Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Doshi J, Deokar K, Gaikwad P. **Novel tuberculosis skin tests for detecting latent tuberculosis infection.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3156

Novel tuberculosis skin tests for detecting latent tuberculosis infection

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Key words: latent TB, tuberculin skin test, C-TB test, Cy-Tb test, diaskintest.

Contributions: JD, KD, conceived the idea; JD, PG, performed the literature search; KD, PG, prepared the manuscript; KD, JD, PG, revised the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: not applicable.

Dear Editor,

We are impressed by the article titled "Latent tuberculosis diagnostics: current scenario and review" by Gupta et al. published in your journal [1]. The authors have reviewed the tests used for diagnosis of latent tuberculosis infection and have given a detailed overview of the purified protein derivative (PPD)-based tuberculin skin test (TST) and interferon γ release assays (IGRA). We would like to draw attention to the fact that in 2022, the World Health Organization has also recommended the use of *Mycobacterium tuberculosis* antigen-based skin tests for the diagnosis of latent tuberculosis (conditional recommendation, very low certainty of evidence). The MTb antigen-based skin tests that have been recommended by WHO include Cy-Tb test, Diaskintest and C-Test. All three tests are ESAT-6/CFP-10 based intradermal tests. The intradermal inoculation results in induration at the local skin site resulting in a delayed type of hypersensitivity which is measured after 48-72 hours [2].

The Cy-TB (erstwhile C-TB) test has been manufactured by Statens Serum Institute, Denmark and is now being produced and marketed by the Serum Institute of India. 0.1 ml is administered via intradermal injection using the Mantoux technique. An induration of more than or equal to 5 mm is considered positive. The Diaskintest has been manufactured by Generium Pharmaceuticals, Russian Federation. Any induration is considered positive. The C-Test or Creative TST (erstwhile EC-skin test) is manufactured by Anhui Zhifei Longcom Biopharmaceutical Co. Ltd, China. An induration of more than or equal to 5 mm is considered positive.

The pooled sensitivity of the Cy-TB test and Diaskintest against the microbiological reference standard in patients with microbiologically confirmed TB was found to be 78.1%. The specificity of the Cy-TB test, Diaskintest and C-Test with respect to IGRA has been found to be 98%, 99.1% and 95.5.% respectively [2]. In patients with active TB, the agreement of Cy-Tb and Diaskintest with IGRA have been found to be 79.8% and 87.16% respectively [3]. They have also been found to be safe and cost-effective [2].

The advantages of the novel TB skin tests include

1. As ESAT-6 and CFP-10 are present only in MTB, the results are not affected by prior BCG vaccination and exposure to environmental Non-Tuberculous Mycobacteria (NTM). Hence, all three tests have better specificity than the TST.
2. Low cost
3. Lower resource requirement - does not require state-of-the-art infrastructure
4. Can be administered by staff who are already trained in administering TST
5. Can be administered in a community setting
6. Does not require venipuncture

The disadvantages of the novel TB skin tests include

1. The result has to be interpreted after 48-72 hours, hence requires follow-up.
2. A cold chain is required for storing the vials.
3. Trained personnel required for administration and interpretation of tests, especially in areas where TST is not routinely performed.

More data with respect to the performance of these tests in HIV-positive individuals, children and adolescents is needed. Also, exploration of methods to prevent follow-up for interpretation of tests are needed to increase the acceptability of the tests and reduce cases lost to follow-up. The other novel TB skin test which is under evaluation is the DPPD test. It uses a recombinant protein produced from a gene Rv0061 which is present only in Mycobacterium Tuberculosis. Intradermal inoculation of the protein results in a delayed type of hypersensitivity resulting in skin induration. An open-label clinical trial conducted in Brazil showed that the test results correlated with that of PPD-based TST [4]. More data on the DPPD test with respect to its performance in different geographical areas, and different subpopulations and comparison with IGRA is needed.

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