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Should all patients undergoing treatment with biologic agents be screened annually for latent tuberculosis infection with an interferon gamma release assay?

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Abstract

Systemic biologic therapy has become commonplace for the treatment of a variety of inflammatory dermatologic conditions, particularly psoriasis. Screening for latent tuberculosis infection (LTBI) is recommended prior to initiation of systemic biologic agents, and an interferon gamma release assays (IGRA) is often used as the screening modality. Annual screening for LTBI is also recommended for patients while on systemic biologic therapy, but the literature does not clearly support how often screening should be performed. In addition, serial testing with IGRAs, particularly among low-risk populations without any new tuberculosis (TB) exposures, has proven to be unreliable with frequent reversions and conversions. We propose that in low-incidence TB regions, repeat LTBI screening should only be considered for patients on systemic biologic therapy if any new TB exposures occurred since initial LTBI screening was performed prior to starting biologic therapy. This strategy aims to reduce false-positive LTBI testing that can expose patients to hazardous antibiotics and result in the unnecessary interruption of systemic biologic therapy.

Keywords

Interferon-gamma release assay; tuberculosis; latent tuberculosis; biologics; screening; diagnostics

An 83-year-old man with psoriasis who has been maintained on adalimumab for two years underwent routine annual screening for latent tuberculosis infection (LTBI) with a QuantiFERON®-TB Gold (Cellestis Ltd., Carnegie, Australia) test. He previously tested negative for LTBI with a QuantiFERON®-TB Gold test prior to initiation of adalimumab and again after one year of therapy, but then had a positive test result (Quantiferon detected, Nil 0.04 IU/mL, Mitogen-Nil 7.96 IU/mL, TB Ag-Nil 0.37 IU/mL) after two years of adalimumab therapy. He had no risk factors for tuberculosis (TB), no known TB contacts and no symptoms of TB with an unremarkable chest radiograph. This clinical vignette

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Declaration of interest

The authors report no conflicts of interest.

illustrates a familiar challenge often presented to healthcare providers who are treating patients with systemic biologic agents. How should this patient be managed?

An interferon-gamma release assay (IGRA) has become a commonplace tool for screening patients with immune-mediated inflammatory diseases for LTBI prior to the initiation of and during treatment with systemic biologic therapy. Current 2010 guidelines according to the Centers for Disease Control and Prevention recommend that an IGRA can be used in place of a tuberculin skin test (TST) in virtually all situations wherein LTBI screening is required (1). IGRAs are purportedly more specific than TSTs, easier to administer and can yield overall cost savings for health systems that adopt IGRAs instead of TSTs (1,2). While screening for LTBI prior to the initiation of systemic biologic therapy is a well-accepted practice, questions remain regarding the reliability and utility of using IGRAs for annually screening patients who are already undergoing treatment with biologic agents (2,3).

Studies of serial IGRA testing among immunocompetent patients demonstrate frequent conversions (from negative to positive) and reversions (from positive to negative) in the absence of new TB exposures or changes in immune status (4,5). Of greater concern, a recent study of healthcare workers in the United States demonstrated significantly higher rates of conversions using IGRAs rather than TSTs, casting doubt on assertions of greater IGRA specificity and raising concerns about false-positive test results when using IGRAs for serial testing (6). Even among patients with HIV, who are at highest risk of progression to active TB if infected, most IGRA conversions are false positive when serial testing is performed in low-incidence TB areas (7). IGRA testing may be even less reliable among immunocompromised patients undergoing treatment with systemic biologic therapy, such as anti-TNF-alpha agents, that can cause blunted interferon gamma responses (2,3,8).

Serial testing of patients at low risk of TB infection, regardless of the screening modality, is most likely to yield false-positive tests with resultant exposure to unnecessary medications. Current guidelines do not provide a clear and consistent message about serial testing. In the United Kingdom, which is a low-incidence TB country, routine serial LTBI testing is not recommended in patients with inflammatory bowel disease undergoing anti-TNF-alpha therapy (9). International rheumatology guidelines are vague regarding serial IGRA testing, with some guidelines not even commenting on long term screening (10). Iannone et al. suggested that in deciding about the need for serial LTBI testing, an overall evaluation of the patient's potential TB exposures and TB risk factors is key (10). Also, as each inflammatory condition and each biologic agent have different mechanisms of action and probability for reactivating LTBI, a patient's disease and concomitant biologic treatment must be considered as well (10). This thoughtful approach to LTBI screening may be translated to other medical specialists, such as dermatologists, gastroenterologists and infectious diseases practitioners who frequently confront these clinical scenarios.

In conclusion, data are lacking about the performance of serial IGRA testing among patients on systemic biologic therapy. Recommendations calling for annual IGRA screening for all patients treated with biologic agents in low-incidence TB regions are unfounded and likely to cause harm to patients due to the interruption of biologic therapy and potentially hazardous exposure to unnecessary antibiotics. While an initial screen for LTBI with an

IGRA or TST is warranted prior to initiating systemic biologic therapy, current literature does not support serial monitoring with IGRAs. We propose that in low-incidence TB regions, repeat LTBI screening should only be considered for patients on systemic biologic therapy if any new TB exposures occurred since initial screening was performed. A simple algorithm is suggested (Figure 1), which can be applied for managing LTBI screening in this population. However, it is important to remember that patients with any signs or symptoms of infectious TB, such as cough for ≥ 3 weeks, fevers/chills, or weight loss, need to be further evaluated for active TB disease with a chest radiograph and sputum testing instead of LTBI screening with an IGRA or TST.

As for the patient in our case vignette, his positive IGRA was questioned because he had no new TB exposures. Thus, he had a repeat IGRA performed 16 days later which was negative. He was maintained on adalimumab and was not given LTBI treatment and continues to show no evidence of active TB after approximately eight months of follow-up.

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Figure 1.

Algorithm for monitoring patients with latent tuberculosis infection while on systemic biologic therapy. IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.