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REVISED ARTICLE**TITLE:****Tuberculin Skin Test – outdated or still useful for Latent TB Infection screening?****AUTHORS:**

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HIGHLIGHTS

- Tuberculin skin test (TST) is over a century old but it continues to be used widely.

- When IGRAs were introduced it was anticipated that they would rapidly replace TST.
- Neither TST nor IGRAs have a high accuracy for predicting active TB.
- Latest WHO recommendation are that either TST or IGRA can be used to test for LTBI.
- TST will be clinically useful until more accurate tests become available.

ABSTRACT

Objective: To make an informed viewpoint on the usefulness of Tuberculin Skin test (TST) compared to Interferon Gamma Release Assays (IGRAs) for diagnosis of Latent TB Infection (LTBI) in different geographical settings.

Methods: We reviewed the current literature on TST compared to IGRA, including national implementation of WHO LTBI recommendations and retrospective data over the past 7 years at the National Institute for Infectious Diseases “L. Spallanzani” as indirect indicator of usage of both tests under actual programmatic conditions.

Results: Current national guidelines vary considerably, reflecting the uncertainty and rapidly evolving evidence about the potential use of these tests. Data from Institute “L. Spallanzani” showed IGRA concordance in TST positive subjects only in 54.74% of subjects, while there was strong concordance between two tests in TST negative subjects (93.78%).

Conclusion: Neither IGRAs nor TST can distinguish active TB from LTBI. TST will continue to be clinically useful in low and high TB endemic areas until more accurate and predictive tests will become available. Clinical judgment remains fundamental in choosing between IGRA/TST tests and interpreting their results.

Introduction

Whilst the tuberculin skin test (TST) (better known as the Mantoux Test to older generation physicians), is over a century old, it continues to be used in high endemic TB settings as diagnostic tool for determining latent *Mycobacterium tuberculosis* (MTB) infection (LTBI) (1). WHO define latent tuberculosis infection as “a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB”. The TST measures delayed type hypersensitivity (DTH) response to intradermal injection of purified protein derivative (PPD), a crude mixture of several mycobacterial antigens, which are common to *M. tuberculosis*, *M. bovis* BCG, and non-tuberculous mycobacteria (NTM). Thus, a positive TST test is of low specificity and cannot differentiate between *M. tuberculosis* infection, prior BCG vaccination, infection with, or exposure to NTM. It also has a low sensitivity in individuals with immunosuppression such as people living with HIV. Operational limitations of test include requirement for two visits up to 72 hours apart, between initial intradermal injection of PPD to reading the skin PPD-DTH response, reader variability, and the need for trained personnel to read the test results.

Interferon- γ release assays versus TST

While TST encompasses antigens recognized by a vast pool of circulating T lymphocytes, the two interferon- γ release assays (IGRAs), the QuantiFERON-TB $\text{\textcircled{R}}$ assay (Cellestis Limited, Australia) and T SPOT-TB $\text{\textcircled{R}}$ (Oxford Immunotec, UK), focus on interferon- γ responses to epitopes from two specific MTB complex associated antigens, namely ESAT-6 and CFP-10. When IGRAs were introduced into clinical practice a decade ago, it was anticipated that they would rapidly replace TST which would become redundant. The reasons were that: IGRAs do not cross-react with BCG, they are less likely to cross-react with NTM and they require only one health-care visit during which a blood sample is drawn and results can be available within 24 hours. Disadvantages of IGRAs are that they require blood samples and a laboratory to process them, quickly after collection (2). While hundreds of papers have been published on comparing performance of TST and IGRAs much remains unknown about the efficacy of IGRAs relative to TST due

methodological limitations, the lack of a compactor gold standard for detecting LTBI and the small sample size and inadequate statistical power (3). IGRAs appear to have a higher specificity than TST in persons vaccinated with BCG, although they have similar sensitivity to TST.

TST versus IGRAs for predicting the risk of LTBI progressing to active TB disease

A large prospective cohort study in the United Kingdom showed that positive IGRAs were significantly better than the TST-10 mm and TST-5 mm strategies in predicting the development of active TB among high-risk individuals from TB-endemic countries. TST-5 mm identified a higher proportion of participants who progressed to active TB (64 [83%] of 77 tested) than all other tests and TST thresholds ($\leq 75\%$) (4). Several published studies have addressed these issues with different results and conclusions: Pai and coll. reported a pooled specificity of 99% among non-BCG vaccinated and 96% among BCG-vaccinated low-risk groups (5). Vesembeth and colleagues assessed the diagnostic accuracy (21% of controls showed test results above 0.35 IU/mL) of the latest generation IGRA in low-incidence areas in Germany (6). In a recent meta-analysis by Sester and colleagues not restricting studies on specificity to low-risk groups (a situation that is closer to the clinical setting), the specificity of QFT-GIT was only 0.79 (95% CI 0.75–0.82). (7). Rangaka and colleagues' systematic review and meta-analysis showed neither TST nor IGRAs have a high accuracy for predicting active TB (8).

