International Journal of Infectious Diseases (2008) 12, e1—e6

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REVIEW

Interferon-gamma release assays (IGRAs) in high-endemic settings: could they play a role in optimizing global TB diagnostics? Evaluating the possibilities of using IGRAs to diagnose active TB in a rural African setting

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Received 15 February 2008; accepted 25 March 2008
Corresponding Editor: William Cameron, Ottawa, Canada

KEYWORDS
Tuberculosis;
Interferon-gamma release assays;
Sub-Saharan Africa;
Epidemiology

Summary The number of patients suffering from tuberculosis (TB) globally is increasing. Due to the HIV epidemic, most patients suffering from TB reside in sub-Saharan Africa. In order to improve TB diagnostics, new tests — interferon-gamma release assays (IGRAs) — have been developed over the last decade. In this paper we evaluate the possible use of these tests in diagnosing or excluding active TB in high HIV-burden, resource-limited settings. The inability to differentiate between active and latent TB, limited data on IGRA performance in HIV-infected patients, observed false-negative results, high costs, and logistic problems limit the potential benefit of IGRAs. We also present two theoretical study designs in order to further assess IGRAs. Setting up a study on this subject is complicated by the frequent unavailability of mycobacterial cultures, the difficulty in acquiring prospective data, and the impossibility of denying treatment to a patient suspected of having active TB. We feel that current evidence does not support the implementing of IGRAs in clinical practice in settings with high endemic latent TB infection (LTBI) and high HIV prevalence. As these settings are the ones that suffer the most from the TB epidemic, we believe that the role of IGRAs in global TB control is questionable.

Introduction

Fuelled by the HIV epidemic, the number of tuberculosis (TB) patients in sub-Saharan Africa is increasing to almost unprecedented levels.[1,2] The majority of the HIV/TB co-infected patients reside in sub-Saharan Africa, resulting in

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1201-9712/$32.00
doi:10.1016/j.ijid.2008.03.026

high morbidity and mortality levels in that area.[3] The World Health Organization has called for ''urgent and extraordinary actions'' to control tuberculosis in Africa and launched the 'Global plan to stop tuberculosis', highlighting the need for accurate, simple, and low-cost diagnostic tests for the detection of TB infection.[4,5] In order to control the TB epidemic, the ability to make an adequate TB diagnosis in resource-limited settings is essential. However, diagnosing TB is challenging, especially in immunocompromised patients.

The gold standard test for the diagnosis of active TB is culture of *Mycobacterium tuberculosis* (MTB) in patients with signs and symptoms of active TB. In some patients it is not possible to isolate MTB from clinical specimens, or obtain clinical specimens. In HIV-positive patients with TB, an increased proportion of smear-negative and extrapulmonary disease is found.[6] Logistic reasons, such as time needed to culture MTB and costs, are additional reasons why culture is often omitted. Lacking a definite mycobacterial culture in patients suspected of having active TB, the decision to treat is often based on clinical signs and symptoms or typical findings on chest X-ray, whether or not combined with acid-fast bacilli (AFB) in sputum smear.

In 2006 the antenatal HIV seroprevalence in South Africa was 29% and the annual TB notification rate exceeded 700/100 000.[7] Because it is nearly impossible to convincingly exclude TB in primary care clinics in such a high-endemic TB country, and for fear of missing patients who are suffering from TB, the threshold to start anti-tuberculosis treatment is low. This might result in a considerable number of patients who are unnecessarily being exposed to a six-month course of tuberculostatics with the associated risks, side effects, and costs. On the other hand, a TB diagnosis may be missed in patients who are suffering from active TB, but who do not have clear symptoms (such as prolonged cough, fever, weight loss, night sweats, or lymphadenopathy) and have a normal chest X-ray and negative AFB on smears, thus running the risk of unnecessary morbidity and mortality and possibly infecting others.

The century-old tuberculin skin test (TST) has low specificity due to false-positive results in populations vaccinated with bacille Calmette—Guérin (BCG) and in patients infected with most non-tuberculous mycobacteria.[8] TST also has low sensitivity in immunocompromised patients and is therefore not recommended for this group by some of the current guidelines.[9]

In order to improve TB diagnostics and care worldwide, simple and reliable tests are needed to reduce false-positive and false-negative results (inherent in TST), equipping clinicians with more accurate tools for TB diagnosis, control, and elimination. However, the frequent inability to definitely confirm the presence of active TB by culture, hampers assessment of the accuracy of new TB tests.

Interferon-gamma release assays (IGRAs) for TB have been developed over the last decade.[10] Two IGRAs are currently commercially available, the QuantiFERON-TB Gold test (Cellestis, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Oxford, UK). Both tests measure the interferon-gamma release by sensitized lymphocytes in response to specific MTB antigens, using methods such as ELISA (QuantiFERON) and enzyme-linked immunospot assay (T-SPOT.TB). IGRAs are considered positive when the amount of produced interferon is over a certain threshold. For reliable results, normal lymphocyte function is crucial. An indeterminate test result is usually due to reduced interferon-gamma production after stimulation with a non-specific antigen (phytohemagglutinin), resulting in a failed positive control. This often reflects underlying immunosuppression.[10]

As IGRAs are based on the cellular immune response, they are incapable of distinguishing between a latent and an active TB infection.

In our view, IGRAs are of little value in diagnosing or excluding active TB in high HIV-burden, resource-limited settings — areas where the TB epidemic rages most fiercely. We describe below the reasons why we believe this is the case, briefly summarize current evidence, and discuss theoretical study designs in order to further assess IGRAs in such settings.

Sensitivity and specificity of IGRAs

A number of papers on IGRA performance have been published. Sensitivity has been estimated by testing people with a confirmed pulmonary TB and specificity has been calculated in low-endemic countries with a high BCG vaccination rate. For immunocompetent patients, sensitivity is estimated to be between 83% and 97% for the T-SPOT.TB test and between 70% and 89% for the QuantiFERON-TB Gold test.[11—16] Specificity would be 96—98% for the QuantiFERON-TB Gold test and might be even higher for the T-SPOT.TB test.[11,12,17,18] Lacking a gold standard for the diagnosis of a latent TB infection (LTBI), most studies have compared IGRA results to the results of TSTs.[11—14,16,17] They have shown higher specificity (especially in BCG-vaccinated populations) and sensitivity rates for the IGRAs as compared to the TST. This is an important advantage of IGRAs over the TST, as BCG vaccine coverage is high in many sub-Saharan African countries. In South Africa, for example, coverage is over 95%.[19]

Diagnostic research on IGRAs

These studies, however, could all be seen as 'test research' as opposed to 'diagnostic research'. In test research, studies merely focus on the 'characteristics' of a test, such as sensitivity and specificity, instead of on the test's performance to confirm or exclude a diagnosis. Diagnostic research, on the other hand, refers to studies that aim to quantify a test's added contribution beyond test results readily available to the physician in determining the presence or absence of a particular disease, in this case TB.[20] A single test's sensitivity and specificity are of limited value in practice as they reflect the probability that a particular test result is positive or negative given the presence (sensitivity) or absence (specificity) of a disease. In practice, however, one is interested in the probability of having a particular disease given the test result. In order to determine whether or not a person is suffering from TB, a test has to truly increase, or decrease, the probability of disease presence as estimated from the previous data, such as clinical signs and symptoms, X-rays, and sputum tests. The 'post-test probability' should be greater or smaller than the 'pre-test probability'.[21] If such a test were available and affordable for TB, it would be of great value in high-endemic countries.

When setting up diagnostic research in order to calculate what added value implementing IGRAs in a sub-Saharan