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Evidence-Based Commentary: Testing and Treating Latent Tuberculosis Before Starting Biologics and Small Molecules in Patients with Inflammatory Bowel Disease

Rinkalben Kakadiya[1] Vishal Sharma[1]

[1] Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Address for correspondence Vishal Sharma, MD, DM, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: docvishalsharma@gmail.com).

What is Latent Tuberculosis?

Simplistically speaking, latent tuberculosis infection (LTBI) represents a stage in tuberculosis infection where persistent immune responsiveness to tubercular antigens is detectable in the absence of active disease. In LTBI, bacterial replication is absent or below some threshold due to a persistent immune response, which prevents the progression to the stage of active tuberculosis. The concept is useful in identifying individuals who harbor dormant tubercular bacilli and therefore potentially could develop tubercular re-activation in the future. The re-activation could be driven by defective or deteriorating host immune responses consequent to nutritional deficits, co-morbidities, or immune-suppressing therapies.[1,2]

There are potential issues with the inclusion of 'persistent immune responsiveness' in the definition because a subset of individuals harboring dormant tubercular infection may not have a detectable immune response on the exposure to tubercular antigens. Also, individuals who have been treated and cured could continue to have a persistent immune memory and responsiveness to tubercular antigens. Of late, a multi-stage infection model of tuberculosis has been proposed that identifies progression from infection to incipient TB followed by preclinical or subclinical TB and then symptomatic tuberculosis (►**Fig. 1**).[3] Those with tubercular infection but no replicating bacilli would represent a stage of intervention to prevent progression to tuberculosis. The challenges are in the appropriate choice of modalities to detect these patients harboring LTBI.

What are the Tests for Latent Tuberculosis and Who Should be Tested for LTB?

As part of the workup before the use of biologics or small molecules, a multipronged approach is used to identify individuals at the risk of reactivation of TB. The approach uses combining clinical evaluation, tests for immune response, and imaging.[4] The clinical history includes the evaluation of a recent exposure to active TB as suggested by the history of TB in close contact, residence in institutional facilities, or travel to an endemic region[5]. In addition, the past history of tuberculosis has also been considered a surrogate of LTBI.[5] It is almost impossible to be certain about the lack of recent exposure to active TB in TB endemic regions.

The test for immune responsiveness includes the tuberculin skin test and interferon-gamma release assays. There is no gold standard, at present, for a sure diagnosis of LTBI. The current tests may fail to identify a subset of those with LTBI, differentiate LTBI from active TB, and could be positive in individuals who have been treated for tuberculosis.

Tuberculin skin test (TST) or purified protein derivative (PPD) test is an age-old test that detects delayed-type hypersensitivity to an intradermal injection of PPD RT23. The test, although cheap, requires a visit 48 to 72 hours after the administration of PPD to assess the induration.[6] Usually, an induration of >5 mm is considered significant.[1,7] Due to the cross-reacting nature of antigens in PPD, the test could be positive in those with previous BCG vaccinations (especially

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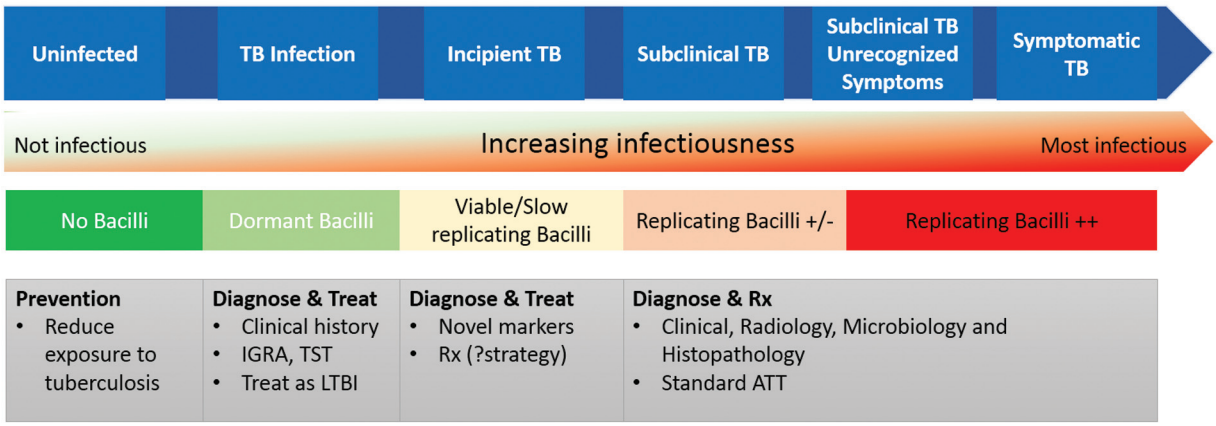


