Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression

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We read with great interest the article by Dias et al.[1] on the prevalence of latent tuberculosis infection (LTBI) among patients with interstitial lung diseases (ILDs) requiring immunosuppression. We would like to share some comments on using the tuberculin skin test (TST) as the only screening strategy.

There is no gold standard for LTBI detection, and both TST and interferon-gamma release assays (IGRAs) are approved for use in all settings.[2] Dias et al.[1] reported positive TST reactions in only 9.1% of patients, while the estimated prevalence of LTBI for Brazil (a country with intermediate tuberculosis incidence) is 19-20%.[1,3] Possibly, the low infection rate reflects the fact that the participants did not belong to high-risk groups for tuberculosis or that tuberculin reaction may have waned over time. It remains unclear if IGRAs would be a better option. Although IGRAs yield fewer false-negative results than does TST in immunosuppressed and elderly patients, they are less sensitive in detecting remote infections.[4] It is also possible that the disease itself may have suppressed the reaction. In a country with high tuberculosis incidence, most patients with sarcoidosis showed negative TST response, but most patients and controls also tested positive on IGRAs.[5]

Interestingly, a large diameter of tuberculin reaction was noted in TST-positive patients, suggesting recent infection (the main risk factor for active tuberculosis). However, the authors did not include information on risk factors for tuberculosis in the study group.[1] Perhaps tuberculosis preventive treatment (TPT) was required because of a recent contact with a patient with pulmonary tuberculosis. It would be interesting to know IGRA results of TST-positive patients. None of the current diagnostic tests for LTBI have a sufficient predictive value for progression to active tuberculosis, although IGRAs might better identify candidates for TPT among BCG vaccine recipients. Thus, IGRAs might have provided additional data on the actual LTBI prevalence among ILD patients. Moreover, 63 patients were excluded because they either failed to schedule the test or did not return for the reading. This might have been avoided with IGRAs, which require only one visit.[4]

Another important question is whether all ILD patients with LTBI need TPT. Identifying target groups is essential. Glucocorticoids and other immunosuppressants may increase the risk of progression to active tuberculosis. However, screening for LTBI is recommended by the WHO only before anti-TNF therapy.[2] The risk-benefit ratio must be carefully considered.[4] Additional research is needed to evaluate whether patients on specific immunosuppressive drugs would benefit more from TPT than from watchful waiting.

Before TPT, it may be insufficient to exclude active tuberculosis solely based on clinical and radiological signs in patients with ILDs due to abnormalities such as fibrosis or nodules. Histopathologic features may mimic tuberculosis in sarcoidosis and hypersensitivity pneumonia. Thus, microbiological analysis should be performed in all candidates for TPT to avoid misdiagnosis.

Finally, screening for LTBI (preferably with TST) in treatment-naïve ILD patients might provide valuable information. In conclusion, further studies are needed to assess the actual prevalence of LTBI in ILD patients and to identify candidates for TPT.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

AK: conceptualization and drafting of the manuscript. MKK: drafting, editing, and reviewing of the manuscript. Both authors approved the final version of the manuscript.

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Authors' reply

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We would like to address some questions that were raised about our recently published study on the prevalence of latent tuberculosis infection (LTBI) in patients with interstitial lung diseases (ILDs) requiring immunosuppression.[1]

The prevalence of LTBI in our sample (9.1%) was indeed lower than that estimated for the world population (about 25%). It should be noted, though, that Kussen et al.[2] reported a similar prevalence (9.0%) in people living with HIV, a known high-risk group, in a study that also took place in the state of Paraná, Brazil, where our center is located, which might reflect a different scenario of infection by *Mycobacterium tuberculosis* in our region.

As for the use of tuberculin skin test (TST) as a screening method, we considered it a plausible choice, given that there is no consensus on a preferred method for immunocompromised patients.[3] Interferon-gamma release assays could be a reasonable choice for these patients, especially when the TST is negative; however, despite having recently been incorporated into the Brazilian public health care system, they are not available for patients with ILDs requiring immunosuppression.

Regarding risk factors for tuberculosis, we excluded patients with high-risk factors, such as those living with HIV, and we found that the frequency of positive TST results was not significantly higher in those with a history of smoking or diabetes. Nevertheless, we acknowledge that other variables associated with a higher risk of tuberculosis, such as recent contact with someone with the disease, were not addressed in our study. Moreover, we reinforce that patients with a positive TST result underwent not only clinical and radiological evaluation for active tuberculosis, but also microbiological evaluation whenever possible.

Finally, the lack of consensus on the need to treat LTBI in patients on immunosuppressants other than TNF inhibitors could be justified by the fact that the literature on the subject is scarce.

In conclusion, we agree that more studies are needed to determine the prevalence of LTBI in patients with ILDs effectively and to decide whether these patients should be prescribed preventive treatment. However, our study definitely marks a starting point to answering these important questions.

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