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Tuberculin skin test before biologic and targeted therapies: does the same rule apply for all?

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Abstract

This study aimed to compare Tuberculin Skin Test (TST) and QuantiFERON®-TB Gold In-Tube (QFT–GIT) test in rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients scheduled for biological and targeted synthetic disease modifying anti-rheumatic drugs (DMARDs) in a Bacillus Calmette-Guérin-vaccinated population. Adult RA ($n=206$) and SpA ($n=392$) patients from the TReasure database who had both TST and QFT–GIT prior to initiation of biological and targeted synthetic DMARDs were included in the study. Demographic and disease characteristics along with pre-biologic DMARD and steroid use were recorded. The distribution of TST and performance with respect to QFT–GIT were compared between RA and SpA groups. Pre-biologic conventional DMARD and steroid use was higher in the RA group. TST positivity rates were 44.2% in RA and 69.1% in SpA for a 5 mm cutoff ($p<0.001$). Only 8.9% and 15% of the patients with RA and SpA, respectively, tested positive by QFT–GIT. The two tests poorly agreed in both groups at a TST cutoff of 5 mm and increasing the TST cutoff only slightly increased the agreement. Among age, sex, education and smoking status, pre-biologic steroid and conventional DMARD use, disease group, and QFT–GIT positivity, which were associated with a 5 mm or higher TST, only disease group (SpA) and QFT–GIT positivity remained significant in multiple logistic regression. TST positivity was more pronounced in SpA compared to that in RA and this was not explainable by pre-biologic DMARD and steroid use. The agreement of TST with QFT–GIT was poor in both groups. Using a 5 mm TST cutoff for both diseases could result in overestimating LTBI in SpA.

Keywords Arthritis · Spondyloarthritis · Interferon-gamma release tests · Tuberculin test · Latent tuberculosis

Abbreviations

ACR	American College of rheumatology
ASAS	Assessment of spondyloarthritis International Society
BCG	Bacillus Calmette-Guérin
CDC	Centers for disease control and prevention
DMARD	Disease-modifying anti-rheumatic drug
EULAR	European league against rheumatism
HIV	Human Immunodeficiency Virus
IFN	Interferon
IGRA	Interferon-γ release assay
LTBI	Latent tuberculosis ınfection
NTM	Non-tuberculous mycobacteria
QFT–GIT	QuantiFERON®-TB Gold In-Tube Test
RA	Rheumatoid arthritis
SpA	Spondyloarthritis
TNF	Tumor necrosis factor
TST	Tuberculin skin test
WHO	World Health Organization

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Introduction

Screening for and the treatment of latent tuberculosis infection (LTBI) is recommended in inflammatory arthritis patients prior to biological and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), particularly the tumor necrosis factor-α (TNF-α) inhibitors [1, 2]. Screening and treatment strategies for LTBI differ across the world because of epidemiological and economic reasons for which many regional guidelines exist in rheumatology practice [2–8].

Tuberculin skin test (TST) has been used for more than a century to detect infection with *Mycobacterium tuberculosis*. Potential false-positive results in Bacillus Calmette–Guérin (BCG)-vaccinated or non-tuberculous Mycobacteria (NTM)-infected people, intra- and interobserver variability, and false-negative results in immunocompromised patients are the major disadvantages of this test along with a need to interpret the test result according to the individual situation [1, 9–11]. It requires 48–72 h and a second visit to obtain the result. The test is not expensive without a need for any sophisticated equipment but well-trained personnel is a must. Interferon-γ (IFN-γ) release assays (IGRAs), QuantiFERON®-TB Gold In-Tube (QFT–GIT) and T-SPOT®.TB, are relatively new tests to detect latent infection with *Mycobacterium tuberculosis* and depend on the measurement of IFN-γ produced by T lymphocytes incubated with *Mycobacterium tuberculosis* antigens. They are not affected by latent infections by most NTMs and BCG vaccination [1, 9, 12]. Direct cost is higher than that of TST and a well-equipped laboratory is needed. The result is obtained faster compared to TST but may be subject to preanalytical errors, such as delayed incubation. Both TST and IGRAs were mostly reported to have comparable sensitivity and specificity to detect LTBI in non-immunocompromised hosts, and either test may be used [1, 12–16]. However, recommendations for the preferential use of IGRAs over TST exist based on the reports with more accurate results by IGRAs [9, 17–19]. Conflicting results on the performance of IGRAs or combination tests (both TST and an IGRA or sequential testing according to an initial TST or IGRA) compared to TST alone have been reported in Human Immunodeficiency Virus (HIV)-uninfected immunocompromised adults [9, 20–28] but IGRAs and combination tests are increasingly being recommended to screen LTBI [3, 5–7]. Combination of tests was conditionally recommended by the Centers for Disease Control and Prevention (CDC) in immunocompromised patients with a high risk of infection or reactivation (also called disease progression) and in BCG-vaccinated patients [12].