Fig. 1 Stages of tuberculosis.

multiple inoculations) or those with underlying NTM disease.[8] The test could also be falsely negative in individuals who are immunosuppressed, have underlying miliary tuberculosis, or if done early after TB exposure (6–10 weeks).[1,2,9] Some of the limitations of the TST have been overcome by the interferon-gamma release assays (►**Fig. 2**). These tests detect the interferon-gamma-producing T cells (T SPOT test done on peripheral blood mononuclear cells) or concentrations of interferon-gamma (QUANTIFERON test on blood). These tests need a single visit and the results are usually available within a day. The tests avoid some of the false positives associated with TST because these utilize TB-specific antigens (ESAT-6, CFP-10, and TB7.7).[2] However, these tests are costly, and can still be false negative with underlying immunosuppression. None of these tests may discriminate between latent and active TB.[1] The ECCO guidelines recommend to perform TST or IGRA or both. A study from India by Mantri et al. showed that a combination of TST and IGRA has supplemental value and increases the diagnostic yield.[10] So, it is preferable to perform both tests. The IGRA should be done first followed by TST, as recent TST can lead to positive IGRA. ►**Fig. 2** shows the currently available tests for LTBI and the interpretation of tests.

Another method to recognize past (or active) pulmonary tuberculosis is performing a chest roentgenogram. The presence of calcifications, cavitary, or fibrotic lesions could represent active or past TB. The use of computed tomography of the chest has been suggested in TB endemic regions but the evidence is limited. In case a CT chest is planned, a chest X-ray may not be done.[8]

Are There Differences Between Strategies for the Diagnosis of LTBI in TB Endemic Regions?

The overall risk of TB reactivation with the use of biologics and small molecules is largely dependent on the TB endemicity in the population. It has been demonstrated in a plethora of reports that the risk of TB reactivation is higher in TB endemic regions with the use of anti-TNF agents and JAK inhibitors.[5] This is an argument in favor of a more stringent strategy to diagnose LTBI. In a recent study, the use of a stringent strategy (including contrast-enhanced computed tomography of the chest) was demonstrated to reduce the risk of TB reactivation in patients started on anti-TNFs for inflammatory bowel disease (IBD).[11] Interestingly, those in the stringent screening cohort were also treated more stringently than in the previous cohort in which less than half of patients with LTBI diagnosis received treatment for LTBI. Therefore, it is not entirely clear if the reduced risk of TB reactivation was related to stringent screening or a stringent treatment but possibly both.[11] Further, there is no head-to-head comparison of screening with or without CECT in patients initiated on biologics or small molecules. However, given the higher risk of TB reactivation, CT may be considered in screening for LTBI in TB-endemic regions.