Latest WHO guidelines for use of TST and IGRAs

The WHO guidelines Group for developing the WHO LTBI management guidelines (WHO, 2018) utilized five IGRA and TST studies from high-TB incidence countries estimated pooled Risk Ratios for test positives and test negatives for each test and found RR 1.49 for TST and 2.03 for IGRA. They concluded that neither test is better for predicting progression to active TB disease and that TST remains an acceptable option for children of less of five years old (1). In HIV-infected individuals, a recent review of comparative

data did not provide robust evidence to support the assertion that the IGRAs are superior to the TST when used in HIV infected subjects without evidence of active TB (9).

Generic WHO recommendation are that either TST or IGRA can be used to test for LTBI. Persons with no known risk factors for TB may be considered for treatment of LTBI if they have a positive skin reaction to the TST of 15 mm or larger.

There is no strong evidence that one test should be preferred over the other to predict progression to active TB disease. IGRAs or TST in clinical practice should be guided by considerations of availability, cost and benefits, and resources (1). European Centre for Disease Prevention and Control's evaluation of cost-effectiveness of screening, from the healthcare perspective, was in favor of using TST, and if positive followed IGRA (10). An official CDC health update highlighted higher costs associated at the use of the IGRA blood tests as substitute for TSTs (11). Other countries, such as England, recommend using TST in BCG- vaccinated subjects. (12)

National guidelines for use of TST or IGRAs

Current national guidelines vary considerably, reflecting the uncertainty and rapidly evolving evidence about the potential uses of these tests (13). In deciding whether to use the TST, IGRAs individual clinical expertise and the best available local evidence are essential tools for developing local guidelines. At the National Institute for Infectious Diseases "L. Spallanzani" in Rome since several years, a protocol for the management of tuberculosis (available at http://www.inmi.it/protocolli_e_linee_guida.html), based on WHO and ECDC recommendations, was adopted. The protocol recommends the use of IGRAs tests in subjects vaccinated with BCG (or coming from countries where the vaccination is routinely performed), in immunosuppressed patients (HIV, especially if $CD4 + <200/ mmc$, or taking immunosuppressive drugs), children >5 years and, according to the clinician opinion, as a TST confirmation test. Observational routinely collected health data in the last 7 years have been evaluated as indirect indicator of test's performance under real-life conditions and are summarized hereafter as end-users' report.

From January 2011 to November 2018, in 6,132 subjects TST (PPD-S 5UI) had been performed with 1,329 positive tests after 72 hours (21.67%). Applying this protocol, IGRA (QuantiFERON-TB ®) test was performed in 346 subjects from this cohort, with 88 positive results (25,43%). Data reported in Table 1 demonstrate clinical use of IGRA test as a confirmatory test in 60.40% of TST- subjects and in 39.60% of TST+ subjects. While IGRA concordance in TST+ve subjects was observed in 54.74% of subjects, data showed strong concordance between two tests in TST-ve subjects, in which group HIV/Immunosuppressed patients are mostly represented. These data are consistent with the local protocol statement who suggest carefully evaluate negativity of TST/IGRA in immunosuppressed patients, especially in ruling out active TB. In our experience, although not in a very large number of patients, IGRAs were able to identify 13 out of 209 individuals (6.22%) candidates to LTBI treatment who were TST negative. These data must be interpreted cautiously considering high variability of context in real life, and need to be confirmed by further studies. In fact, choice of one test or both and interpretation of their results need to be defined considering the clinical or epidemiological characteristics of the subjects, available resources and turn-round time.

Conclusion

Clinical use of the TST as opposed to IGRAs should be according to availability of reagents, resources, national recommendations, specific clinical scenario. Clinical judgement remains fundamental in selecting the LTBI tests, interpreting the results of IGRA/TST tests. The ultimate test awaited is one that can more specifically distinguish active TB from LTBI. The use of IGRAs has increased in low TB endemic areas but TST will continue to be clinically useful in low and high TB endemic areas, until more predictive tests become available to allow for identification of individuals at the highest risk of progressing to developing active TB diseases.