Although treatment with biological and targeted synthetic DMARDs itself puts patients with LTBI into an increased risk of disease progression [1, 9, 12, 25], the interpretation of the LTBI screening with TST before initiation of these drugs may not necessarily be the same in different patient groups with inflammatory arthritis since the degree of immunosuppression, mainly determined by the drugs used, comorbid diseases, and rheumatic disease itself, is not the same. World Health Organization (WHO) indicated the evaluation of the performance of LTBI tests in various at-risk populations as a research priority [1]. Current guidelines and society recommendations for the screening and treatment of LTBI before biological and targeted synthetic DMARDs do not distinguish patients with different rheumatic diseases from each other [2, 5, 8]. Several societies make specific recommendations for LTBI screening or refer to local tuberculosis guidelines before biological and targeted synthetic DMARDs in rheumatoid arthritis (RA) [3, 4, 6, 7] but not other inflammatory arthritides, such as spondyloarthritis (SpA) requiring biological and targeted synthetic DMARDs [26–28]. The European League Against Rheumatism (EULAR) has no recommendation regarding LTBI in any rheumatic disease.

This study aimed to compare TST and QFT–GIT in RA and SpA patients scheduled for biological and targeted synthetic DMARDs in a BCG-vaccinated population.

Materials and methods

Patients and design

Patients were selected from the TReasure registry, a web-based database to which users connect through a URL (https://www.trials-network.org/treasure) with their unique identifier and passwords provided for data entry and access. TReasure records demographic and clinical features, comorbidities, radiology and laboratory results, measures of disease activity, and treatment data of inflammatory rheumatic diseases, such as RA and SpA [29]. Patients older than 18 years of age, with a diagnosis of RA or SpA, fulfilling 2010 American College of Rheumatology (ACR)/EULAR [30] and Assessment of Spondyloarthritis International Society (ASAS) criteria [31] were initially screened. 2690 RA and 4995 SpA patients were identified by the end of March 2019. 1091 (40.6%) and 1413 (52.5%) patients in RA and 2377 (47.6%) and 2509 (50.2%) patients in the SpA group underwent testing with TST and QFT–GIT, respectively. 241 (9%) and 439 (8.8%) patients had both TST and QFT–GIT in RA and SpA groups. 35 RA and 47 SpA patients were excluded due to the presence or history of active tuberculosis, HIV infection, solid organ or hematopoietic stem cell transplantation, diabetes, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease or persistent asthma, or malignancy. Finally, 206 RA and 392 SpA patients who had both TST and QFT–GIT were recruited for further analysis.

Demographic and disease-related features including age, sex, education status, smoking status, disease duration, systemic steroid and conventional DMARD use prior to initiation of biologic and targeted synthetic DMARDs were identified retrospectively from the database along with BCG vaccination history, presence of a BCG scar, TST (in millimeters) and QFT–GIT (positive, negative, and indeterminate) results, and LTBI treatment based on the physician's decision. RA and SpA study groups were compared in terms of demographic and disease-related features, BCG vaccination status, TST and QFT–GIT results, and LTBI treatment rates. To avoid selection bias, the study groups were also compared with the entire RA and SpA populations in the database (Supplementary Table 1).

TST and QFT–GIT

TST has traditionally been performed in Tuberculosis Dispensaries and Chest Diseases Departments of hospitals in Turkey in a standardized way according to the national tuberculosis guidelines [32]. Briefly, 0.1 mL 5-tuberculin unit purified protein derivative (PPD) is administered intradermally in the forearm according to the Mantoux method. The largest induration diameter is measured 48–72 h later by an expert and reported. QFT–GIT (Cellestis Ltd, Carnegie, Victoria, Australia) test is available in many public and private hospitals and laboratories and increasingly used in Turkey. It is performed according to the manufacturer's instructions.

