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Tuberculin skin test – Outdated or still useful for Latent TB infection screening?

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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 a diagnostic tool for determining latent *Mycobacterium tuberculosis* (MTB) infection (LTBI) (World Health Organization, 2018). 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*, *Mycobacterium 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 h 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.

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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® assay (Cellestis Limited, Australia) and T SPOT-TB® (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 h. Disadvantages of IGRAs are that they require blood samples and a laboratory to process them, quickly after collection (Wilson et al., 2016). 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 (LoBue and Castro, 2012). 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 (≤75%) (Abubakar et al., 2018). Several published studies have addressed these issues with different results and conclusions: Pai et al. reported a pooled specificity of 99% among non-BCG vaccinated and 96% among BCG-vaccinated low- risk groups (Pai et al., 2008). Vesembecth et al. 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 (Vesenbeckh et al., 2012). In a recent meta-analysis by Sester et al. 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) (Sester et al., 2011). Rangaka et al. systematic review and meta-analysis showed neither TST nor IGRAs have a high accuracy for predicting active TB (Rangaka et al., 2012).

Latest WHO guidelines for use of TST and IGRAs

The WHO guidelines Group for developing the WHO LTBI management guidelines (World Health Organization, 2018) utilized five IGRA and TST studies from high-TB incidence countries and 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 than five years old (World Health Organization, 2018). 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 (Overton et al., 2018).

Generic WHO recommendations 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 (World Health Organization, 2018). 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 (European Centre for Disease Prevention and Control, 2011). An official CDC health update highlighted higher costs associated with the use of the IGRA blood tests as substitute for TSTs (Mazurek et al., 2010). Other countries, such as England, recommend using TST in BCG- vaccinated subjects (National Institute for Health and Clinical Excellence, 2016).

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 (Denkinger et al., 2011). 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, for 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, has been adopted. The protocol recommends the use of IGRA tests in

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	BCG vaccinated 39	BCG vaccinated 84
	Clinician opinion 26	Clinician opinion 22	Clinician opinion 48
	HIV/immunosuppressed 4	HIV/immunosuppressed 1	HIV/immunosuppressed 5
	Children > 5 years 0	Children > 5 years 0	Children > 5 years 0
TST− n. (%)	**13 (6.22%)**	**196 (93.78%)**	**209 (60.40%)**
	BCG vaccinated 2	BCG vaccinated 74	BCG vaccinated 76
	Clinician opinion 8	Clinician opinion 102	Clinician opinion 110
	HIV/immunosuppressed 3	HIV/immunosuppressed 20	HIV/immunosuppressed 23
	Children > 5 years 0	Children > 5 years 0	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.

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), in 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 an indirect indicator of test performance under real-life conditions and are summarized hereafter as end-users' report.

From January 2011 to November 2018, in 6132 subjects TST (PPD-S 5UI) had been performed with 1329 positive tests after 72 h (21.67%). Applying this protocol, the 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 the IGRA test as a confirmatory test in 60.40% of TST- subjects and in 39.60% of TST+ subjects. While IGRA concordance in TST+ subjects was observed in 54.74% of subjects, data showed strong concordance between two tests in TST− subjects, in which group HIV/Immunosuppressed patients are mostly represented. These data are consistent with the local protocol statement which suggests carefully evaluating the 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 (6.22%) candidates for LTBI treatment who were TST negative. These data must be interpreted cautiously considering the high variability of context in real life, and need to be confirmed by further studies. In fact, the 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, and specific clinical scenario. Clinical judgement remains fundamental in selecting the LTBI tests and 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.

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Conflict 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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