Time for a change? Updated guidelines using interferon gamma release assays for detection of latent tuberculosis infection in the office setting

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Treatment with tumor necrosis factor-alfa inhibitors and other systemic medications increases the risk of reactivating a latent tuberculosis (TB) infection. Therefore, screening for latent TB infection is important in dermatology patients eligible for treatment with these medications. Although the tuberculin skin test (TST) has its limitations, it has been the standard choice for diagnosis of latent TB infection. Since the development of interferon gamma release assays (IGRAs), the role of the TST has been re-evaluated and IGRAs have increasingly been incorporated into national guidelines. Although there are situations when either test may be performed, in individuals who have received a BCG vaccination and in those who are unlikely to return for a TST reading, IGRAs may be particularly helpful in distinguishing patients at risk for TB. This article discusses the advantages and disadvantages of both the TST and the IGRA and presents a summary of the Centers for Disease Control and Prevention 2010 guidelines for using IGRAs. (J Am Acad Dermatol 2012;66:148-52.)

Key words: anti–tumor necrosis factor; interferon gamma release assay; latent tuberculosis; psoriasis; screening.

Latent tuberculosis (TB) infection (LTBI), a condition during which an individual is infected with *Mycobacterium tuberculosis* (MTB) organism but is not symptomatic, affects approximately 11 million US residents, and approximately 2 billion persons worldwide.[1] LTBI differs from active TB in that individuals with active TB are symptomatic with unexplained weight loss, fever, and cough. Those persons who are immunocompromised are at a greater risk of developing active TB than those who are not[2] and individuals on biologics, even more specifically, on anti–tumor necrosis factor (TNF)-alfa agents are at a high risk of progression from LTBI to active TB.[3,4] In the developed world, TB is primarily controlled through targeted screening, identification, and treatment of individuals with LTBI. Before 2001, the tuberculin skin test (TST) was the only available test to aid in the detection of LTBI. As such, the TST, although not a gold standard for diagnosis, had been the standard choice during the last century.[1] Things have dramatically changed since then and dermatologists need to be aware of these updates, as screening for LTBI is critical in patients with psoriasis eligible for treatment with anti–TNF-alfa agents, given the risk of reactivation in this population.[5]

Abbreviations used:

BCG:	Bacillus Calmette-Guerin
CDC:	Centers for Disease Control and Prevention
IGRA:	interferon gamma release assay
LTBI:	latent tuberculosis infection
MTB:	*Mycobacterium tuberculosis*
QFT-G:	QuantiFERON tuberculosis Gold test
TB:	tuberculosis
TNF:	tumor necrosis factor
TST:	tuberculin skin test

In the past 10 years, 4 interferon gamma release assays (IGRAs) have been approved by the US Food and Drug Administration to assist in diagnosing both latent and active TB. These include the QuantiFERON-TB test (Cellestis Ltd, Carnegie, Australia), the QuantiFERON-TB Gold test (QFT-G)

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(Cellestis Ltd), the QuantiFERON-TB Gold In-Tube test (Cellestis Ltd), and the T-SPOT.TB test (Oxford Immunotec Ltd, Oxford, United Kingdom).[1] These in vitro blood tests measure the production of interferon gamma by T cells exposed to certain antigens, including early secretory antigen target-6, and culture filtrate protein-10, which are specific for MTB. As a result, these whole-blood IGRAs assess the immune response to antigens not found in either the Bacillus Calmette-Guerin (BCG) vaccine or most nontuberculous mycobacteria, thus offering more specificity than the TST in diagnosing latent TB. Although false-negative results may result with use of IGRAs, for LTBI, IGRAs have a higher sensitivity than the TST,[5,6] particularly in an immunocompromised population.[7] Other advantages include the convenience of only one required patient visit, availability of results within 24 hours, and that IGRAs do not boost responses measured by subsequent tests. Limitations of IGRAs include errors in blood collection or transport, the need for blood processing within 8 to 16 hours of sample collection, and difficulty diagnosing active TB. Additionally, there is limited data to predict who with a positive IGRA result will progress to active TB disease and to evaluate the use of IGRAs in immunocompromised individuals.[1,8]

In contrast, the TST detects a cutaneous delayed-type hypersensitivity reaction to a purified protein derivative, a component of MTB. There are well-known disadvantages associated with the TST. Aside from inconvenience caused by multiple required visits, there is subjective interpreter variability and no uniform standard for which a TST finding is considered positive. It has been reported that individuals with psoriasis have enhanced responses to the TST when compared with those without psoriasis and, furthermore, that the TST reaction correlates positively with the Psoriasis Area and Severity Index score, raising concern about its use in this population.[9] In addition, the TST has a low specificity related to the false-positive results seen in both BCG-vaccinated individuals and those infected with nontuberculous mycobacteria, a decreased sensitivity in immunocompromised individuals as a result of anergic responses,[5] and does not distinguish LTBI from active TB. It is important to note that reactivity to BCG vaccination wanes over time and should not influence a TST reaction if greater than 15 years has passed since time of BCG vaccination. As such, a strongly positive TST finding in individuals with previous BCG vaccination still warrants further investigation.

The importance of screening patients with psoriasis for LTBI before treatment with TNF-alfa inhibitors, T-cell blockers, cyclosporine, or methotrexate has been established[10] and just 3 years ago, the National Psoriasis Foundation recommended TST for screening. The frequency of LTBI in patients with psoriasis has been reported to be as high as 29%.[11] It is widely recognized that anti—TNF-alfa agents may reactivate LTBI, as TNF-alfa helps to kill mycobacteria by activating macrophages and prevents TB dissemination by contributing to the formation of granulomas[12]; thus patients with evidence of LTBI must be treated before starting anti—TNF-alfa therapy. Black-box warnings exist for infliximab,[13] adalimumab,[14] and most recently, etanercept[15] for the risk of reactivation of LTBI. Although it has been reported that infliximab carries a greater potential risk of TB compared with the other TNF inhibitors,[16] other studies report no significant difference in the rate of active TB among the different agents.[17] No clear recommendations have been made as to which anti—TNF-alfa agent is best in the setting of LTBI, although the necessity to screen for LTBI is apparent.

Studies in the dermatologic literature suggest that although the TST has been the standard, there may be reason to incorporate IGRAs into clinical practice. One retrospective study by Laffitte et al[18] found that a positive T-SPOT.TB test result (Oxford Immunotec Ltd) is strongly associated with the presence of risk factors for LTBI, an association that was not found for the TST, encouraging the authors to recommend the use of IGRAs instead of the TST in patients with psoriasis requiring TNF-alfa inhibitors. Another study concluded that IGRAs may be helpful for screening LTBI in patients with psoriasis who are eligible for anti—TNF therapy, particularly when false-negative results are suspected on TST or to confirm positive TST results.[19] Furthermore, Desai et al[20] sought to compare the results of the QFT-G test with the TST in patients with moderate to severe psoriasis who qualified for anti—TNF-alfa therapy. Although 8 of 11 QFT-G test findings were negative, 3 of the test results were indeterminate. All but one TST finding was negative, so the authors suggest that because the QFT-G result was negative in the presence of a positive TST result, chemoprophylaxis was avoided. Although the authors conclude that QFT-G should replace TST, they do not provide an explanation for the indeterminate results with the QFT-G, which could represent a potential shortcoming of this test; indeterminate results likely occur in immunosuppressed individuals and in those at the extremes of age (<5 and >80 years old).[5] This is of importance when considering IGRAs in the psoriasis population, as those eligible for TNF-alfa blockade may be immunocompromised from other medications. However, among individuals with other