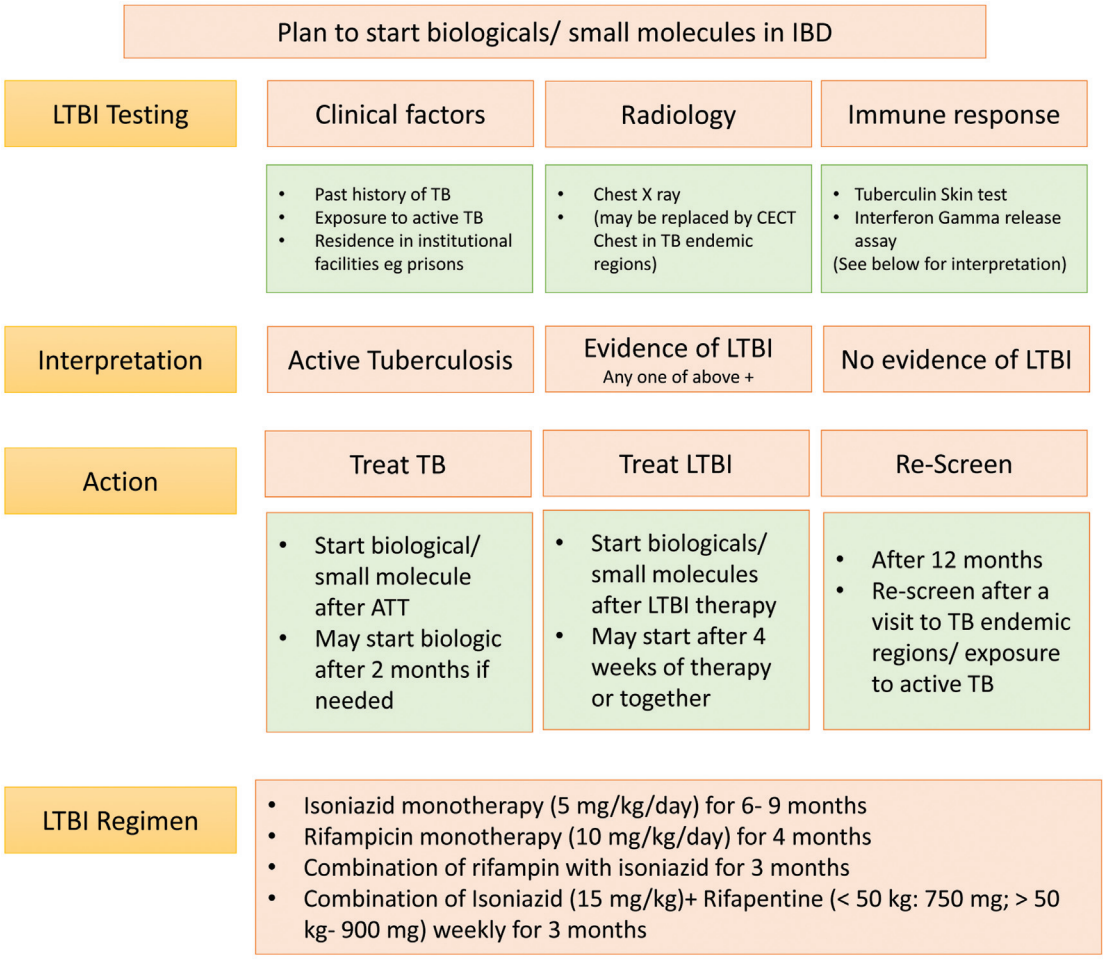
When to Screen for LTBI?

LTB reactivation risk is increased with biological/small molecule therapy, and the disease tends to be severe and more often, extra-pulmonary. LTBI screening should be performed at the time of diagnosis of IBD, and before initiation of certain therapies (immunosuppression), which increases the risk of re-activation.[12] This is because the screening tests that detect immune responses may be affected by the use of immune-suppressing therapies.[13] If a patient needs biological/small molecule later in the disease course and screening was done remotely (more than a year), repeat screening is advisable. The testing may be needed to be repeated in case of new exposure and travel to an endemic region.[12]

When Should LTBI Screening be Repeated?

In patients who are on ongoing biological therapies, periodic screening for LTBI is important to detect any recent exposure to TB and treat these patients. The evidence regarding the frequency of screening is limited but a 6 monthly to a yearly re-screening is considered appropriate.[12] Re-screening should probably be limited to TST, IGRA, and chest X-ray while repeat CT should be avoided.

Quantitative IGRA has additional advantage in LTBI surveillance while the patient is on biological therapy. A large study on young children reported interferon gamma more than 4.00 IU/mL has 40 times higher risk of having active tuberculosis in the next 6 to 24 months compared to value of 0.35 to 4.00 IU/mL, which has low predictive value for tuberculous disease.[14] Lee et al has reported a similar finding in their study. Six patients had IGRA conversion while on anti TNF therapying and were treated with isoniazid. IGRA was



