CLINICS

ORIGINAL ARTICLE

Ankylosing spondylitis and psoriatic arthritis: revisiting screening of latent tuberculosis infection and its follow-up during anti-tumor necrosis factor therapy in an endemic area

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OBJECTIVES: To retrospectively evaluate the performance and distinctive pattern of latent tuberculosis (TB) infection (LTBI) screening and treatment in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) under anti-tumor necrosis factor (TNF) therapy and determine the relevance of re-exposure and other risk factors for TB development.

METHODS: A total of 135 and 83 patients with AS and PsA, respectively, were evaluated for LTBI treatment before receiving anti-TNF drugs via the tuberculin skin test (TST), chest radiography, and TB exposure history assessment. All subjects were evaluated for TB infection at 3-month intervals.

RESULTS: The patients with AS were more often treated for LTBI than were those with PsA (42% *versus* 30%, p=0.043). The former also presented a higher frequency of TST positivity (93% *versus* 64%, p=0.002), although they had a lower frequency of exposure history (18% *versus* 52%, p=0.027) and previous TB (0.7% *versus* 6%, p=0.03). During follow-up [median, 5.8 years; interquartile range (1QR), 2.2-9.0 years], 11/218 (5%) patients developed active TB (AS, n=7; PsA, n=4). TB re-exposure was the main cause in seven patients (64%) after 12 months of therapy (median, 21.9 months; IQR, 14.2-42.8 months) and five LTBI-negative patients. TB was identified within the first year in four patients (36.3%) (median, 5.3 months; IQR, 1.2-8.8 months), two of whom were LTBI-positive. There was no difference in the TB-free survival according to the anti-TNF drug type/class; neither synthetic drug nor prednisone use was related to TB occurrence ($p > 0.05$).

CONCLUSION: Known re-exposure is the most critical factor for incident TB cases in spondyloarthritis. There are also some distinct features in AS and PsA LTBI screening, considering the higher frequency of LTBI and TST positivities in patients with AS. Annual risk reassessment taking into consideration these peculiar features and including the TST should be recommended for patients in endemic countries.

KEYWORDS: Latent Tuberculosis; Spondyloarthritis; Tuberculin Skin Test; *Mycobacterium tuberculosis*; Tumor necrosis factor-alpha.

INTRODUCTION

Over the last decades, the advent of immunobiological drugs has led to advances in the treatment of spondyloarthritis (SpA), especially in the use of anti-tumor necrosis factor (TNF) agents. Drugs, such as infliximab (INF), adalimumab (ADA), etanercept (ETA), golimumab (GOL), and certolizumab pegol (CER), have improved therapeutic objectives and reduced disease progression for affected patients. TNF plays a critical role in the immune mechanism and maintenance of granulomas against *Mycobacterium tuberculosis*, which is related to the increased risk of latent tuberculosis (TB) infection (LTBI) reactivation in patients using anti-TNF agents in comparison to that in patients using drugs with other mechanisms (1-3).

Recommendations and guidelines were developed to reduce TB reactivation in patients treated with immunobiological agents. However, local differences among countries

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and risk exposures reinforce that different screening strategies might be needed. In Brazil, owing to the endemic prevalence of TB (34.8 per 100,000 population; São Paulo, 39.6 per 100,000 population) (4) and the increased risk of LTBI reactivation in patients with SpA, the identification and treatment of patients at a higher risk are essential before starting anti-TNF therapy.

Despite LTBI screening before anti-TNF therapy, TB reactivation and new exposure remain a relevant problem. Canadian and American guidelines suggest periodical rescreening for high-TB-risk patients (5,6). The legitimacy of this systematic reassessment is controversial, especially for endemic countries, as there is an evidence of overdiagnosis and consequent unnecessary treatment (7,8) owing to the expected higher frequency of false-positive tuberculin skin test (TST) findings. Solving this problem requires the definition of re-exposure frequency in patients with incident TB under anti-TNF therapy, despite initial preconized LTBI screening. However, there are no data in the literature regarding the relevance of new TB exposure compared to other possible risk factors in patients with SpA under TNF blockage therapy.

