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Original research article

Do higher cut-off values for tuberculin skin test increase the specificity and diagnostic agreement with interferon gamma release assays in immunocompromised Bacillus Calmette-Guérin vaccinated patients?

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ABSTRACT

Purpose: Immunocompromised patients with latent tuberculosis infection (LTBI) are at high risk of progression to active tuberculosis. Detection and treatment of LTBI in this group of patients are very important to control active tuberculosis. Tuberculin skin test (TST) and interferon gamma release assays (IGRAs) are two methods for detection of LTBI. Diagnostic agreement between two tests are poor especially in Bacillus Calmette-Guérin (BCG) vaccinated immunocompromised patients. In this study, we tried to figure out if the use of a higher cut-off for TST increases diagnostic agreement with IGRAs and TST specificity and or not.

Materials/Methods: In this retrospective study, BCG vaccinated solid organ transplantation (SOT) candidates and patients scheduled for anti-tumor necrosis factor-alpha (anti- TNFα) treatment patients who underwent both TST and IGRAs between 2011 and 2017 were enrolled in the study. Diagnostic agreement between the two tests was assessed for 5, 10, 15 mm cut-off values for all participants, SOT candidates and anti- TNFα treatment subgroups separately.

Results: Fifty female and 55 male total 105 patients were included. In the anti- TNFα treatment group 92.8% of the patients were receiving at least one immunosuppressive drug. For all participants kappa (κ) values were 0.303, 0.370, 0.321 respectively for 5, 10 and 15 mm cut-offs. For SOT candidates κ values were 0.488, 0.422, 0.288 respectively. For anti- TNFα treatment group κ values were 0.235, 0.332, 0.275 respectively.

Conclusions: In BCG vaccinated immunocompromised patients, the agreement between TST and QFT-GIT was poor regardless of cut-off value. And increasing the cut-off does not improve agreement.

1. Introduction

Latent tuberculosis infection (LTBI) is defined as the presence of immune response against *Mycobacterium tuberculosis* (Mtb) antigens without clinical signs of active tuberculosis (TB). Detection and treatment of LTBI is very important to control active TB [1]. Especially solid organ transplantation (SOT) candidates and patients scheduled for anti-tumor necrosis factor-alpha (anti- TNFα) treatment are accepted as immunocompromised. Because SOT candidates require immunosuppressive drugs after transplantation. Anti- TNFα medications are approved for many diseases which cause immunosuppression, such as rheumatoid arthritis. Also, these patients usually receive other immunosuppressive drugs, like steroids. Furthermore, anti- TNFα medications themselves are well known for increasing the risk of active TB. Thus, diagnosis of LTBI is the utmost importance for the benefits of these patients [2].

Tuberculin skin test (TST) and interferon gamma release assays (IGRAs) are two methods for detection of LTBI. TST, however, has some limitations such as potential false-positive results in Bacillus Calmette-Guérin (BCG) vaccinated or Nontuberculous Mycobacterium (NTMB) infected persons. Also, interobserver variability is high [3]. IGRAs, depend on the measurement of interferon-gamma (IFN-γ) produced by T cells in response to *Mtb* antigens. IGRAs are not affected by BCG vaccination or most NTM [4]. IGRAs have higher specificity compared to TST, especially in subjects with BCG vaccination [5,6].

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Table 1
Characteristics of patients.

Gender	n (%)
Male	55(52.4%)
Female	50(47.6%)
Age [median (min-max)]	
Solid organ transplant candidates group	60 (27–69)
Anti-TNFα treatment group	43.5 (20–76)
Underlying disease	n (%)
Rheumatoid arthritis	25(23.8%)
Ankylosing spondylitis	22(20.9%)
Inflammatory bowel diseases	19(18.1%)
Psoriatic arthritis	6(5.7%)
Scleroderma	2(1.9%)
Liver transplantation candidate	24(22.8%)
Renal transplantation candidate	7(6.6%)

In immunocompromised patients, TST is defined as positive if ≥5 mm. This means if induration is 5 mm or larger, the risk of progression to active TB is high and these patients require preventive treatment [7]. However, published articles have demonstrated poor diagnostic agreement between IGRAs and TST in immunocompromised patients. BCG vaccination appears to be one of the reasons for poor agreement between the tests [8]. In patients with BCG vaccination, this cut-off value may cause an overestimation of LTBI. In BCG vaccinated healthy subjects, the agreement between the two tests was improved with the higher cut-off for TST [9–13].