Tuberculin skin test - Interpretation	
≥ 5 mm-	Child < 5 years, Immunosuppressed – HIV, Anti-TNF, Chemotherapy, Prednisolone > 15 mg/day, Tofacitinib, ?Anti Il12/23
> 10 mm – 15	Treat even if low to medium risk of progression (Thiopurines, Methotrexate, ?Vedolizumab)
≥ 15 mm-	Treat even if underlying risk deemed to be low
False positives	Prior BCG vaccine (risk of false positive minimal after 10 year of BCG vaccine) Non tubercular mycobacterial infection
False negative	Immunodeficient, Recent MMR vaccine, Severe malnutrition, Recent exposure (within 6-8 week)
Advantages	In vivo study, Inexpensive, Helpful if IGRA indeterminate
Drawbacks	48-72 hours for result, Needs two Visit, Need trained person, risk of subjectivity
IGRA – Interpretation	
Positive threshold is same for all patient	
Indeterminate	May occur in acute IBD flare, Prednisolone >20 mg/day, and others; may need to redo the test later
Advantages	Rapid, Do not affected by previous BCG or NTM infection, Single visit, Laboratory-based – less subjectivity
Drawbacks	Expensive, Indeterminate result need further testing, Affected by previous TST

Fig. 2 Testing, diagnosis, and management of latent TB prior to biological/small molecule use in inflammatory bowel disease.

negative in all at the end of the treatment except one with an IGRA of 20.57 at the time of conversion and remained elevated at 7.58 after 3 months of completion of treatment. This patient developed active tuberculosis subsequently.[15]

Some studies have addressed the issue of ongoing surveillance for tuberculosis during treatment with anti-TNF therapy with the use of IGRA and/or TST.[15,16] The ECCO guidelines also recommend rescreening with IGRA and/or TST.[12] However, it is reasonable to perform CXR in rescreening who are initially negative for LTBI. As subsequent new lesion on CXR either incidental finding or in symptomatic patients suggest active tuberculosis. Repeat CXR can be most useful during initial stage of anti-TNF therapy when tuberculosis reactivation risk is the highest.[5,15]

What is the Risk of TB Reactivation with Various Biological Agents and Small Molecules?

The biological agents associated with the highest risk of TB reactivation are the anti-TNF agents.[12,17] There may be some differences in the TB reactivation risk between the various anti-TNFs. Apart from anti-TNFs, JAK-inhibitors (Tofacitinib) are associated with a high risk of TB reactivation.[2,17] The strategy for screening of LTBI for these drugs should be similar to anti-TNFs. Vedolizumab, because of its gut selectivity, may have a lower risk of TB reactivation and therefore may not necessitate stringent LTBI screening. However, until more data emerges from TB-endemic regions, we continue to screen patients initiated on vedolizumab for LTBI. The data for Il12/Il23 inhibitor i.e Ustekinumab is emerging but it is believed that TB risk may be low.

How and When should LTBI be Treated?

A large multicentric retrospective study in high endemic areas demonstrated that universal chemoprophylaxis does not decrease the risk of tuberculosis reactivation. The incidence of active tuberculosis was similar between both groups with higher adverse events in the universal chemoprophylaxis group.[18] This study suggests benefit of testing for LTBI before treating over a universal tuberculosis chemoprophylaxis in patients with IBD and planned for anti-TNF therapy.

The LTBI treatment should be done in patients with IBD who have been diagnosed to have LTBI. IBD is a disease characterized by the occurrence of flares that necessitate the initiation of various immunosuppressive agents. Therefore, it is prudent to treat LTBI at the earliest to avoid any significant drug interactions with various immunosuppressive therapies. In cases where immunosuppressive medications are required emergently, a concomitant therapy for LTBI may be administered.[1,2,12] The various therapeutic options for the treatment of LTBI are listed in ►**Fig. 2**. One should be aware of the significant interactions between various drugs such as rifampin reduce tofacitinib levels and may compromise clinical action.

What are Some of the Areas of Uncertainty in Prebiological Assessment and Treatment of LTBI?

One area of uncertainty is regarding the management of patients who have received adequate therapy for tuberculosis in the past. While there is no direct evidence to answer this question, reports from endemic regions have used past TB as one of the criteria for the diagnosis of LTBI. We prefer to treat patients with a past history of tuberculosis as LTBI if the treatment for tuberculosis was in the remote past (>1 year). This strategy is likely to be helpful for patients living in endemic areas, as one can never be certain about repeat exposure.

Another concern is the emergence of drug resistance, especially in certain regions. It is unclear if any changes to the strategy of treatment need to be made for LTBI in these regions.

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Not applicable.

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There are no data associated with this work.

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