Advances in Medical Sciences 63 (2018) 237–241

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

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?

Serhat Erol*, Fatma Arslan Ciftci, Aydin Ciledag, Akin Kaya, Ozlem Ozdemir Kumbasar

Ankara University School of Medicine, Department of Pulmonary Diseases, Ankara, Turkey

ARTICLE INFO

Article history:
Received 29 May 2017
Accepted 14 December 2017
Available online xxx

Keywords:
Latent tuberculosis infection
Immunocompromised
Tuberculin skin test
Solid organ transplantation

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].

* Corresponding author at: Department of Pulmonary Diseases, Ankara University School of Medicine, Ankara Universitesi Tip Fakultesi Cebeci Kampusu Goğus Hastaliklari ABD, Mamak/Ankara, Turkey. Tel.: +90 312 5956560; fax: +90 312 3190046.

E-mail addresses: serol@ankara.edu.tr (S. Erol), fciftci@ankara.edu.tr (F.A. Ciftci), aciledag@ankara.edu.tr (A. Ciledag), akaya@medicine.ankara.edu.tr (A. Kaya), okumbasar@ankara.edu.tr (O.O. Kumbasar).

https://doi.org/10.1016/j.advms.2017.12.001
1896-1126/

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.

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

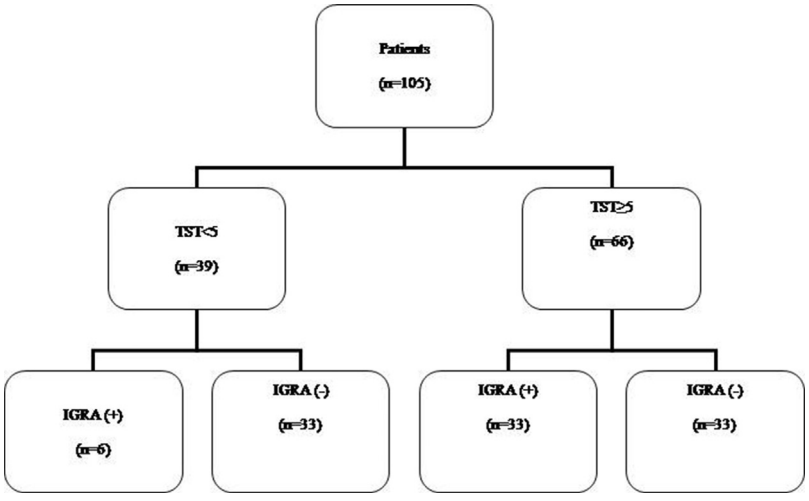

Fig. 1. Distribution of patients according to TST (tuberculin skin test) and IGRA (interferon gamma release assay) results.