# Approach to Latent Tuberculosis Infection Screening Before Biologic Therapy in IBD Patients: PPD or IGRA?

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The use of biological agents for the treatment of chronic inflammatory conditions such as inflammatory bowel diseases (IBD) has been on the rise.[1,2] Current biological therapies include antitumor necrosis factor-α (anti-TNF-α), anti-interleukin-12/23, and anti-integrin agents. Before initiation of biological drugs, screening for *Mycobacterium tuberculosis* infection is required to avoid reactivation or worsening of disease after immunosuppression. It has been shown that anti-TNF-α treated patients have a 14-fold increased risk of tuberculosis (TB) infection/reactivation compared with healthy controls.[3] The methods for screening for TB have evolved over time and vary from region to region.

**Key Words:** PPD, IGRA, QuantiFERON-Gold, biologic therapy

## HOW TO SCREEN FOR TB INFECTION?

Assessing for tuberculosis (TB) infection should be based on an individual's risk factors including prevalence in the country of origin, physical examination, chest x-ray, and either tuberculin skin testing (TST) or interferon-gamma release assays (IGRAs).[4]

Tuberculin skin testing has historically been the most widely used modality for TB testing. The TST makes use of a purified protein derivative (PPD)-tuberculin, a protein precipitate of heat-inactivated tubercle bacilli to detect a cell-mediated immunity to *Mycobacterium tuberculosis* through a delayed-type hypersensitivity reaction.[5] The Mantoux method is used, whereby 0.1 mL of liquid containing 5 tuberculin units of PPD is intradermally injected in a patient's forearm and then evaluated for an induration 48 to 72 hours after injection. The test is interpreted as positive or negative depending on the size of the diameter of the induration and the patient's risk factors. In healthy individuals residing in a nonendemic area, an induration of 15 mm or greater is considered positive.[6] This induration size threshold is lowered to 10 mm in individuals who reside in countries with high incidence of TB or in those individuals who are at a higher risk for TB exposure due to their occupation.[6] For individuals who are immunosuppressed, those in close contact with a documented TB case, and those with clinical or radiographic evidence of prior or current TB infection, the induration size threshold is lowered even more to 5 mm.[6]

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Tuberculin skin testing is a low cost test that is easy to perform. Limitations of this test are related to the need for follow-up for reading and availability of trained people to interpret the test. False positive reactions could be seen in patients with prior Bacillus Calmette-Guerin (BCG) vaccinations and in patients with an infection from nontuberculous bacteria due to cross-reactivity to PPD antigens. False negative results can also occur in young individuals (infants and young children), if checked within a short duration after TB infection (less than 6–8 weeks), in patients with recent viral vaccination, in patients with overwhelming illness including extensive TB, and in patients receiving immunosuppression such as anti-TNF-α agents or steroids.[6]

Interferon-gamma release assay is a newer test that relies on a cellular immune response to determine the presence of a *Mycobacterium tuberculosis* infection. It measures the release of interferon-gamma by T cells when exposed to *Mycobacterium tuberculosis* antigens. The assay offers a more specific immune response compared with TST, and unlike TST, IGRA does not react with BCG strains and most nontuberculous bacteria. The available IGRA tests include QuantiFERON-TB Gold In-Tube, QuantiFERON-TB Gold Plus, and the T-SPOT.TB test. QuantiFERON-TB Gold In-Tube involves placing a patient's blood in 3 tubes: (1) a tube coated with antigen, (2) a mitogen control to ensure presence of viable cells, and (3) a nil control tube. The concentration of interferon-gamma in response to the *Mycobacterium tuberculosis* antigen is then measured via ELISA. When the difference in concentrations between the antigen tube and the nil control is ≥0.35 international units (IU), the test is considered positive. When there is lack of response in the mitogen control with a concentration ≤0.5 IU, the test is considered indeterminate. Also, when the nil control has a concentration >8 IU, then the test is considered indeterminate.

There is a new generation QuantiFERON-TB Gold test, the QuantiFERON-TB Gold Plus, which includes an



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additional antigen tube, resulting in a better CD8 T-cell response. Vanini et al compared the accuracy of these assays, and they found similar specificity but higher sensitivity for the QuantiFERON-TB Gold Plus assay at 95% for active TB detection, 75% for cured, TB and 100% for latent TB infection as compared with 84%, 67%, and 100% for QuantiFERON-TB Gold In-Tube assay, respectively.[7]

The T-SPOT.TB test is based on the ELISPOT enzyme-linked immunospot assay. Blood is drawn into a tube, and peripheral mononuclear cells are separated and added to microtiter wells that are coated with interferon-gamma antibodies.[6] Peptides are then added, and via a capture technique, interferon-gamma is detected by conjugation with secondary antibodies that result in a spot. The spot-forming units are used to interpret the results. Based on the revised FDA criteria, the test is considered positive when there are ≥8 spots, negative with ≤4 spots, and borderline (equivocal) when there are 5 to 7 spots.[6]

