageous than the QFT-GIT assay in detecting LTBI, and this is mainly related to a less proportion of indeterminate results in patients with SLE compared with inflammatory arthritis. These outcomes are supporting the application of T-SPOT as a test for LTBI screening in individuals with SLE.

Author Contributions

(I) Conception and design—JZ, JL; (II) Administrative support—SC, LL; (III) Provision of study materials or patients—LL and LZ; (IV) Collection and assembly of data—JZ, PY and SY; (V) Data analysis and interpretation—LZ and JZ; (VI) Manuscript writing—LZ and JZ; (VII) Final approval of manuscript—All authors.

Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics committee of the Renji Hospital (No. 2016-Clinical-Res-011) and individual consent for this retrospective analysis was waived.

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Conflict of Interest

The authors declare no conflict of interest.

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