In this study, we evaluated the diagnostic agreement between TST and IGRAs and tried to figure out if the use of a higher cut-off for TST increases TST specificity in immunocompromised patients.

2. Materials and methods

This is a retrospective single center study. SOT candidates and patients scheduled for anti- TNFα treatment who underwent both TST and IGRAs between 2011 and 2017 were enrolled in the study. Patients with a previous history of active TB or who were diagnosed as active TB during the tests were excluded. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study has been approved by the institutional ethics committee (Number: 13–805-17).

One-step TST was performed in the forearm according to the Mantoux method with PPD tuberculin mammalian (Manufacture by BB-NCIP, Bulgaria) and the largest induration diameter was measured 72 h later. The QuantiFERON-TB Gold In-Tube test (QFT–GIT) (Cellestis Ltd., a QIAGEN Company, Australia) was used as IGRA and was performed according to the manufacturer's instructions. QFT-GIT was performed 5 to15 days after the TST.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Age was not normally distributed. Therefore we compared the median age of two groups with nonparametric tests. The concordance of the tests was carried out by calculating the kappa coefficient value (κ) with a 95% confidence interval. Diagnostic agreement between the two tests was assessed for 5, 10, 15 mm cut-off values for all participants, SOT candidates and anti- TNFα treatment subgroups separately.

Table 2
Positive and negative rates for all participants at 5, 10, 15 mm cut-offs.

Cut-off	TST/QFT-GIT			
	−/−	−/+	+/−	+/+
5 mm	31.4%	5.8%	31.4%	31.4%
10 mm	40.9%	9.5%	21.9%	27.7%
15 mm	50.5%	19.1%	12.3%	18.1%

mm: millimeters; TST: tuberculin skin test; QFT-GIT: QuantiFeron TB-Gold In Tube.

Table 3
Positive and negative rates for solid organ transplant candidates at 5, 10, 15 mm cut-offs.

Cut-off	TST/QFT-GIT			
	−/−	−/+	+/−	+/+
5 mm	32.3%	6.5%	19.4%	41.9%
10 mm	32.3%	9.7%	19.4%	38.7%
15 mm	35.5%	19.4%	16.1%	29%

mm: millimeters; TST: tuberculin skin test; QFT-GIT: QuantiFeron TB-Gold In Tube.

3. Results

There were 111 patients who underwent both TST and IGRA. Of these, three were excluded due to a diagnosis of active tuberculosis during the tests. And three were excluded due to indeterminate result of QFT-GIT. None of the patients or control subjects were HIV-positive. All patients had BCG vaccination scarring.

Remaining 50 female and 55 male total of 105 patients were included. Of these, 74 (70.5%) patients were scheduled for anti-TNFα treatment and 31 (29.5%) were SOT candidates. In the anti-TNFα treatment group 92.8% of the patients were receiving at least one of the following: azathioprine, cyclophosphamide, prednisolone, methotrexate, leflunomide or rituximab. In the SOT group, seven patients were renal transplantation candidates and 24 were liver transplantation candidates. The median age of SOT candidates and the anti-TNFα treatment groups were 60 and 43.5 years respectively and the difference was statistically significant (p = 0.003) (Table 1).

Thirty-nine patients had a TST <5 mm. Remaining 66 patients had a TST ≥ 5 mm. Among these 66 patients, 33 had a positive and 33 had a negative QFT-GIT (Fig. 1). Positivity rates for QFT-GIT for all participants, SOT candidates and anti- TNFα treatment were 37.1%, 48.4%, 32.4%, respectively. Positivity rates for TST in all participants, SOT and anti-TNFα treatment subgroups for 5 mm cut-off were: 68.8%, 71.4% and 68.1%; for 10 mm: 49.6%, 58.1%, 45.8%; for 15 mm: 29.4%, 45.1% and 24.3%, respectively (Tables 2–4).

