Journal of Positive School Psychology
2022, Vol. 6, No. 7, 3707-3713 http://journalppw.com

Utility Of Tuberculin Skin Test (TST) Versus Interferon Gamma Release Assay (IGRA) In Detecting Latent Tubercular Infection (LTBI) Among Patients Infected With HIV: A Review

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Abstract

The aim of this review is to compare the efficacy of tuberculin skin testing (TST) and interferon gamma release assay (IGRA) in detecting latent tuberculosis in patients with human immunodeficiency virus infection (HIV). The diagnosis of latent TB infection in HIV patients is critical to the disease's overall control. Individuals with latent tuberculosis infection (LTBI) who get anti-tubercular medication have a lower risk of developing active tuberculosis. Because LTBI testing is used to identify people who will acquire active TB and would benefit greatly from treatment, the accuracy of these tests can only be determined by measuring their ability to predict active TB development. A study that evaluates the sensitivity,specificity and predictive values of two techniques may help clinician to personalize the treatment in HIV patients with latent TB, hence better clinical outcome.

Key words: latent tuberculosis, HIV, tuberculin skin tests, interferon gamma release assay.

I. INTRODUCTION

Around the world, two billion people are infected with Mycobacterium tuberculosis[1]. Latent tuberculosis infection (LTBI) is an M.tuberculosis infection that is not manifested clinically, bacteriologically, or radiologically. A positive tuberculin skin test (TST) can detect the majority of the asymptomatic (latent) infections. These dormant infections have the potential to resurface later. This vast reservoir of latent tuberculosis is a major source of origin of infection in the neighbourhood.

Patients having a positive tuberculin test and no additional risk factors, according to longitudinal research have a 0.1 percent chance of developing active tuberculosis every year[2]. In some circumstances, the risk is greater. Contacts of infectious tuberculosis patients who test positive for tuberculin have a 5%–10% chance of having active tuberculosis in the next two to five years, and another 5%–10% in their lifetime[3]. Old tuberculosis with lung scarring, HIV infection,organ transplantation , immunosuppression,end-stage renal failure ,diabetes mellitus and malignancies are all variables that enhance the likelihood of latent TB reactivation[4].

The diagnosis of latent tuberculosis infection (LTBI) is critical for disease control. Individuals with LTBI who get anti-tuberculous medication have a lower risk of developing active tuberculosis[5]. The TST was used to diagnose LTBI infection for many years. The latter is known to have a number of flaws that affect its sensitivity and specificity. Immune-based blood assays have recently been developed in the hopes of enhancing LTBI diagnosis.

With an estimated 1.4 million people worldwide, HIV-associated tuberculosis (TB) continues to be a major global public health concern. Co-infection with HIV makes tuberculosis diagnosis and treatment more difficult. Furthermore, rates

of drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDRTB), which are difficult to treat and contribute to higher mortality, have grown. Due to the poor performance of sputum smear microscopy in HIV-positive patients, other diagnostic techniques that are sensitive and specific and can reliably detect latent tuberculosis must be tried.

The most major risk factor for developing active TB is HIV co-infection, which increases the vulnerability to primary infection or re-infection, as well as the likelihood of TB reactivation in patients with latent TB. Detecting latent tuberculosis in HIV patients is critical because, in addition to having a deleterious impact on the immunological response to HIV, HIV progression to AIDS, and so on, it also adds to the tuberculosis disease burden.

The tuberculin skin test (TST) is commonly utilized for diagnosing latent tuberculosis infection (LTBI) . In terms of sensitivity and specificity, the latter has significant drawbacks. People who have had bacilli Calmette-Guérin (BCG) immunisation or who have been exposed to non-tuberculous mycobacteria may test positive. In individuals with reduced functioning of T-cells , false negative results with TST are common. As a result, TST results must be interpreted in light of the risk of TB infection or reactivation prior to the test. Due to anergy, many HIV-positive people may have skin test negative despite tubercular infection or illness. As a result, TST may not be a good screening test for latent TB in HIV patients.

For the diagnosis of LTBI, interferon gamma release assays (IGRA) were developed. The QuantiFERON®-TB and T-SPOT-TB Gold tests are two of them. These assays evaluate the amount of interferon gamma released when T-cells are stimulated by antigens from Mycobacterium TB. Because they are not impacted by BCG vaccination, these investigations have been demonstrated to have a higher specificity than TST. Their sensitivity was on par with the TST's, and in some instances, they showed a stronger correlation with the level of exposure. In patients with impaired immune systems, their sensitivity was greater than the TST. In those with LTBI, IGRA tests have been demonstrated to have a higher predictive value for the development of active illness.

