C-Tb: A latent tuberculosis skin test for the 21st Century?

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The United Nations sustainable development goals have led to the development of global plans to end the tuberculosis (TB) epidemic. Individuals with latent tuberculosis infection (LTBI) are at risk of reactivation disease and onward transmission to their contacts; prompt identification of these persons before they develop infectious TB will therefore help to control the epidemic. Unfortunately, there is no gold standard test for LTBI diagnosis and existing tests have uniformly poor ability to predict which individuals will go on to develop active TB. Currently used tests are the tuberculin skin test (TST), which is relatively cheap and simple to administer in the field but can be falsely positive in people who are BCG-vaccinated or exposed to non-tuberculous mycobacteria1, and interferon gamma release assays (IGRAs), which are more specific but are costly and require specialist laboratory processing.

In The Lancet Respiratory Medicine, Morten Ruhwald and colleagues2 report an assessment of C-Tb (Statens Serum Institut, Copenhagen, Denmark), a diagnostic skin test for latent tuberculosis infection. This test is based on the Mycobacterium tuberculosis-specific RD1 antigens ESAT-6 and CFP10 that are used in IGRAs. C-Tb combines the simplicity of administering a skin test without the need for laboratory processing and high specificity because of the use of M tuberculosis-specific antigens that are not present in the BCG vaccine or most environmental mycobacteria. The authors compared C-Tb with the QuantiFERON TB Gold In-Tube (QFT) IGRA and the TST in 979 people separated into subgroups of varying degrees of risk of infection with M tuberculosis, ranging from people with no known history of exposure to tuberculosis (n=263), to occasional contacts (n=299) and close contacts (n=316) of people with tuberculosis, to patients with culture-confirmed tuberculosis (n=101), as has been used previously to assess IGRAs.3 All participants older than 5 years were tested with QFT. People were then randomised to be tested with the TST in the left arm and C-Tb in the right arm or vice versa or, in a small subgroup, C-Tb alone to test for an interaction with the TST. A trend was found towards positivity with increasing risk of infection, with concordant results seen between C-Tb and QFT in 785 (94%) of 834 participants. C-Tb, however, was classified as positive in fewer patients with tuberculosis than was QFT (68 [67%] vs 82 [81%], p=0.003). The overall safety profiles of C-Tb and TST were similar, although injection-site pain and haematoma were seen more often with C-Tb than with the TST (14% vs 2%).

Current World Health Organization recommendations encourage testing and treatment of contacts of pulmonary TB patients as well as individuals with various forms of immunosuppression, including HIV in low incidence countries, while treatment without testing is an option for children under 5 years in contact with infectious TB and for HIV infected individuals in high burden countries4. The high levels of concordance between C-Tb and QFT and the ease of administration of C-Tb raises the prospect that the new test could be used at the point of care to diagnose LTBI with increased specificity, thus reducing the number of uninfected people who receive unnecessary treatment with the associated risk of adverse events such as hepatotoxicity 5.

While differences between the TST and IGRA can be attributed to BCG and non-tuberculous mycobacteria sensitisation, the reason for, and clinical significance of, discordant results between the commercial ELISA and ELISPOT versions of IGRAs remain unclear. Similarly, the reasons for discordance between C-Tb and QFT are unclear. The different route of administration between the blood based IGRA and the skin based C-Tb may explain some of the observed difference. While further research is needed to understand the difference, this modest level of discordance should not affect the practical application of the test. The lower sensitivity of C-Tb among TB patients relative to QFT suggests a better ability of the blood assay to measure the presence of interferon gamma. By contrast, a previously published study of C-Tb by the same investigators showed a comparable level of sensitivity between C-Tb and QFT in 273 recently diagnosed active TB patients (73.9% (95% CI 67.8–79.3%) for C-Tb versus 75.1% (95% CI 69.3–80.2%) for QFT) 6.

Ultimately, a major aim of tests for LTBI is to identify individuals at the highest risk of progressing to active TB. A systematic review and meta-analysis reported that the relative risk of developing active TB among IGRA positive individuals compared to negative persons was weak to moderate (about 2–3)[6]. It is unlikely that those with a positive C-Tb test will have a higher chance of progressing to active TB compared to those with a positive IGRA, as the tests use the same antigens. A further limitation of a skin test is the requirement for a return visit to read the size of the induration. Innovative healthcare delivery methods utilising new technologies could allow reading of the skin test immune response without direct healthcare contact, reducing loss to follow-up and encouraging appropriate treatment where necessary.

Ruhwald and colleagues found a higher level of injection site haematomas with C-Tb compared to TST (14% vs. 2%). While this is not a serious adverse event, further data from larger studies are needed to confirm whether there is an increased risk of haematomas in post marketing surveillance.

C-Tb potentially provides an upgrade to the diagnosis of LTBI by combining the specificity of IGRA with the logistical simplicity of TST. Further research into operational, economic and predictive aspects of C-Tb, including cost-effectiveness and acceptability, will allow a fuller assessment of its potential use in TB control programmes in different epidemiological settings – for example, in settings with different burdens of TB, HIV and co-morbidities. In the meantime, the search for a highly predictive assay for LTBI continues.

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