Conflicts of Interest: All authors declare no conflict of interest

Contributions

FNL, AZ and GI conceived the idea and developed key concepts in the manuscript, contributed to the literature review, the first draft and revisions of the manuscript. GG, PMe, FP collected and analyzed data, contributed to the literature review, the first draft and revisions of the manuscript. SM, PMw, JC contributed to the original text and subsequent revisions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

All enrolled patients provided written informed consent to the utilization of anonymous clinical data for research purpose approved by L. Spallanzani Institute Ethical Committee.

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References

1. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. fLicence: CC BY-NC-SA 3.0 IGO. Available at apps.who.int/iris/bitstream/10665/260233/1/9789241550239-eng.pdf. [Accessed November 29, 2018].
2. Wilson FA, Miller TL, Stimpson JP. Mycobacterium Tuberculosis Infection, Immigration Status, and Diagnostic Discordance: A Comparison of Tuberculin Skin Test and QuantiFERON-TB Gold In-Tube Test Among Immigrants to the U.S. *Public Health Rep* 2016; 131: 303-10.
3. LoBue P A, Castro K G. Is it time to replace the Tuberculin skin test with a blood test? *JAMA* 2012; 308: 241-2.
4. Abubakar I, Drobniewski F, Southern J, et al. Prognostic value of interferon- γ gamma release assays and tuberculin skin test in predicting the development of active tuberculosis: the UK PREDICT tuberculosis cohort study. *Lancet Infect Dis* 2018; 18: 1077-87. doi: 10.1016/S1473-3099(18)30355-4.
5. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008; 149: 177-84.
6. Vesenbeckh SM, Schönfeld N, Mauch H, et al. The use of interferon gamma release assays in the diagnosis of active tuberculosis. *Tuberc Res Treat* 2012; 2012:768723. doi: 10.1155/2012/768723.
7. Sester M, Sotgiu G, Lange C, et al. Interferon- γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2011; 37: 100-11.
8. Rangaka MX, Wilkinson KA, Glynn JR. Predictive value of interferon-release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12: 45-55.
9. Overton K, Varma R, Post JJ. Comparison of Interferon- γ Release Assays and the Tuberculin SkinTest for Diagnosis of Tuberculosis in Human Immunodeficiency Virus: A Systematic Review. *Tuberc Respir Dis* 2018; 81: 59-72.

10. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm: ECDC; 2011. Available at <https://ecdc.europa.eu/en/publications-data/public-health-guidance-use-interferon-gamma-release-assays-support-tb-diagnosis>. [Accessed December 9, 2018].
11. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. IGRA Expert Committee. Centers for Disease Control and Prevention (CDC). Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection-United States, 2010. *MMWR Recomm Rep* 2010; 59: 1-25.
12. National Institute for Health and Clinical Excellence. NICE guidelines: Tuberculosis; 13 January 2016. Available at <https://www.nice.org.uk/guidance/ng33/resources/tuberculosis-1837390683589>. [Accessed November 25, 2018].
13. Denkinger CM, Dheda K, Pai M. Guidelines on interferon- γ release assays for tuberculosis infection: concordance, discordance or confusion? *Clin Microbiol Infect* 2011; 17: 806-14.

Table 1. Concordance of TST and IGRA results among subjects referred at National Institute for Infectious Diseases Lazzaro Spallanzani in Rome

	IGRA +	IGRA -	TOTAL
TST+ n. (%)	75 (54.74%)	62 (45.26%)	137 (39.60%)
	BCG Vaccinated 45 Clinician opinion 26 HIV/Immunosuppressed 4 Children > 5 years 0	BCG Vaccinated 39 Clinician opinion 22 HIV/Immunosuppressed 1 Children > 5 years 0	BCG vaccinated 84 Clinician opinion 48 HIV/Immunosuppressed 5 Children > 5 years 0
TST- n. (%)	13 (6.22%)	196 (93.78%)	209 (60,40%)
	BCG Vaccinated 2 Clinician opinion 8 HIV/Immunosuppressed 3 Children > 5 years 0	BCG Vaccinated 74 Clinician opinion 102 HIV/Immunosuppressed 20 Children > 5 years 0	BCG Vaccinated 76 Clinician opinion 110 HIV/Immunosuppressed 23 Children > 5 years 0
IGRA n. (%)	88 (25.43%)	258 (74.57%)	346

TST: Tuberculin Skin Test

IGRA: interferon- γ release assay (QuantiFERON-TB Gold In-Tube)

BCG: Calmette Guèrin Bacillus