Percentage of TST(−)/QFT-GIT(−), TST(−)/QFT-GIT(+), TST(+)/QFT-GIT(−) and TST(+)/QFT-GIT(+) patients for different cut-off values are presented in Tables 2–4. As cut-off for TST increased, the percentage of TST(−)/QFT-GIT(+) patients increased and TST(+)/QFT-GIT(−) patients decreased in both groups. However even among the patients with a TST ≥ 15 mm, percentage of TST(+)/QFT-GIT(−) cases was 16.1% for SOT candidates and 10.8% for anti-TNFα treatment patients.

Kappa (κ) values were calculated according to 5, 10, 15 mm cut-off values. For all participants κ values were 0.303, 0.370, 0.301 respectively for 5, 10 and 15 mm cut-offs. For SOT candidates κ

Table 4
Positive and negative rates for Anti-TNFα treatment patients at 5, 10, 15 mm cut-offs.

Cut-off	TST/QFT-GIT			
	−/−	−/+	+/−	+/+
5 mm	31.1%	5.4%	36.5%	27%
10 mm	44.6%	9.5%	22.9%	22.9%
15 mm	56.8%	18.9%	10.8%	13.5%

mm: millimeters; TST: tuberculin skin test; QFT-GIT: QuantiFeron TB-Gold In Tube.

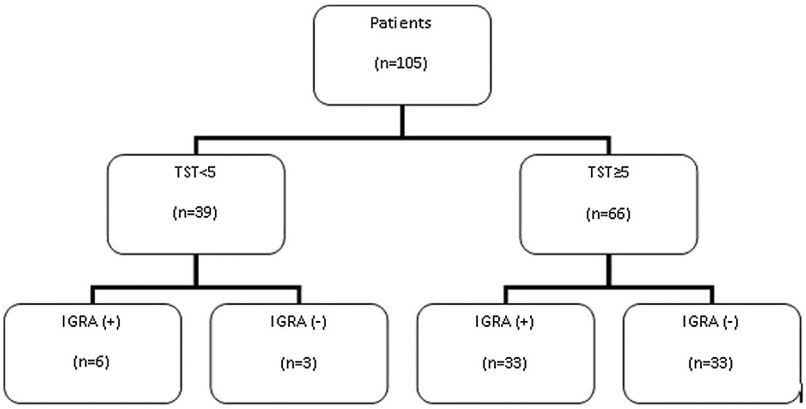

Fig. 1. Distribution of patients according to TST (tuberculin skin test) and interferon gamma release assay (IGRA) results.

values were 0.488, 0.422, 0.288 respectively. And for the anti- TNFα treatment group, κ values were 0.235 0.332 0.275 (Table 5).

In our country cost of TST is below 1 euro. We accepted as 1 euro per person. The cost of QFT-GIT per person is approximately 40 euros. We compared the direct costs of three screening strategies. TST alone, QFT-GIT alone and two-step testing first with TST and QFT-GIT as confirmation in patients with a TST ≥ 5 mm. If patients were screened only with TST, the cost was 105 euros. If tested only with IGRA, the cost was 4200 euros. With two-step strategy, 39 patients would be tested only with TST (39 euros) and remaining 66 patients would be first tested with TST (66 euros) and then with IGRA (2640 euros) (Fig. 1). As a result, the total cost of two-step testing was 2745 euros. Direct costs of two-step strategy were 34.6% less than QFT-GIT alone strategy.

Percentage of patients that require preventive treatment according to TST alone, IGRA alone and two-step strategies were 62.9%, 37.1%, 31.4% respectively (Fig. 1).

4. Discussion

In this study, we evaluated the diagnostic agreement between TST and QFT-GIT at different cut-off values in immunocompromised patients with BCG vaccination history. In our study, for a cut-off of 5 mm, diagnostic agreement between the two tests was poor for both SOT candidates and anti-TNFα groups. Diagnostic agreement increased slightly at 10 mm cut-off in the anti-TNFα treatment group, but in SOT candidates there was an inverse correlation between TST cut-off and κ values. In both groups, higher cut-off for TST didn't improve agreement and resulted in decreased sensitivity and higher false negative rates for TST.

