



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

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ABSTRACT

Objective: To characterize the prevalence of latent tuberculosis infection (LTBI) in patients with interstitial lung diseases (ILDs) requiring immunosuppression. Only 5 to 10% of individuals infected with *Mycobacterium tuberculosis* develop tuberculosis, and certain groups of patients have an increased risk of illness, such as the immunocompromised. Patients with ILDs are frequently treated with immunosuppressants and, therefore, might have a higher risk of developing the disease. **Methods:** Prospective study conducted at the ILD reference center of the Federal University of Paraná from January 2019 to December 2020. The screening of LTBI was performed with the use of the tuberculin skin test (TST). **Results:** The sample consisted of 88 patients, of whom 64.8% were women, with a mean age of 61.4 years. The most frequent diagnoses were autoimmune rheumatic disease ILD (38.6%) and hypersensitivity pneumonitis (35.2%). The most common immunosuppressant in use at the time of the TST was prednisone, either in combination with mycophenolate (19.3%) or alone (17.1%). The majority of participants had fibrotic lung disease, characterized by a reticular interstitial pattern on chest computed tomography (79.5%) and moderate to severe functional impairment (mean FVC 69.2%). A prevalence of LTBI of 9.1% (CI 95%, 2.1%-15.1%) was found, with a TST median of 13. **Conclusion:** Patients with ILD who are treated with immunosuppressants are not commonly screened for LTBI, despite being under a greater risk of progression to active disease. This study suggests the need for a more cautious approach to these patients.

Keywords: Latent tuberculosis infection; Interstitial lung diseases; Immunosuppression; Tuberculin test.

INTRODUCTION

Tuberculosis, a disease caused by *Mycobacterium tuberculosis* (Mtb), is a major public health issue and one of the leading global causes of death. In 2019, about 10 million cases of tuberculosis were reported and there were almost 1.5 million tuberculosis-related deaths worldwide.⁽¹⁾ The WHO lists Brazil as one of the priority countries regarding tuberculosis due to its high number of cases, as well as its high rate of HIV co-infection.⁽²⁾ In 2019, approximately 74,000 cases of tuberculosis were reported⁽³⁾ and there were close to 4,500 tuberculosis-related deaths countrywide,⁽⁴⁾ with 2,209 cases⁽³⁾ and 157 deaths⁽⁴⁾ in the state of Paraná.

It is estimated that about a quarter of the world's population is infected with Mtb. However, most of the infected individuals do not develop active disease, exhibiting only a persistent immune response to Mtb antigens, a phenomenon known as latent tuberculosis infection (LTBI). Only 5 to 10% of infected individuals develop the illness during their lifetime and the risk of getting sick is higher for certain groups, such as the

immunocompromised.⁽¹⁾ The diagnosis of LTBI is based on a response to Mtb antigens in the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA).⁽⁵⁾ Treating LTBI reduces the risk of progression to active disease by up to 90% and is one of the components of the WHO's End TB Strategy. Screening for LTBI should be considered for people with a higher risk of illness, such as people living with HIV,⁽⁶⁾ as well as for patients initiating TNF inhibitors or systemic corticosteroids on a dose equal or equivalent to 15 mg of prednisone a day for more than 1 month.⁽⁵⁾ Currently, there are no specific recommendations for patients on other immunosuppressants.

Interstitial lung diseases (ILDs) are a group of conditions characterized by inflammation and/or fibrosis of the lung tissue, whose treatment frequently includes the use of immunosuppressants, such as corticosteroids.⁽⁷⁾ Hence, patients with ILD and LTBI under immunosuppression might have a higher risk of developing active tuberculosis. However, there are no studies investigating the prevalence

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of LTBI and the risk of progression to active disease in this population.

Given this gap in current knowledge, this study aimed to evaluate the prevalence of LTBI in patients with ILD about to initiate immunosuppressive therapy or already on one or more immunosuppressants using the TST. The participants were patients in follow-up at the ILD reference center of the Federal University of Paraná.

METHODS

This was a prospective study performed at the ILD reference center of the Federal University of Paraná from January 2019 to December 2020, approved by the Committee for Ethics in Research on Human Beings under the opinion 02458018.6.0000.0096.