Statistical analysis

PASW Statistics v.18.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analyses. Data were expressed as numbers with percentages for the categorical variables and means ± standard deviations for the continuous ones. Categorical data were compared using chi-square or Fisher's exact tests. Distributions of the continuous data were analyzed by histograms and tested for normality by Lilliefors-corrected Kolmogorov–Smirnov test. Continuous data were compared using the *t* test or Mann–Whitney *U* test according to the distribution. Percent agreement of TST with QFT-GIT and Cohen's kappa coefficients were provided in RA and SpA groups separately. Multiple logistic regression analyses were performed with the potential predictors of TST positivity. Odds ratios (ORs) with 95% confidence intervals were calculated for risk assessments. $p < 0.05$ was considered statistically significant.

Ethics approval and consent to participate

Written informed consent was obtained from each patient regarding the use of clinical data for research purposes. The study was in accordance with the 2013 amendment of the Helsinki declaration. Ethical approval was obtained from Hacettepe University Institutional Review Board (KA17/058, May 2017) and Ministry of Health of Turkey (93189304-14.03.01, October 2017).

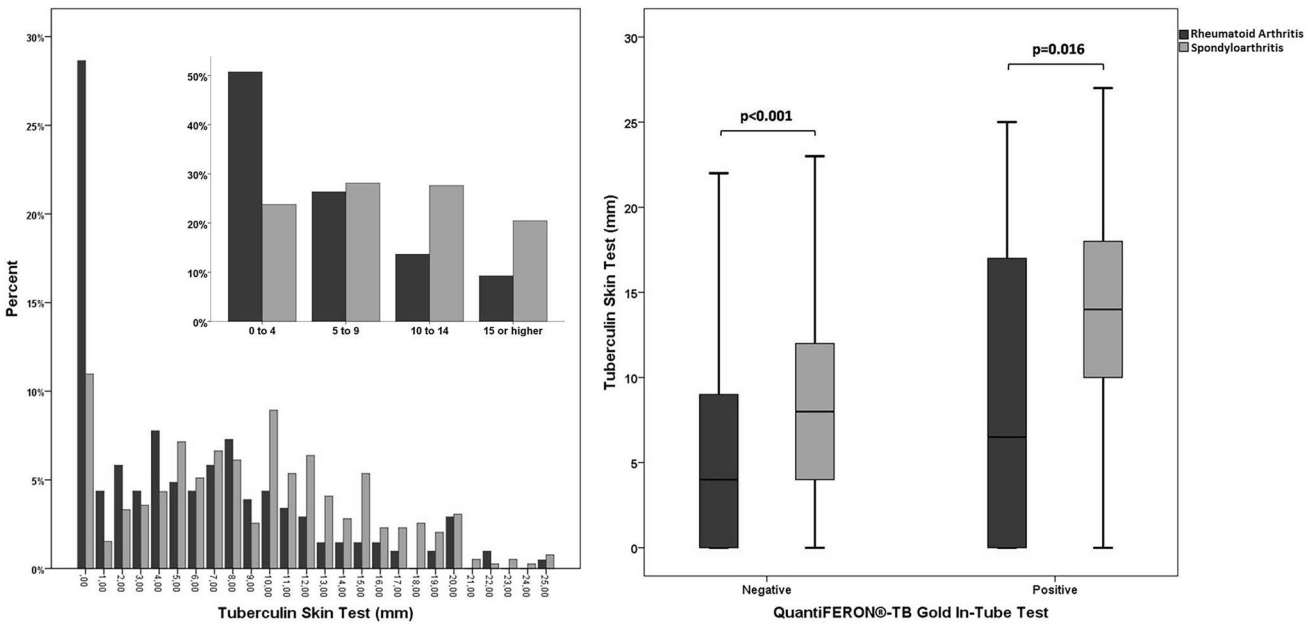

Fig.1 Distribution of TST in rheumatoid arthritis and spondyloarthritis (left) and TST results according to the QFT–GIT status in disease groups (right)

