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. 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 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. 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. 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.

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), and the T-SPOT.TB test (Oxford Immun dinetics). These tests are based on measuring the production of interferon gamma (IFN-γ) by T cells in response to specific antigens of MTB. The Quantiferon-TB test and the QuantiFERON-TB Gold test are both based on the use of whole MTB antigens, while the T-SPOT.TB test uses recombinant MTB antigens.

These tests have been shown to be more sensitive and specific than the TST, particularly in individuals who have received a BCG vaccination or who are unlikely to return for follow-up. The TST may result in a false-negative test in these individuals, whereas the IGRAs are able to detect latent TB infection in the absence of a positive TST. In addition, the IGRAs are not affected by the use of BCG vaccination, whereas the TST may be falsely positive in individuals who have received a BCG vaccination.

The Centers for Disease Control and Prevention (CDC) has updated its guidelines for the use of IGRAs in the context of TB screening. The updated guidelines recommend that IGRAs be used as the first-line test for TB screening in individuals at high risk for TB, including those with a positive TST result, those with a history of TB exposure, and those with a history of human immunodeficiency virus (HIV) infection. The guidelines also recommend that IGRAs be used as a confirmatory test for TB screening in individuals who have received a BCG vaccination or who are unlikely to return for follow-up.

The updated guidelines also provide recommendations for the use of IGRAs in the context of treatment for TB. The guidelines recommend that IGRAs be used to monitor the effectiveness of TB treatment in individuals who are not completing their course of medication and in those who are at risk for reactivation of TB. The guidelines also recommend that IGRAs be used to monitor the effectiveness of TB treatment in individuals who are at risk for reactivation of TB in the context of ongoing therapy for chronic medical conditions, such as rheumatoid arthritis.

In conclusion, the updated guidelines for the use of IGRAs in the context of TB screening and treatment emphasize the importance of using these tests to accurately diagnose and monitor the effectiveness of TB treatment. The use of IGRAs in the context of TB screening and treatment is particularly important in individuals at high risk for TB, including those with a positive TST result, those with a history of TB exposure, and those with a history of human immunodeficiency virus (HIV) infection.

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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 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 IGRAst 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 IGRAst, for LTBI, IGRAst have a higher sensitivity than the TST, particularly in an immunocompromised population. Other advantages include the convenience of only one required patient visit, availability of results within 24 hours, and that IGRAst do not boost responses measured by subsequent tests. Limitations of IGRAst 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 IGRAst in immunocompromised individuals.

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. 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, 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, 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 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%. 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, thus patients with evidence of LTBI must be treated before starting anti–TNF-alfa therapy. Black-box warnings exist for infliximab, adalimumab, and most recently, etanercept 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, other studies report no significant difference in the rate of active TB among the different agents. 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 IGRAst into clinical practice. One retrospective study by Laffitte et al 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 IGRAst instead of the TST in patients with psoriasis requiring TNF-alfa inhibitors. Another study concluded that IGRAst 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. Furthermore, Desai et al 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). This is of importance when considering IGRAst in the psoriasis population, as those eligible for TNF-alfa blockade may be immunocompromised from other medications. However, among individuals with other
immune-mediated inflammatory diseases, including inflammatory arthritides, studies show that IGRAs may be useful when screening for LTBI. Over the past 10 years IGRAs have gained recognition, and as such, they have been integrated into national guidelines. The United Kingdom–based National Institute for Health and Clinical Excellence recommends the use of IGRAs in individuals with a positive TST finding to confirm the diagnosis of LTBI and to replace the use of TST in immunosuppressed individuals for whom the TST may not be accurate. These recommendations are based on economic analysis that determined that the two-step strategy of TST and confirmatory IGRA approach is the most cost-effective. Meanwhile in the United States, the most recent guidelines published by the Centers for Disease Control and Prevention (CDC) in 2010 advise that IGRAs may be used in place of a TST to screen for LTBI in all situations in which the CDC recommends the TST as an aid in diagnosing MTB infection (Fig 1). Either IGRAs or the TST may be used to test recent contacts of persons with infectious TB or for periodic screening for those with occupational exposures. Routine testing with both TST and IGRA is not recommended; however, there are few situations in which the results from both tests might be helpful (Fig 2): if there is a strong clinical suspicion of TB or high risk for infection, but the initial test result is negative; if the initial test result is positive, but confirmation of infection is needed to encourage acceptance and adherence of diagnosis by patient; or if there is an individual with a low risk of infection, but a positive test result, performing an additional test can help to demonstrate a true positive result. If the initial IGRA result is indeterminate, borderline, or invalid, performing a TST might also be useful. Specific populations in which the IGRAs are preferred include individuals who have received BCG vaccines and those who are unlikely to return for a TST reading, whereas TSTs should continue to be used for testing in children younger than 5 years of age.

As with the TST, live-virus vaccines may interfere with IGRA test results, although this has not been extensively studied. Recommendations from the CDC suggest that IGRA testing should be done either on the same day as vaccination with live-virus vaccine or 4 to 6 weeks after administration of the live-virus vaccine and at least 1 month after the smallpox vaccination.

We write to address the recent advances that have been made in testing for LTBI, resulting in the role of IGRAs as an important screening tool for TB. Further research needs to be done to identify the predictive value of a positive IGRA result for the development of active TB disease and to enable IGRAs to distinguish between active and latent TB.

How should dermatologists make use of these guidelines? Should dermatologists consider these recommendations for patients treated with any immunosuppressive therapy? Although methotrexate can cause reactivation of LTBI when used in psoriasis, reactivation of LTBI has not been reported with
T-cell inhibitors, or at the doses of cyclosporine used for psoriasis. Despite this, given the immunosuppressive effect of all of these therapies, it is standard for dermatologists to perform both baseline TB testing before treatment and continue to screen during therapy. Moreover, should these recommendations for use of IGRAs extend to the annual TB testing performed in patients with psoriasis on immunosuppressive treatment? As the conversion criteria for IGRAs is thought to be more lenient when compared with that for TSTs, what are the implications of converting from a negative to a positive response with serial testing with IGRAs? Although further research needs to confirm the value of these tests in dermatologic practice, it is important that dermatologists acknowledge these updates and reconsider their recommendations for screening methods for TB in patients with psoriasis who wish to begin treatment with anti-TNF-alfa agents.

REFERENCES