Therefore, the objective of this study was to retrospectively evaluate the performance of LTBI screening in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) under anti-TNF therapy in a TB endemic area and determine the relevance of re-exposure and other causal factors for this complication, aiming to improve the prevention of this infection.

MATERIAL AND METHODS

Population

This study retrospectively evaluated 221 patients with AS (n=138) or PsA (n=83) followed up in the Spondyloarthritis Outpatient Clinic from June 2004 to June 2018. The patients were referred to the Immunobiological Drugs Infusion Center (Centro de Dispensação de Medicação de Alto Custo of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) with indication to undergo biological therapy with anti-TNF drugs for disease activity refractory to conventional treatment. The subjects were followed up at 3-month intervals, with the possibility of unscheduled visits, as necessary. All patients who started anti-TNF therapy were included, except for three patients with AS for not having LTBI screening data documented correctly.

Study design

The data of the patients with AS and PsA under anti-TNF therapy (INF, ADA, ETA, GOL, and CER) were obtained from an ongoing longitudinal database protocol established in January 2000, which was conducted for all patients and included data on demographics, clinical and laboratory findings, treatments, LTBI screening, and TB occurrence.

According to Brazilian guidelines, all patients with AS and PsA recommended for immunobiological treatment were submitted to LTBI screening before initial therapy (9-13). Active infection was excluded by mycobacterial tests when indicated. LTBI treatment was prescribed to patients with at least one of the following characteristics: positive TST finding ($\geq$5 mm); signs of TB sequelae, such as fibrotic lesions on chest radiography (CXR); or previous known exposure to active TB. The latest was defined as present or past household and occupational contact with known TB cases at any time during adulthood. Previously, a report from our department has shown the importance of establishing the exposure history for LTBI treatment in Brazilian patients with rheumatoid arthritis (10). Patients treated for previous TB infection with documented complete therapy and no new contact history were not indicated for LTBI treatment.

The tuberculin used in the Mantoux method (TST) was PPD-RT 23, which was applied intradermally into the volar surface of the left forearm at a dose of 0.1 mL, containing 2-UT tuberculin units and biological equivalence with 5 UT of PPD-S. The result corresponded to the greater transverse diameter of the area of the palpable induration after 48-72 hours (12,13). The readings were performed by a trained nurse.

The LTBI-positive patients received isoniazid (INH) at 5 mg/kg up to 300 mg/day for at least 6 months or 180 daily doses according to national guidelines (12,13). The regular use of medication was checked at each medical appointment, in addition to the pharmacy dispensing report. One month of INH treatment was required before the initiation of anti-TNF therapy. TST repetition occurred during follow-up only in cases of clinical TB suspicion or owing to extended ($>$12 months) interruption and re-start of anti-TNF therapy.

Data related to the treatment of LTBI, e.g., adverse effects, such as hepatotoxicity and allergic reactions, and interruption, were also collected.

This study was approved by the Local Ethics Committee on Human Research of the University of São Paulo (CAPPesq) under number 1298/06. All participants provided their written informed consent in compliance with the Helsinki Declaration before initiating biological therapy.

Statistical analysis

The results were presented as means and standard deviations (SD) or medians and interquartile ranges (IQRs) for continuous variables (age, duration of disease and anti-TNF use, and prednisone dose) and compared using the t-test or Mann–Whitney test for normally and non-normally distributed variables. Conversely, the results were reported as percentages for categorical variables [sex, disease-modifying antirheumatic drug (DMARD) and prednisone use, TST finding of $>$5 mm, LTBI, TB exposure, and altered CXR finding] and evaluated using Fisher's exact test or the chi-squared test when indicated. Log-rank (Kaplan–Meier) analysis was conducted for TB-free survival on different anti-TNF courses. Statistical significance was considered when the p-value was $\leq$0.05. Statistical analyses were performed using the SigmaStat version 3.1 (2005) and GraphPad/Prisma software.