We included patients who were 18 years old or older, had a diagnosis of ILD according to national and international guidelines,⁽⁸⁻¹¹⁾ were either about to initiate immunosuppressive therapy, or were already on one or more immunosuppressants, and agreed to participate in the study.

We excluded patients with silicosis, patients on TNF inhibitors, and people living with HIV, who are known to have a higher prevalence of tuberculosis, as well as people with a prior history of tuberculosis, who cannot undergo TST.

Participants were assessed for the presence of a BCG vaccination scar through direct visualization by one of the investigators. Those not previously tested underwent TST, performed using the Mantoux technique. Reactions equal to or larger than 5 millimeters were considered positive. Participants with a positive TST underwent clinical and radiological evaluation for active tuberculosis, and, when possible, sputum analysis. Those with no evidence of active disease were treated with a

6-month course of isoniazid. Demographic data, such as sex and age, and clinical data, such as type of ILD and comorbidities, were collected from medical records. Functional and radiological data were collected from spirometries and computed tomography (CT) scans performed at dates close to when TST was performed.

Data were stored and analyzed with the SPSS Statistics v. 22.0 software. The exploratory analysis included means, minimum values, maximum values, and standard deviations for quantitative variables, and frequencies and percentages for qualitative variables. Association analysis was performed through Fisher's Exact Test. Values of p under 0.05 were considered significant.

RESULTS

From January 2019 to December 2020, 474 patients were followed up at the ILD reference center, with 281 not meeting the inclusion criteria (53 had another diagnosis, 224 were not eligible for immunosuppression and 4 did not agree to participate) and 42 met the exclusion criteria (8 had silicosis, 24 were or had been on TNF inhibitors, 4 had HIV infection and 6 had a prior history of tuberculosis). Of the remaining 151 patients, 63 were not tested, either for failing to schedule the test or for not returning for the reading. Thus, 88 patients were included in the study. The study design, describing inclusion and exclusion criteria, is shown in Figure 1.

Participants (Table 1) were predominantly female (64.8%), with a mean age of 61.4 years old. The most frequent diagnoses were autoimmune rheumatic disease (AIRD)-ILD (38.6%) and hypersensitivity pneumonitis (35.2%). The most common immunosuppressant in use at the time of the TST was prednisone, either in combination with mycophenolate (19.3%) or alone

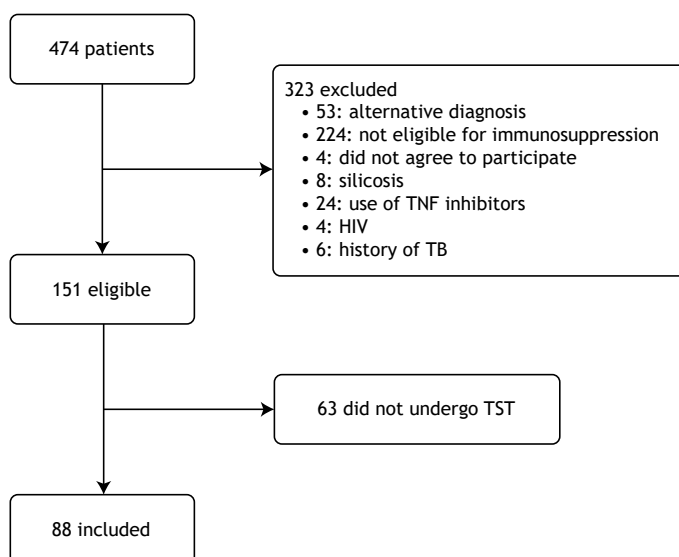


Figure 1. Included and excluded patients.

Table 1. Characteristics of the studied population.