Regarding the advantages of IGRA, this assay requires only one visit to the laboratory and avoids cross-reactivity with BCG and nontuberculous bacteria. However, it has a higher cost as compared with TST and needs blood withdrawal; additionally, its interpretation is not straightforward in view of the inconsistency of reproducibility.[8–10]

## WHAT FACTORS AFFECT TEST RESULTS?

It is not uncommon to encounter an indeterminate IGRA test result with rates as high as 11%, particularly in patients with rheumatologic conditions and those who are immunosuppressed.[11] As described previously, this could be due to lack of immune response to the mitogen control or an elevated immune activity in the nil/control tube. A case-control study of 400 IBD patients revealed that systemic corticosteroids and hypoalbuminemia (<3.5 g/dL) contributed to a higher likelihood for an indeterminate QuantiFERON-TB In-Tube test.[12] In this study, 11.5% of patients had an indeterminate QuantiFERON test. In a separate study that included non-US-born individuals in the United States, risk factors that have been associated with an indeterminate IGRA included hypoalbuminemia, anemia, and Asian race.[13] Acute critical illness was also found to be a risk factor for an indeterminate IGRA result due to a low mitogen response.[14] Patients with indeterminate results were more critically ill and had lower albumin levels.[14]

Over the past decade, numerous studies have compared the different available latent TB infection screening tests between IBD and non-IBD patients and between IBD patients receiving immunosuppressive medications and IBD patients not on immunosuppressive medications.

A study evaluating the performance of IGRA in IBD patients compared with non-IBD patients showed that there is no difference in IGRA performance among both populations; however, immunosuppressive therapy negatively impacted IGRA performance, especially with patients taking azathioprine.[15] These results were further validated in a study performed on patients with immune-mediated diseases to evaluate the performance of IGRA (QuantiFERON-TB Gold and T-spot), and this study showed that immune-mediated diseases negatively affect IGRA performance.[16] Among Crohn's disease (CD) patients, these were most affected by their drug profile.[16]

A study on 166 consecutive patients with moderate to severe IBD showed a moderate correlation between IGRA and TST (kappa: 0.39–0.41). All patients included in the study were on immunosuppressive and/or biologic therapy, but none of these factors nor disease phenotype influenced IGRA positivity.[17] Similarly, Mantzaris et al found that immune-mediated therapy does not significantly influence TST and QuantiFERON-TB Gold test results.[18] These results showed a substantial concordance between TST and IGRA-QuantiFERON-TB Gold test (kappa: 0.7) in the immunosuppressed group compared with moderate agreement (kappa: 0.498) in patients who were on 5-aminosalicylic acid only or not receiving any medication.[18]

Another study showed that agreement between TST and QuantiFERON-TB Gold dropped from a moderate (kappa: 0.508) to fair agreement (kappa: 0.388) in patients on immunosuppressive therapy compared with IBD patients not taking any immunosuppressive medication.[19] These results were replicated in another study on patients with immune-mediated diseases (eg, rheumatoid arthritis, psoriasis, IBD, and spondyloarthropathy), in which agreement between TST and IGRA dropped to poor (kappa: 0.041) in immunosuppressed patients, mainly due to the influence of immunosuppression on IGRA. This suggests the limited role of IGRA in screening for TB infection in patients who are already on immunosuppressive therapy.[20] Another study performed on 155 IBD patients before anti-TNF-α therapy showed only a fair concordance between the 2 tests (kappa: 0.21), with IGRA being negatively influenced by immunosuppressive therapy contrary to TST.[21] In one of the largest prospective studies performed for latent TB infection (LTBI) screening with TST showed that the performance of TST is highly influenced by any immunosuppressive medication, especially steroids and dual therapy, and the authors of this study suggested TST be performed at an earlier stage of the disease.[22]

Finally, in a large prospective study in patients with immune-mediated diseases, prednisone was found to be strongly associated with negative TST and indeterminate QuantiFERON-TB Gold, but azathioprine, methotrexate, and 5-aminosalicylic acid did not have similar influence.[23] Another study found that in addition to systemic corticosteroids, immunomodulators were also significantly associated with indeterminate IGRA results in IBD patients.[24]

In patients who have an indeterminate IGRA, repeating the IGRA is recommended, and if the result remains indeterminate, it is recommended to proceed with a TST.[25]

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## AVAILABLE GUIDELINES

There are several published gastroenterology and infectious disease guidelines addressing the need to check for active or latent TB infection before initiation of biologic therapy. The recently published American College of Gastroenterology guidelines on the management of Crohn's disease states that patients should be assessed for latent and active tuberculosis before initiation of anti-TNF-α therapy, corticosteroids, or immunomodulators.[26] Interferon-gamma release assay testing can likely complement TST and is preferred in patients who had previously received BCG vaccine.[26] Similarly, the European Crohn's and Colitis Organisation (ECCO) guidelines propose complementing the TST with IGRA, with a preference for IGRA in patients who had received BCG vaccination in the past.[27] In immunocompromised patients who have an initial negative TST, it may be appropriate to perform a second TST 1 to 3 weeks after the initial TST.[28]