RESULTS

One hundred and thirty-five patients with AS and eighty-three patients with PsA received anti-TNF agents from 2004 to 2018 and were included in this analysis. The patient group was predominantly men (n=148, 68%). The mean age was 49.2 (SD, 13.1) years, and the mean disease duration was 19.3 (SD, 11.5) years. Half of the patients were treated with the same TNF inhibitor, while 110 (50%) had their drug treatment switched once (n=67), twice (n=35), or thrice (n=8). A total of 422 anti-TNF courses were assessed, including 190 (45%) treatments with INF, 128 (30%) with ADA, 92 (22%) with ETA, 11 (3%) with GOL, and 1 (0.2%) with CER. The median treatment duration was 5.8 (IQR, 2.2-9.0) years (Table 1). Seventy-four percent (three-quarters) used synthetic

Table 1 - Baseline characteristics.

	SpA (N=218)	AS (n=135)	PsA (n=83)	p*
Age (years)	49.2 (±13.1)	47.5 (±12.4)	52.2 (±13.9)	0.01
Disease duration (years)	19.3 (±11.5)	17.5 (11.5–26.3)	17.0 (10.3–22.9)	0.35
Male sex (%)	149 (68%)	111 (82%)	38 (46%)	<0.01
Anti-TNF therapy duration (years)	5.9 (2.2–9.0)	6.4 (2.2–9.2)	5.4 (2.3–8.2)	0.39
Synthetic DMARD use (%)	161 (74%)	99 (73%)	62 (75%)	0.75
Prednisone use (%)	59 (27%)	41 (30%)	18 (22%)	0.07

Values are expressed as means (standard deviations), medians (interquartile ranges), or percentages. SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DMARD, disease-modifying antirheumatic drug. *AS *versus* PsA.

Table 2 - LTBI screening in 218 patients with SpA under anti-TNF therapy.

	SpA (N=218)	AS (n=135)	PsA (n=83)	p*
LTBI +	82 (38%)	57 (42%)	25 (30%)	0.04
TST finding, ⩾5 mm	69/82 (84%)	53/57 (93%)	16/25 (64%)	<0.01
Only TST finding, ⩾5 mm	58/82 (71%)	46/57 (81%)	12/25 (48%)	<0.01
Exposure	23/82 (28%)	10/57 (18%)	13/25 (52%)	0.03
Only exposure	10/82 (12%)	3/57 (5.2%)	7/25 (28%)	0.01
Altered CXR finding	5/82 (6.1%)	2/57 (3.5%)	3/25 (12%)	0.16
Previous TB	6/218 (2.8%)	1/135 (0.7%)	5/83 (6%)	0.03

SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; LTBI, latent tuberculosis infection; TST, tuberculin skin test; CXR, chest radiography; TB, tuberculosis; TNF, tumor necrosis factor. *AS *versus* PsA.

DMARDs associated with the biological drug at the beginning of treatment, and sixty-seven percent presented peripheral arthritis.

The patients with PsA were older (52.2 ± 13.9 *versus* 47.5 ± 12.4 years, p=0.01), consisted of a lower proportion of men (46% *versus* 82%, $p<0.01$), and presented a higher frequency of peripheral arthritis (95% *versus* 50%, $p<0.01$) than did the patients with AS. The disease duration (p=0.35) and anti-TNF use duration (p=0.39) as well as synthetic DMARD (p=0.75) and prednisone use (p=0.07) and the frequency of anti-TNF drug switch (p=0.16) were similar between the groups (Table 1).