Table 1 Demographic data, disease-related features, TST and QFT–GIT results at the time of LTBI testing prior to initiation of biological and targeted synthetic DMARDs, and LTBI treatment rates of the study groups

	n	RA	*n*	SpA	*p*
Female sex, *n* (%)	206	160 (77.7)	392	154 (39.3)	**< 0.001**
Age, years	206	49 ± 15	392	43 ± 11	**< 0.001**
Education status, *n* (%)					
Primary or lower	201	91 (45.2)	379	85 (22.4)	**< 0.001**
Higher education		110 (54.8)		294 (77.6)	
Smoking status, *n* (%)					
Never smoked	202	130 (64.4)	369	154 (41.7)	**< 0.001**
Ex-smoker		35 (17.3)		63 (17.1)	
Active smoker		37 (18.3)		152 (41.2)	
Disease duration, years	202	11.8 ± 8	392	8.7 ± 6	**< 0.001**
Systemic steroid use, *n* (%)	206	113 (54.9)	392	73 (18.6)	**< 0.001**
cDMARD use, *n* (%)	206	172 (83.5)	392	245 (62.5)	**< 0.001**
Methotrexate		137 (66.5)		89 (22.7)	**< 0.001**
Hydroxychloroquine		93 (45.1)		38 (9.7)	**< 0.001**
Sulfasalazine		110 (53.4)		217 (55.4)	0.647
Leflunomide		76 (36.9)		18 (4.6)	**< 0.001**
TST, mm	206	5.7 ± 5.8	392	9.3 ± 6.4	**< 0.001**
TST, *n* (%)					
≥ 5 mm	206	91 (44.2)	392	271 (69.1)	**< 0.001**
≥ 10 mm		38 (18.4)		154 (39.3)	**< 0.001**
≥ 15 mm		16 (7.8)		60 (15.3)	**0.009**
QFT–GIT, *n* (%)					
Positive	206	20 (9.7)	392	59 (15.1)	0.075
Negative		185 (89.8)		333 (84.9)	
Indeterminate		1 (0.5)		-	
LTBI treatment, *n* (%)	206	92 (44.7)	382	230 (60.2)	**< 0.001**

Continuous variables were given as means ± standard deviations

Statistically significant differences were indicated in bold

n Number, *RA* Rheumatoid arthritis, *SpA* Spondyloarthritis, *cDMARD* Conventional disease-modifying anti-rheumatic drug, *TST* Tuberculin skin test, *QFT–GIT* Quantiferon®-TB Gold In-Tube, *LTBI* Latent tuberculosis infection

Results

Mean disease duration of RA and SpA patients were 11.8 ± 8 and 8.7 ± 6 years, respectively. Demographic data, disease-related features, TST and QFT–GIT results at the time of LTBI testing prior to initiation of biological and targeted synthetic DMARDs and LTBI treatment rates were given in Table 1. Of 135 RA and 251 SpA patients questioned, 94.4% and 88.8% recalled a previous BCG vaccination ($p = 0.051$). 87/89 (97.8%) and 172/182 (94.5%) patients in RA and SpA groups, respectively, checked for the presence of a BCG scar, had at least one scar as expected due to the national immunization program ($p = 0.348$). Systemic steroids and conventional DMARDs were more frequently used in patients with RA compared to those with SpA at the time of LTBI testing (Table 1), whereas the daily steroid doses were similar in those who were exposed (prednisone equivalent of less than 2.5 mg: 5.2% and 2.9%, 2.5 to 7.5 mg: 60.5% and 50.1%, 7.5 to 15 mg: 25.9% and 34%, higher than 15 mg: 8.4% and 13% in RA and SpA, respectively). Previous exposure to systemic steroids (76.5% vs. 28.6%, $p < 0.001$) and two or more DMARDs (89.5% vs. 27.4%, $p < 0.001$) were also more frequent in RA compared to SpA. The mean TST result was lower in RA compared to that in SpA patients (5.7 ± 5.8 vs. 9.3 ± 6.4 mm, $p < 0.001$). The distribution of TST in study groups is represented in Fig. 1. The rates of positive TST at 5, 10, and 15 mm cutoff values were significantly higher in the SpA group (Table 1). 59 (28.6%) and 43 (11%) patients in the RA and SpA groups, respectively, were completely anergic to TST with no induration ($p < 0.001$). QFT–GIT positivity rate was slightly higher in the SpA (15.1%) compared to the RA group (9.7%) but the difference was not statistically significant (OR = 1.64 [0.96–2.82], $p = 0.075$). The treatment rate of latent tuberculosis was also higher in the SpA group [OR = 1.88 (1.33–2.64)] (Table 1).