There are a few studies comparing diagnostic agreement between IGRAs and TST at different cut-off values in immunocompromised patients. Manual et al. [14] reported a high concordance between tests in patients awaiting liver transplantation. However, diagnostic agreement decreased as cut-off was increased to 10 mm from 5 mm. The% agreement and κ values were 85.1% (κ = 0.60) and 82.2% (κ = 0.48) for cut-off values of 5 and 10 mm respectively. Among these patients, 82% were BCG vaccinated and vaccination was not associated with a discordant result. Hanta et al. [15] reported low agreement between the two tests in patients with rheumatologic diseases prior to anti- TNFα treatment. There wasn't correlation between cut-off values and diagnostic agreement. TST and IGRA positivity were significantly lower in those who received immunosuppressive treatment. In this study, 92% of patients were vaccinated. As expected, false positivity rates decreased with higher cutoff values. However, false negative results increased. Also, Lin et al. reported poor concordance between the TST and IGRA at any TST cutoff values, in HIV-infected patients. Among these patients, 75% were vaccinated. The overall agreement between TST and QFT-GIT ranged from 75.7% to 94.3% in HIV-infected persons for TST cut-offs varying between 5 mm and 15 mm, and the concordance was fair (k < 0.5). In this study BCG vaccination was the most important reason for TST(+)/QFT(−) results [16]. The authors concluded that IGRAs may be unreliable in BCG-vaccinated and/or HIV-infected persons compared to TST. On the other hand, Kurti et al. [17] showed that in BCG vaccinated inflammatory bowel disease patients, higher cut-off values for TST improve the diagnostic agreement with moderate-to-good kappa values if TST cut-off was ≥15 mm (kappa: 0.39–0.41). However, the authors didn't find any association between immunosuppressive treatment and TST or IGRA positivity.

Studies have shown that in patients who received BCG, TST may be false positive [3]. The timing of vaccination and type of TST affect the TST reactivity. For example, compared to PPD, RT 23 is much more likely to be associated with positive TST [18]. Among the subjects who were vaccinated in infancy, TST is not affected by BCG 10 to 15 years after vaccination and TST of 10–15 mm can be accepted as true positive [18,19]. However, vaccination after infancy or repeated vaccination resulted in longer positive TST reactivity despite waning [18–20].

In our country, BCG vaccination is mandatory and given twice, first during infancy and second at school age. And estimated TB incidence rate per 100,000 persons was 18 in 2015 [21]. Majority of the discordant results were TST (+)/QFT-GIT(−) patients in our study. It was 19.4% for SOT candidates and 36.5% for patients scheduled for anti-TNFα treatment. For a cut-off of 15 mm, there were still TST (+)/QFT-GIT(−) patients in both groups. We think that the main reason for the false positive TST results even at a cut-

Table 5
Diagnostic agreement between TST and QFT-GIT.

		Concordance	κ
Solid organtransplant candidate	5 mm	74.2%	0.488
	10 mm	77.4%	0.422
	15 mm	64.5%	0.288
Anti- TNFα treatment Group	5 mm	58.1%	0.235
	10 mm	67.6%	0.332
	15 mm	70.3%	0.275
All participants	5 mm	62.9%	0.303
	10 mm	68.6%	0.370
	15 mm	68.6%	0.301

mm: millimeters; TST: tuberculin skin test; QFT-GIT: QuantiFeron TB-Gold In Tube.

off of 15 mm is vaccination after infancy. As mentioned above, the rate of TST (+)/QFT-GIT(−) patients was nearly double in the anti-TNFα treatment group compared to SOT candidates. The median ages of SOT candidates group and the anti-TNFα treatment group were 60 and 43.5 years respectively. And this difference was statistically significant ($p = 0.003$). The time interval between the last vaccination and TST was shorter in Anti- TNFα treatment group. Therefore the effect of BCG on TST might be more prominent in the anti-TNF treatment group due to their younger age.