The World Health Organization (WHO) does not make a preference between the TST and IGRA, except in patients who have had the BCG vaccine within 10 years from the TST.[29] The BCG vaccine is usually given at birth and has shown to have a limited effect on specificity of TST, especially when it is done more than 10 years from the BCG vaccine administration. However, if the BCG vaccine is given later in life, then IGRA is the test of choice.[30] The Official American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention recommend that diagnosis of latent TB infection is based on both the possibility of infection with *Mycobacterium tuberculosis* and on the risk of developing tuberculosis in the setting of an infection.[6] High-risk patients include those who are on immunosuppressive therapy. For these high-risk patients (who are more than 5 years of age), it is recommended to use either a TST or an IGRA as a first diagnostic test because the available data do not recommend one test over the other.[6] For low- or intermediate-risk patients who are more than 5 years of age, in whom testing for TB is warranted, IGRA rather than a TST is recommended. In these low- to moderate-risk patients, a second confirmatory test should be done in case of positivity of the first test, and the patient is considered to be infected only if both tests return positive.[6]

## WHAT ABOUT ACUTE SEVERE ULCERATIVE COLITIS PATIENTS?

Patients with acute severe ulcerative colitis usually need to receive rescue anti-TNF-α therapy with infliximab shortly after admission. These patients are often hypoalbuminemic from their underlying disease, and many of them are already on corticosteroids. In these patients, physicians do not have the luxury of time to await the results of IGRA testing, which may be indeterminate due to the aforementioned risk factors, but instead may need to only rely on the more rapidly interpreted TST, which also could be affected by immunosuppression. The question that arises is if physicians should check both IGRA and TST and induce the patient with infliximab as soon as the first negative result returns. In the case of discordance between the 2 tests, more consideration should be given to IGRA given the higher false positive rates associated with TST.

It would be ideal for patients to undergo screening for latent TB infection before they become ill. Either a TST or IGRA can be performed, except in patients who have a prior history of BCG vaccine, in which case IGRA is the preferred test.

## DO WE NEED SERIAL TESTING FOR LATENT TB INFECTIONS IN PATIENTS ON BIOLOGIC THERAPY?

There are no available guidelines addressing the need to perform serial testing for TB in patients already on immunosuppression. Both IGRA and TST are negatively affected by immunosuppressive medications.[31] For this, it is recommended to screen patients for TB infection before initiation of immunosuppressive medications. Investigators looked at the rate of test conversion after initial LTBI screening. Comparing 2 cohorts of patients, one receiving anti-TNF-α and the others not receiving anti-TNF-α, Taxonera et al showed that patients not receiving anti-TNF-α had higher TST conversion rate at 1 year (11.4% vs 5.2%). Also, TST conversion was correlated with fewer immunosuppressive therapies between the 2 serial tests.[32] Meanwhile, in a prospective study on patients receiving biologic therapy, latent TB infection test conversion (whether through IGRA or TST) was not associated with any immunosuppressive therapy.[3] It has been suggested that yearly chest x-ray be performed on patients receiving anti-TNF-α therapy.[33] The chest x-ray needs to be complemented with an IGRA test in patients who are health care workers or who have other risks of exposure to TB.[33] Other studies have proposed not doing surveillance for latent TB infection in patients on anti-TNF-α therapy if they had negative baseline TST and IGRA.[34]

## CONCLUSION

We suggest that all IBD patients undergo baseline IGRA or TST testing (authors prefer IGRA) at their initial outpatient clinic visit. Interferon-gamma release assay is preferred in patients with prior BCG vaccination and according to the local prevalence of TB and to the national recommendations. It is important to be aware of the factors for indeterminate TB testing, most importantly hypoalbuminemia and immunosuppression—particularly corticosteroids—and an acute critical illness. In patients who have an indeterminate IGRA, repeating the IGRA is recommended, and if the result remains indeterminate, it is recommended to proceed with a TST. Some experts suggest initiating treatment for presumptive latent TB in high-risk patients with 2 consecutive indeterminate IGRA results particularly if patients are not on steroids. In acutely ill patients who need urgent rescue therapy with anti-TNF-α agents, we

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would recommend checking an IGRA. After patients initiate their biologic agents, we propose yearly chest x-ray in addition to IGRA in patients who live in high TB endemic areas. As for patients in low endemic areas who are at no risk for TB exposure, we do not perform yearly chest x-rays nor do we check yearly IGRA unless mandated by a patient's insurance.

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