Male sex, higher education, and smoking were more frequent in patients with a TST of 5 mm or higher compared to those with TST less than 5 mm, if RA and SpA groups were collated. The mean age was lower and systemic steroid, methotrexate, and leflunomide use were less frequent in TST ≥ 5 mm group as well (Table 2).

Multiple logistic regression analysis with the covariates age, sex, education, smoking, systemic steroid, methotrexate, and leflunomide use, disease category (SpA), and QFT–GIT positivity identified the disease category (SpA) and QFT–GIT positivity as the only significant predictors of a TST ≥ 5 mm. The adjusted OR of a positive TST was 2.03 (1.31–3.14) in SpA with reference to RA (Table 3).

The distribution of TST according to the QFT–GIT status were quite different in RA and SpA groups (Fig. 1). TST results according to the QFT–GIT status for a 5 mm cutoff value are represented in Table 4. The two tests poorly agreed with κ coefficients of 0.02 and 0.08 in RA and SpA groups, respectively. Note that TST with a 5 mm cutoff value could detect only half of the QFT–GIT positive patients in RA and was positive in two-thirds of the QFT–GIT negative SpA patients (Table 4). Increasing the TST cutoff only slightly increased the agreement between the two tests (Supplementary Table 2).

Discussion

We were able to show that TST positivity rate was significantly higher in SpA patients compared to that of RA patients prior to initiation of biological and targeted

Table 2 Factors associated with TST positivity for a 5 mm cutoff value

	n	TST < 5 mm	*n*	TST ≥ 5 mm	*p*
Female sex, *n* (%)	236	152 (64.4)	362	162 (44.8)	**< 0.001**
Age, years	236	46.3 ± 14.1	362	43.9 ± 12	**< 0.001**
Education status, *n* (%)					
Primary or lower	226	85 (37.6)	354	91 (25.7)	**0.002**
Higher education		141 (62.4)		263 (74.3)	
Smoking status, *n* (%)					
Never smoked	224	132 (58.9)	347	152 (43.8)	**0.001**
Ex-smoker		35 (15.6)		63 (18..2)	
Active smoker		57 (25.4)		132 (38)	
Systemic steroid use, *n* (%)	236	89 (37.7)	362	97 (26.8)	**0.007**
cDMARD use, *n* (%)	236	178 (75.4)	362	239 (66)	**0.014**
Methotrexate		103 (43.6)		123 (34)	**0.017**
Hydroxychloroquine		57 (24.2)		74 (20.4)	0.284
Sulfasalazine		133 (56.4)		194 (53.6)	0.507
Leflunomide		54 (22.9)		40 (11)	**< 0.001**
Disease category, n(%)					
Rheumatoid arthritis	236	115 (48.7)	362	91 (25.1)	**< 0.001**
Spondyloarthritis		121 (51.3)		271 (74.9)	
QFT–GIT, *n* (%)					
Positive	236	10 (4.2)	362	69 (19.1)	**< 0.001**
Negative		225 (95.4)		293 (80.9)	
Indeterminate		1 (0.4)		–	

Age was given as mean ± standard deviation

Statistically significant differences were indicated in bold

n Number, *cDMARD* Conventional disease-modifying anti-rheumatic drug, *TST* Tuberculin skin test, *QFT–GIT* Quantiferon®-TB Gold In-Tube

Table 3 Multiple logistic regression analysis for TST positivity for a 5 mm cutoff value

	Odds ratio	95% CI	*p*
Male sex	1.43	0.97–2.11	0.074
Age (per year)	0.99	0.98–1.01	0.640
Higher education	1.25	0.83–1.88	0.284
Ever-smoking	1.24	0.86–1.80	0.258
Systemic steroid use	0.85	0.55–1.31	0.470
Methotrexate use	1.20	0.79–1.85	0.393
Leflunomide use	0.74	0.43–1.27	0.270
Disease category (SpA)	2.03	1.31–3.14	**0.002**
QFT–GIT positivity	2.56	1.41–4.65	**0.002**

Statistically significant differences were indicated in bold

CI Confidence interval, *TST* Tuberculin skin test, *QFT–GIT* Quantiferon®-TB Gold In-Tube, *SpA* spondyloarthritis

synthetic DMARDs, although BCG scar rates were similar and QFT–GIT positivity rates were only slightly different. Although the smoking rate was higher, and systemic steroid and conventional DMARD use were less frequent in SpA compared to RA, a higher rate of TST positivity was not attributable to those (Table 3).