Clinical-epidemiological characteristics [n = 88]	
Female sex, n (%)	57 (64.8)
Age in years, mean ± standard deviation	61.4 ± 12.5
Diabetes, n (%)	21 (23.9)
Current or previous smoking, n (%)	45 (51.5)
Presence of vaccination scar, n (%) [n = 70]	54 (77.1)
Type of ILD [n = 88]	
AIRD-ILD, n (%)	34 (38.6)
Hypersensitivity pneumonitis, n (%)	31 (35.2)
IPAF, n (%)	5 (5.7)
Sarcoidosis, n (%)	4 (4.5)
Undetermined, n (%)	11 (12.5)
Others*, n (%)	3 (3.4)
Type of AIRD [n = 34]	
Rheumatoid arthritis, n (%)	8 (23.5)
Systemic sclerosis, n (%)	7 (20.6)
Antisynthetase syndrome, n (%)	7 (20.6)
Sjögren's syndrome, n (%)	2 (5.9)
Dermatopolymyositis, n (%)	1 (2.9)
Others*, n (%)	9 (26.5)
Immunosuppressant(s) at the time of the TST [n = 88]	
None, n (%)	31 (35.2)
Prednisone and mycophenolate, n (%)	17 (19.3)
Prednisone, n (%)	15 (17.1)
Azathioprine, n (%)	4 (4.5)
Prednisone and azathioprine, n (%)	4 (4.5)
Prednisone and methotrexate, n (%)	4 (4.5)
Mycophenolate, n (%)	3 (3.5)
Cyclophosphamide, n (%)	2 (2.3)
Others, n (%)	8 (9.1)
Function characteristics [n = 82]	
Absolute FVC, mean ± standard deviation	2.09 ± 0.84
Relative FVC, mean ± standard deviation	69.2 ± 22.8
Tomographic findings [n = 88]	
Reticular interstitial pattern, n (%)	70 (79.5)
Ground-glass opacities, n (%)	54 (61.4)
Honeycombing, n (%)	12 (13.6)
Distribution of lesions on CT [n = 88]	
Peripheral, n (%)	48 (54.5)
Diffuse, n (%)	21 (23.9)
Peribronchovascular, n (%)	15 (17.0)

FVC = forced vital capacity; ILD = interstitial lung disease; AIRD = autoimmune rheumatic disease; IPAF = interstitial pneumonia with autoimmune features; CT = (chest) computed tomography. *: bronchiolitis obliterans [n = 1], hard metal lung disease [n = 1], pulmonary capillary hemangiomatosis [n = 1]; +: granulomatosis with polyangiitis [n = 3], eosinophilic granulomatosis with polyangiitis [n = 1], overlap of rheumatoid arthritis and Sjögren's syndrome [n = 1], overlap of rheumatoid arthritis and systemic lupus erythematosus [n = 1], overlap of systemic lupus erythematosus and Sjögren's syndrome [n = 1], overlap of systemic sclerosis and Sjögren's syndrome [n = 1], psoriatic arthritis [n = 1]; ++: patients with vasculitides or ILDs with airway-predominant disease, with no apparent tomographic findings; n = number of participants.

Table 1. Continued...

Not applicable**, n (%)	4 (4.5)
Predominance on CT [n = 88]	
Lower-lobe, n (%)	52 (59.1)
None, n (%)	22 (25.0)
Upper-lobe, n (%)	10 (11.4)
Not applicable**, n (%)	4 (4.5)

FVC = forced vital capacity; ILD = interstitial lung disease; AIRD = autoimmune rheumatic disease; IPAF = interstitial pneumonia with autoimmune features; CT = (chest) computed tomography. *: bronchiolitis obliterans [n = 1], hard metal lung disease [n = 1], pulmonary capillary hemangiomas [n = 1]; +: granulomatosis with polyangiitis [n = 3], eosinophilic granulomatosis with polyangiitis [n = 1], overlap of rheumatoid arthritis and Sjögren's syndrome [n = 1], overlap of rheumatoid arthritis and systemic lupus erythematosus [n = 1], overlap of systemic lupus erythematosus and Sjögren's syndrome [n = 1], overlap of systemic sclerosis and Sjögren's syndrome [n = 1], psoriatic arthritis [n = 1]; ++: patients with vasculitides or ILDs with airway-predominant disease, with no apparent tomographic findings; n = number of participants.

Table 2. Participants with a positive TST.