Studies comparing the efficacy of these tests using indicators for sensitivity or specificity or a measure of exposure as the reference standard [6,7] have produced results that are not clinically applicable.It is critical to explore and compare the sensitivity, specificity, and predictive qualities of IGRA and TST in finding latent tuberculosis in HIV patients with inadequate immunity who are at higher risk of tuberculosis.As a result, the purpose of this study is to assess the sensitivity, specificity, and predictive values of TST and IGRA in diagnosing latent TB in HIV patients.

II. HIV AND TB

Tuberculosis is the commonly prevalent opportunistic illness in HIV-positive people, and patients who are co-infected are more likely to die [8,9]. The following are estimations of the burden of illness caused by tuberculosis globally in 2019: There were 9.4 million incident cases, 1.3 million HIV-negative TB fatalities, and 0.38 million TB deaths among HIV-positive . The majority of tuberculosis cases were found in Southeast Asia, Africa, and the Western Pacific (35, 30 and 20 percent , respectively). HIV infection was found in 11-13 percent of incident cases[10]. TB can develop among HIV patients at any stage and is typically the first ever sign of underlying HIV infection[11,12]. People living with HIV have a 20-fold increased chance of developing tuberculosis than people without HIV [13].As CD4 cell levels decrease, the risk of infection increases[11]. At any stage of HIV infection, active TB can occur. It not only hastens the progression of HIV infection, but also adds to the societal burden of tuberculosis. As a result, detecting latent tuberculosis in HIV patients and initiating appropriate medication regimens is critical.

III. DIAGNOSIS OF LTBI

LTBI is an M. tuberculosis infection with no clinical, bacteriological, or radiological

indications of the disease. The TST is the gold standard for LTBI diagnosis. This includes injecting pure protein derivative (PPD) into the skin, which causes a delayed-type hypersensitivity reaction that causes cutaneous induration at the injection site that lasts 48-72 hours. PPD is made up of around 200 antigens that are also seen in other mycobacteria. A positive TST implies M. TB or other non-tuberculous mycobacteria infection or recent BCG vaccination[6,7]. In many countries, the latter is usually included in the vaccination schedule and given at birth or during childhood. Ninety percent of people develop tuberculin induration of less than 10 mm 12 weeks after receiving BCG vaccination[14]. If the immunisation was administered in childhood, the reaction normally fades after a year[15]. Tuberculin reactions may last 1–5 years in the majority of patients if BCG is given after the first year of life[16]. Tuberculin reactivity might remain up to 15 years following vaccination in some cases. BCG-vaccinated subjects in any age group are more likely to have positive results of TST, according to several studies[7,17]. After BCG vaccination, the booster phenomenon is more prevalent; if the tuberculin test is performed within 1-4 weeks, 20% of individuals will test positive[18]. Stronger tuberculin reactions are observed with repeated tuberculin testing (for instance, in healthcare personnel)[19].

TST's limited specificity, particularly in subjects vaccinated with BCG, calls it a doubtful usage as a "standard" test for diagnosing latent TB. In the absence of any gold standard test for diagnosing LTBI, determining the exact specificity and sensitivity of TST is problematic. In subjects with reduced T-cell activity, TST may also be mistakenly negative. These patients are at a significant risk of getting tuberculosis, but TST's low sensitivity prevents it from being used in these cases[20].

The dose of PPD as well as variability of operators in both reading and inoculation may alter the interpretation of tuberculin skin tests[21]. A low PPD dose can result in a false negative , whereas a high dose can result in a false positive[22]. There is no international agreement on what TST positive entails. Despite its flaws, TST is nevertheless widely used due to a lack of superior options. This emphasises the importance of continuing to look for more diagnostic tests for latent tuberculosis which are more accurate.

IV. ALTERNATIVE TESTS FOR THE DETECTION OF LTBI

It is a difficult task to show that any investigation is superior to TST in the absence of a gold standard test for diagnosing LTBI. For the diagnosis of tuberculosis, immune-based blood tests were created. These are the levels of interferon gamma released in response to mycobacterial antigen stimulation of sensitised T-lymphocytes[23]. The first commercially accessible test was the QuantiFERON® TB assay, which measures interferon gamma production by ELISA following in vitro stimulation of white blood cells with PPD[24]. Two commercially available diagnostic tests that use specific antigens, ESAT-6 and CFP10, are QuantiFERON®-TB gold test and T-SPOT-TB assay [25,26].

In healthy low-risk people who had received BCG vaccination, the specificity of interferon gamma release assays was investigated. In a Japanese population with no evident risk parameters of exposure to TB and a positive vaccination status, the QuantiFERON®-TB test was found to be highly specific [27]. A study carried out in Korean population that investigated QuantiFERON®-TB Gold among healthy persons with no risk of tuberculosis found similar results[28]. In another investigation, all 50 healthy medical students (74 percent BCG vaccinated) were negative for QuantiFERON®-TB, but tuberculin test was positive in 36 percent of them[29]. These and other studies clearly show that IGRA tests are much more specific than TST for the diagnosis of LTBI [30-35].In patients with active TB and contacts of infectious TB patients, the sensitivity of IGRA testing was investigated.