TST was reported to be 10.3 ± 7.3 and 13.5 ± 5.3 mm and the rates of a TST greater than 10 mm were 58.6% and 76.4% in healthy Turkish people with one and two BCG vaccination scars, respectively [33]. These rates were higher than those of both RA and SpA groups. Similar results in healthy population were later reported as well [34] although more recent small-scale regional studies in BCG-vaccinated younger adults reported lower TST induration widths comparable to those of patients with SpA [35, 36]. This was probably because of reduced number of BCG vaccine doses in Turkey over time that had a great impact on test results. It is rational to adjust the TST cutoff according to the vaccination status [33, 36], age [33, 36], and tuberculosis prevalence [37] in general population. However, lowest possible cutoff value (mostly 5 mm) was applied in high risk patients, such as those who will be treated with TNF-α inhibitors [2].

Treatment with immunosuppressive medications has been known to block the immune response against tuberculin and *Mycobacterium tuberculosis*-specific antigens to some degree and may be responsible for false-negative TST and QFT–GIT results [11, 38]. A higher rate of complete cutaneous anergy and slightly lower QFT–GIT positivity in RA compared to the SpA group in the present study may be caused by higher current and cumulative exposure to

Table 4 TST results according to the QFT–GIT status in study groups for a 5 mm cutoff value

	RA		SpA	
	QFT–GIT negative ($n=185$)	QFT–GIT positive ($n=20$)	QFT–GIT negative ($n=333$)	QFT–GIT positive ($n=59$)
TST < 5 mm	104 (56.2%)	10 (50%)	113 (33.9%)	8 (13.5%)
TST ≥ 5 mm	81 (43.8%)	10 (50%)	220 (66.1%)	51 (86.5%)
	Agreement = 55.6%		Agreement = 41.8%	
	Cohen's κ = 0.02		Cohen's κ = 0.08	

n Number, *RA* Rheumatoid arthritis, *SpA* Spondyloarthritis, *TST* Tuberculin skin test, *QFT–GIT* Quantiferon®-TB Gold In-Tube

systemic steroids and conventional DMARDs in RA. The potential impact of intrinsic immune dysregulation in rheumatic diseases on LTBI and screening tests was not evaluated before. However, diminished immune response against microbes and vaccines was attributed not only to immunosuppressive medications but the disease itself in patients with RA [39–41].

Conflicting results on the performance of IGRAs compared to TST in terms of sensitivity and specificity to detect LTBI have been reported in immunocompromised adults without HIV infection [20–24]. The principal reason for that is the lack of a gold standard test for LTBI, which is, by definition, the presence of an immune response—assumed to be caused by a previous sensitization—against *Mycobacterium tuberculosis* antigens with no evidence of active tuberculosis [1]. It is not a direct microbiological diagnosis, and false-positive and -negative results are of great concern both by TST and IGRAs [1, 11, 12]. It is also difficult to evaluate the progression to active tuberculosis in immunocompromised patients tested by TST and IGRAs comparatively, since patients with positive results of either test are usually given treatment due to a high risk of reactivation. According to the present and two previous studies [20, 24], increasing the TST cutoff value slightly improved the agreement between the two tests but to a moderate level at most. Therefore, TST–QFT–GIT disagreement in the immunocompromised adult population without HIV infection does not seem to be caused primarily by a cutoff issue. BCG vaccination is a well-known factor for false-positive TST results and a potential reason to use IGRAs to detect LTBI [3, 5–7, 12] but cannot explain the discrepant study results conducted in BCG-vaccinated patient groups [20–24]. A possible reason why studies report different TST–QFT–GIT agreement rates in BCG-vaccinated patients may be the difference in the patient groups (i.e., patient groups with different diseases and durations of disease) and the degree of immunosuppression of the study groups. According to a meta-analysis of long-term extension studies, not only TST–QFT–GIT agreement but the actual tuberculosis risk was different as well in different rheumatic diseases including RA and SpA independent of the treatment with biologics [42]. Treatment with TNF-α inhibitors increased the risk of tuberculosis in both RA and SpA but to a higher level in RA [42]. Not so unexpectedly, studies conducted in different patient groups, such as inflammatory bowel disease patients under treatment with various immunosuppressive agents, TNF-α inhibitor-scheduled patients with rheumatic diseases under DMARDs, and solid organ transplantation candidates with no immunosuppressive medication use reported different agreement rates between TST and QFT–GIT [20, 24]. Different TST results were reported even in psoriasis and psoriatic arthritis patients despite similar QFT–GIT results [43]. Different agreement rates between TST and QFT–GIT in RA and SpA in the present study may represent an example of this situation. To overcome the effect of conventional DMARD and steroid treatment on screening tests, the Australian Rheumatology Association suggests screening LTBI at the initial diagnosis of inflammatory arthritis [5]. Anyway, candidates for biological and targeted synthetic DMARDs have traditionally been screened in the same way regardless of their underlying rheumatic disease, although both the tuberculosis progression (reactivation) rates and the screening test results may differ. It should additionally be stated that TST procedures with different types and units of tuberculin products in different countries may also contribute to discrepant study results [11, 20–24].