False negative TST is another problem in immunocompromised patients. Despite opposing results [17], studies showed that screening tests,especially TST, is affected by the underlying immunosuppressive disease or drugs [15,16,22–24]. In our study, there were two different groups with different levels of immunosuppression. In the SOT candidates group, most of the patients were awaiting liver transplantation. Compared to end-stage renal diseases, chronic liver disease patients have a lesser degree of immunosuppression. On the other hand, in the anti-TNFα treatment group, 92.5% of patients received at least one immunosuppressive drug and the level of immunosuppression in this group was expected to be higher compared to SOT candidates. Thus, we expected to see higher rates of TST(−)/QFT-GIT(+) patients in this group compared to SOT candidates. However, the percentage of TST(−)/QFT-GIT(+) patients were similar in groups, both below 10%. There are two possible explanations for this situation. First is BCG vaccination. And the second is the younger age of Anti-TNFα treatment group. Among the 39 patients with a TST < 5 mm, 33 were also IGRA (−) (Fig. 1). But higher cut-off values increased the TST(−)/QFT-GIT(+) patients in both groups.

Many cost-effectiveness studies have been published. These studies performed cost analysis using a computer-based analysis model and compared the direct costs of the tests as well as the costs of probable consequences of different screening strategies. For instance, they compared the cost of diagnosis and treatment of LTBI and active TB; prices of laboratory tests, hospital visits between different screening strategies. Most of these studies support IGRA alone or two-step testing: first TST and then IGRA for confirmation [25–27]. However, some studies concluded that due to the higher cost of IGRAs, TST is the most cost-effective screening method [28].

We only compared the direct costs of the tests. These analysis don't include the cost of second hospital visit for reading of TST. Therefore, according to our study,due to its very low price, TST alone was the least expensive screening strategy as expected. Two-step testing was second and IGRA alone was the most expensive strategy. However, if TST alone is selected as a screening strategy, 62.8% of patients will receive preventive treatment. This rate was 37.2% for IGRA alone and 31.4% for the two-step strategy. This means if screening is solely based on TST, most of the population in countries where BCG is mandatory should receive preventive treatment. This may cause to unnecessary treatment, waste of resources, resistance to anti-TB drugs and complications related to treatment. Thus, It seems reasonable to prefer one of the IGRA alone or two step screening strategies.

Our study suggests that, compared to IGRA alone, two-step testing strategy,first with TST and QFT-GIT as confirmation if TST ≥ 5 mm, prevents unnecessary testing with high-cost IGRAs. And also requires fewer preventive treatment. However, 5.4% of the anti-TNFα treatment group and 6.5% of the SOT candidate group were TST(−)/QFT-GIT(+). As a result, with two step strategy, false negative results will increase and these patients would be undiagnosed and wouldn't receive preventive treatment despite they require according to current guidelines.

What is the risk of progression to active TB for screening negative patients? Studies revealed that both TST and IGRAs have low positive predictive value. Furthermore, negative predictive value is low especially in immunocompromised patients [29]. Therefore, a negative test does not rule out the progression to active TB. Regarding the risk of progression to active TB, IGRAs were not superior to TST [24,30,31]. Nonetheless, some researchers claim that active TB cases that occur among the screening negative individuals have a negligible impact on TB control [32]. Progression to active TB is affected by many factors such as underlying disease and local incidence of active TB [7,24].

The new evidence-based guidelines published by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA)/Centers for Disease Control and Prevention (CDC) recommend that there are insufficient data to recommend either TST or IGRA as the first-line diagnostic test for individuals who are likely to be infected with *Mtb* and have a high risk of progression to disease. Immunocompromised patients are included in this group [7]. However specific guidelines for immunocompromised patients recommend IGRAs over TST for SOT candidates and patients scheduled for anti- TNFα treatment with a history of BCG vaccination [33–35].

Each strategy has its benefits and limitations. Clinicians have to balance the costs and the risks of unnecessary treatment with effective screening of LTBI. The incidence of active TB, availability and the costs of the tests are important while deciding the screening strategy.

There are a few limitations of our study. This is a retrospective study with a heterogeneous cohort. Level of immunosuppression and underlying immunosuppressive diseases are different within the groups. There were a small number of SOT candidates. And not performing tests concomitantly might affect the results especially IGRA positivity.

5. Conclusions

As a conclusion, in BCG vaccinated immunocompromised patients, increasing the cut-off does not improve agreement between TST and QFT-GIT. There were TST(+)/QFT-GIT(−) patients even at a TST ≥ 15 mm. Agreement between two tests was poor regardless of cut-off value.

Conflict of interests

The authors declare no conflict of interests.

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