TST had a sensitivity of 64–69% in this cohort, while IGRA tests were found to have a

sensitivity of 74–96% [28–30]. In contact-tracing investigations, IGRA tests were said to be as sensitive as TST for LTBI and, in some circumstances, they even better corresponded with the degree of exposure[36-38]. They also showed good specificity in contacts who had received the BCG vaccine. In the largest of these studies[36], the T-SPOT-TB test was evaluated in 535 secondary school students who had been exposed to an infectious TB case.

The majority of them had received BCG vaccinations. The degree of exposure (closeness and duration of contact) corresponded more significantly with T-SPOT-TB than TST, showing the test's better sensitivity. It was likewise unaffected by the presence or absence of BCG vaccination.

In contact tracing of 85 BCG-unvaccinated persons, QuantiFERON®-TB Gold was evaluated[39]. Its sensitivity was discovered to be comparable to TST. Other researchers were in consensus with these findings. Data on immunocompromised patients is insufficient to draw any firm conclusions.

The efficacy of IGRA tests in predicting development of TB in future has been investigated in a few studies[40]. The emergence of active disease is the evidence for LTBI. This can only be evaluated by long-term cohort studies that monitor individuals who have been tested for tuberculosis. Diel and colleagues evaluated 601 close contacts of infectious TB patients in Germany. Of these, 278 (46.3 percent) had received the BCG vaccine. QuantiFERON® -TB Gold was positive in 66 connections and 243 contacts (about 40%) tested positive for TST (11 percent).

Only contacts who had a positive QuantiFERON®-TB test were given isoniazid. Ioniazid was refused by 41 of my contacts. All connections were tracked for a period of two years. During follow-up, six of the contacts developed active tuberculosis, and all six were QuantiFERON® positive. QuantiFERON®-TB Gold is a more accurate biomarker of LTBI and a better predictor of TB development, according to this significant study.

In comparison to TST, IGRA tests provide significant operational advantages. They simply require one blood sample visit. The bias by the reader in interpretation is reduced by automated reading. Because the test has no booster effect, repeated testing (for example, in health care employees) has no effect on the results.

Within 24 hours, the results of the test were available. A basic laboratory and certain technical expertise are required for IGRA tests. Within 6 hours of venipuncture, blood must be processed. Longer storage of samples reduces the reliability of the results. This issue is anticipated to be solved with the introduction of the QuantiFERON® in-tube assay.

The excellent specificity of IGRA tests over TST is their main advantage. In BCG-vaccinated individuals, this substantially eliminates false positive results, saving money and preventing the negative effects of unnecessary therapy. Similar to TST testing, IGRA tests are sensitive. In contact-tracing experiments, they showed a strong correlation with the level of exposure to an index case.

The IGRA tests have superior sensitivity in some studies, especially among immune-compromised patients. Because these individuals have a higher chance of developing active disease, early detection of LTBI is critical. As previously stated, IGRA testing have a number of operational advantages. However, their biggest downside is its exorbitant price. As a result, a cost-benefit analysis of these tests is required to evaluate their applicability in resource-constrained settings such as India.The question is whether IGRA tests should be used in addition to or instead of TST. The latter test is both inexpensive and effective in detecting LTBI.

For screening high-risk individuals in nations like India where the BCG vaccination rate is high, the two-step procedure (TST followed by IGRA) is probably more effective.It enhances diagnostic accuracy and lowers the number of false positives. This will almost certainly have a big positive influence on latent TB control.

Interferon gamma tests have a key role as the hunt for assay for latent TB diagnosis. More

research, particularly in immunocompromised individuals, is needed to increase their performance. To assess the effectiveness of these tests in foretelling the emergence of active TB and to show that they are superior than the TST, longitudinal investigations are also required.

V. FUTURE RESEARCH PERSPECTIVE

The validity of diagnostic methods in finding latent tuberculosis in HIV patients has received little attention in the literature. The study comparing the two approaches may show that IGRA assays can provide precision diagnosis for latent TB in HIV patients with a sensitivity greater than the tuberculin skin test. This study could emphasise the clinical validity and efficacy of IGRA testing, which could help with mass screening of HIV patients for latent TB detection. The study could focus on the use of IGRA testing to diagnose and treat latent TB in HIV patients early on, reducing the risk of transmission.

VI. CONCLUSION

Diagnosing latent tuberculosis in HIV patients is critical to the disease's overall control. Individuals with LTBI who receive anti-tubercular medication have a much lower chance of progressing to active TB. Because LTBI testing is used to identify people who will acquire active tuberculosis and would be benefited from treatment, the accuracy of these tests can only be determined by measuring their ability to predict active TB development. It could help overcome the difficulties in treating HIV patients who are at risk of tuberculosis. Early identification of latent tuberculosis may aid in lowering TB transmission and thereby disease burden in society.

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