Turkey is an intermediate tuberculosis burden country with an estimated incidence rate of 13 to 18 per 100000 population per year [44]. A conjoint guideline prepared by the Turkish Society for Rheumatology, Turkish Thoracic Society, and Ministry of Health recommends LTBI screening by TST or an IGRA before biologic and targeted therapies, particularly the TNF-α inhibitors [8]. Combination of both tests was conditionally recommended as suggested by the CDC [8, 12]. Positivity of either test is considered as LTBI. Since disease progression risk is potentially high under biologic and targeted therapies, a 5 mm cutoff value was adopted for TST positivity regardless of the vaccination status as is in most other international guidelines [2]. In correlation with the TST positivity rate for a 5 mm cutoff as suggested, LTBI treatment rate was higher in SpA compared to RA group (Table 1). There lies a paradox here. RA patients, who

were more immunosuppressed and more prone to tuberculosis reactivation, were given less LTBI treatment, since they had lower TST positivity compared to SpA patients. The opposite seems true for SpA patients. This particular point implies the necessity of studies in separate at-risk disease groups rather than pre-biologic patient pools as prioritized by WHO [1].

IGRA-only and combined test approaches were proved effective and safe particularly to reduce overtreatment with antituberculosis drugs in immunocompromised and BCG-vaccinated patients [21, 45–48] but debate exists on this topic [15, 22, 23, 38]. In a longitudinal study of inflammatory arthritis patients that compared different baseline LTBI screening strategies before TNF-α inhibitors in a high tuberculosis burden BCG-vaccinated population, incidence rates of active tuberculosis, after a mean exposure of 4 ± 2.4 years to TNF-α inhibitors, were 1348.0, 862.1, and 540.2 cases per 100000 patient-years in TST (cutoff ≥ 10 mm), TST (cutoff ≥ 5 mm), and QFT groups, respectively, although the difference was not found statistically significant [49]. Cost-effectiveness and antituberculosis drug-related toxicity are also important concerns regarding LTBI screening and treatment strategies but beyond the scope of this study.

There were several limitations of this study. This was a cross-sectional study and tuberculosis progression (reactivation) rates were not available. A healthy control group was also not included. TST and QFT–GIT were performed in different centers and it was not known which test was performed first. Test intervals were also not known. Since the study population had at least two doses of BCG vaccine in the infancy and childhood (first school class), the missing data on BCG scar and vaccination history do not seem to cause confusion to interpret the study results. There were some differences in age, education status, pre-biologic systemic steroid and conventional DMARD use, and TST results between the study groups and the entire RA and SpA populations (Supplementary Table 1). Cumulative exposure to systemic steroids and DMARDs were also not available. However, these were not thought to have a major impact on the main results since pre-biologic systemic steroid and conventional DMARD use were even less frequent in the RA study group compared to the entire RA population (Supplementary Table 1). Overall, this study adds valuable information to the relevant field regarding the difference in the performance of LTBI screening tests in RA and SpA.

In conclusion, TST positivity was more pronounced in SpA compared to RA and this was not explainable by pre-biologic DMARD and steroid use. The agreement of TST with QFT–GIT for latent tuberculosis was poor and increasing the TST cutoff only slightly increased the agreement between the two tests. Using a 5 mm TST cutoff for both diseases could result in overestimating LTBI in SpA.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval Ethical approval was obtained from Hacettepe University Institutional Review Board (KA17/058, May 2017) and Ministry of Health of Turkey (93189304-14.03.01, October 2017).

Consent to participate Written informed consent was obtained from each patient regarding the use of clinical data for research purposes. The study was in accordance with the 2013 amendment of the Helsinki declaration.

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