Participant	Sex	Age	BCG	Type of ILD	IS	FVC%	Fibrosis	TST
A. G. K.	F	75	yes	AIRD-ILD	PDN+MMF	64.8	no	15
D. S. A. N. L.	F	59	yes	AIRD-ILD	PDN	38.8	yes	7
F. M. F.	M	73	no	Undetermined	None	51.2	yes	14
G. A. G.	M	57	yes	Undetermined	None	68.4	yes	15
J. A. P.	M	68	no	AIRD-ILD	PDN+MMF	48.0	yes	10
J. M. R. C.	M	62	-	AIRD-ILD	PDN+MTX	37.4	yes	20
M. F. F. L.	F	68	yes	HP	None	64.0	yes	11
W. R. S.	M	65	-	Undetermined	None	-	yes	13

AIRD: autoimmune rheumatic disease; BCG: BCG vaccination scar; FVC%: relative FVC; HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; IS: immunosuppressant(s); MMF: mycophenolate mofetil; MTX: methotrexate; PDN: prednisone; TST: tuberculin skin test; F = female, M = male.

Table 3. Associations between the studied variables and the TST.

	n	Negative TST	Positive TST	p
Diabetes, n (%)	21	19 (90.5)	2 (9.5)	1.000
Current or previous smoking, n (%)	45	38 (84.4)	7 (15.6)	0.059
Presence of vaccination scar, n (%)	54	50 (92.6)	4 (7.4)	0.614
TST while on immunosuppressant(s), n (%)	57	53 (93.0)	4 (7.0)	0.445
CT with reticular interstitial pattern, n (%)	70	63 (90.0)	7 (10.0)	1.000
CT with ground-glass opacities, n (%)	54	49 (90.7)	5 (9.3)	1.000
CT with honeycombing, n (%)	12	10 (83.3)	2 (16.7)	0.299

TST = tuberculin skin test; CT = (chest) computed tomography; n = number of participants, p = p value.

(17.1%). Most of the participants had moderate to severe functional impairment (mean FVC 69.2%). Some of them could not undergo spirometry (n = 6). The majority of participants had fibrotic lung disease, characterized by the presence of reticular pattern on chest CT (79.5%), though only some had extensive fibrosis with honeycombing (13.6%). The tomographic findings were predominantly of peripheral (54.5%) and lower-lobe (59.1%) distribution. Since the presence of a BCG vaccination scar was assessed by direct visualization, we were unable to assess participants evaluated remotely (n = 18).

We found 8 participants with a positive TST (Table 2), resulting in an LTBI prevalence of 9.1% (95% CI, 2.1%-15.1%). These individuals were mostly male (62.5%), older (mean age 65.9), and had moderate

functional impairment (mean FVC 53.2%), with evidence of fibrotic lung disease (reticular pattern on chest CT in 87.5%). The TST median was 13 (minimum of 7, maximum of 20).

The frequency of positive reactions was slightly higher among individuals with a current or previous history of smoking, but this finding was not significant (p = 0.059). No significant association between prior BCG vaccination and positive reactions was found (p = 0.614). Though it is known that the use of immunosuppressants may lead to false-negative reactions, there was no association between immunosuppression and a negative TST (Table 3).

No active tuberculosis cases were observed among the participants during the study period.

DISCUSSION

The prevalence of LTBI found in the studied population (9.1%), though lower than that estimated for the world population (around 25%),⁽¹⁾ is similar to a study with people living with HIV, another at-risk population, in the state of Paraná (9.0%),⁽¹²⁾ which might reflect the local prevalence of the infection. Data on LTBI in patients with ILDs are scarce in the literature. One study evaluated 62 patients with sarcoidosis and found a positive IGRA in 16 (25.8%) of them.⁽¹³⁾ Another study evaluated 244 patients with coal workers' pneumoconiosis and found a positive IGRA in 162 (66.4%) of them.⁽¹⁴⁾ There are no studies on LTBI in patients with other types of ILD. It is not possible to ascertain whether the prevalence found in our study reflects the true prevalence in this population. However, given that many of these patients have a higher risk of progressing to active disease due to immunosuppression, finding a prevalence of close to 10% in this group is extremely relevant, since identifying the infection and offering preventive treatment might diminish the risk of developing the illness.

Regarding risk factors for tuberculosis, smoking is one of the most well-established,⁽¹⁵⁾ as well as diabetes.⁽¹⁶⁾ In our study, neither smoking ($p = 0.059$) nor diabetes ($p = 1.000$) were significantly associated with a positive reaction. Since diabetes was only identified through data from medical records, underreported diagnoses might have interfered with this association.

Though BCG vaccination is frequently associated with false-positive reactions on the TST, implying low specificity for vaccinated individuals,⁽¹⁷⁾ several authors affirm that vaccination in childhood has little impact on TST in adulthood.⁽¹⁸⁻²⁰⁾ However, a recent study found data suggesting otherwise.⁽²¹⁾ It is recommended that people who were vaccinated late, that is, after the first few years of life, be screened with IGRAs.⁽²²⁾ In Brazil, BCG vaccination, which is available free of charge in the Brazilian public health system, is universal and administered on the first few days of life, making it unlikely to interfere with TST's results in adults. Corroborating these data, we did not find an association between the presence of BCG vaccination scar and positive TST ($p = 0.614$).

Patients with AIRDs have a higher rate of false-negative TSTs.⁽²³⁾ Furthermore, the chronic use of prednisone, which is one of the most prescribed corticosteroids for treating these diseases, negatively impacts the response to PPD,^(21,24) especially in doses higher than 15 mg a day.⁽²⁵⁾ However, the effect of other immunosuppressants on TST and IGRAs is scarcely described in the literature and there is no consensus on the best method for diagnosing LTBI in immunocompromised patients,⁽²⁶⁾ although IGRAs seem to have higher sensibility and specificity than TST in this population.^(23,24) Some authors suggest that TST

and an IGRA should be performed concomitantly.⁽²⁶⁾ Although the majority (64.8%) of participants in this study underwent TST when already on one or more immunosuppressants, the association between being tested while immunosuppressed and a negative reaction was not statistically significant ($p = 0.445$). It is suggested to screen these patients before starting treatment, if possible.⁽²²⁾ Currently, the only available method for LTBI detection in the Brazilian public health system is the TST.⁽²⁰⁾ The incorporation of IGRAs into Brazil's public health system was recently approved, but only for people living with HIV, for children who are tuberculosis contacts, and for patients receiving hematological transplantation.⁽²⁷⁾

Patients with ILDs have a higher risk of tuberculosis,^(28,29) especially those with silicosis,⁽³⁰⁾ as well as patients with AIRDs,⁽³¹⁾ in particular when associated with ILD.⁽³²⁾ The use of immunosuppressants such as corticosteroids,⁽³³⁻³⁵⁾ azathioprine,⁽³⁶⁾ cyclophosphamide,⁽³¹⁾ and TNF inhibitors⁽³⁵⁾ is also, by itself, associated with a higher risk of tuberculosis. The diagnosis of tuberculosis in patients with ILDs is more difficult due to parenchymal abnormalities related to the interstitial disease.⁽³⁰⁾ The participants of this study had several of those risk factors, however, none developed active tuberculosis during the study period.

In a study with another at-risk population, renal transplantation recipients, the participants with an initial negative TST were tested a second time to evaluate immune response reactivation,⁽³⁷⁾ a strategy recommended by some authors for immunocompromised patients.⁽²²⁾ In Brazil, this is usually performed in a periodic screening of health care workers⁽³⁸⁾ and was not performed in this study. However, in case of contact with an active tuberculosis patient after the initial investigation, the test should be repeated.⁽³⁹⁾

This was one of the first studies to screen LTBI on patients with different ILDs, an at-risk population that is little addressed. The choice to screen only patients requiring immunosuppression prevents the generalization of the findings for all patients with ILD; however, it is justified by the fact that these individuals are the ones with a higher risk of developing tuberculosis. Since the screening was performed with TST, which can be more affected by immunosuppression, the prevalence found in this study might have been underestimated. Unfortunately, IGRAs are not currently offered by the Brazilian public health system, and though they are soon to be included, they will not be available for patients on immunosuppressants. There might have also been confounding biases related to other variables associated with the risk of tuberculosis, such as family income.

Early detection of LTBI is of vital importance, to allow for prompt indication of preventive treatment, as recommended by the WHO's End TB Strategy. Patients with ILD who are treated with immunosuppressants

are not commonly screened for this infection, despite being under a greater risk of progression to active disease. This study showed a prevalence of LTBI of 9.1% in a sample of such individuals, suggesting the need for a more cautious approach to these patients. Further research is needed to establish a

more thorough definition of the role of LTBI screening in this population.

AUTHOR CONTRIBUTIONS

Both authors actively participated in all stages of the development of this manuscript.

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