LTBI treatment before anti-TNF therapy was indicated for 82 (38%) patients, being more frequent for the patients with AS (n=57) than for those with PsA (n=25) (42% *versus* 30%, p=0.04), although previous TB was more prevalent in the latter (0.7% *versus* 6%, p=0.03) (Table 2). The most frequent condition among the patients with LTBI was TST positivity (69/82, 84%), followed by previous contact/exposure (23/82, 28%), and TB sequelae findings on CXR (5/82, 6.1%). Furthermore, synthetic DMARD (72% *versus* 74%, p=1.00) and prednisone use (32% *versus* 25%, p=0.33) was comparable between the TST-positive and TST-negative patients.

In comparison to that among the patients with PsA, TST positivity was the most prevalent condition among the patients with AS, with positive screening (93% *versus* 64%, $p<0.01$) even as an isolated criterion (81% *versus* 48%, $p<0.01$). Conversely, history of exposure was the most important associated (18% *versus* 52%, p=0.03) or single condition found among the patients with PsA (5.2% *versus* 28%, p=0.01).

According to the recommendations of the Brazilian Society of Rheumatology for rheumatoid arthritis (14), two patients received treatment for LTBI owing to a temporary shortage of the TST, despite no history of exposure or altered CRX findings.

Among the six patients with previous TB, three were re-treated with INH owing to a new contact history or an occupational exposure. None of these patients had a new TB episode during follow-up.

TST retest protocol

According to the internal protocol, the TST was repeated in cases of TB infection suspicion (n=12) or extended (>12 months) interruption and re-start of anti-TNF therapy (n=16) and previous negative test findings. Half of the 16 (50%) patients who were re-tested owing to interruption presented TST finding conversion; LTBI treatment was then indicated, and none developed TB until the end of this study. Among the 12 patients investigated for active infection, four patients presented TST finding conversion, being subsequently diagnosed and treated for active TB.

LTBI treatment and side effects

Of the 82 patients treated for LTBI, only 8.5% did not complete the INH regimen for the recommended period. Among the reasons for interruption were allergic reactions, transfer to another service, and development of active TB. Hepatotoxicity was seen in 24.3% of the patients, with most of them having elevated transaminase levels up to twice the normal upper limit. Two patients had INH treatment suspended for higher level elevations. Moreover, the eight patients who subsequently tested positive in the TST completed the LTBI treatment uneventfully.

TB cases

Eleven (5%) patients were diagnosed with TB during follow-up, and one patient had two events. The analysis of possible causal factors revealed no difference in sex, age, disease duration, and co-medication among the patients with or without reactivation/new infection ($p>0.05$) (Table 3). The assessment of the 422 anti-TNF courses revealed the presence of monoclonal and non-monoclonal anti-TNF antibodies in the general sample (p=0.69) and that the patients with AS (p=0.71) and PsA (p=0.98) had a comparable TB-free survival.

Anti-TNF therapy duration and TB

During follow-up, 4/12 (33.3%) TB episodes occurred within the first year, at a median duration of 5.3 (IQR, 1.2-8.8)

Table 3 - Comparison between 11 patients with and 207 patients without TB during follow-up.

	TB + (n=11)	TB – (n=207)	*p*
Age (years)	46.4 (13.1)	49.4 (13.2)	0.46
Disease duration (years)	16.5 (9.8–26.5)	17.5 (10.5–24.5)	0.75
Male sex (%)	10 (91%)	139 (67%)	0.18
Anti-TNF therapy duration (years)	1.3 (0.7–3.5)	6.3 (2.5–9.1)	<0.01
Synthetic DMARD use (%)	7 (64%)	154 (74%)	0.48
Prednisone use (%)	2 (18%)	57 (28%)	0.73
Prednisone dose (mg)	15 (10–20)	10 (5–10)	0.21
LTBI	4 (36%)	80 (39%)	1.00

TB, tuberculosis; TNF, tumor necrosis factor; DMARD, disease-modifying antirheumatic drug; LTBI, latent tuberculosis infection.

Table 4 - Description of the TB cases.

		Sex	Age (years)	Occupation	Risk factors	LTBI	Anti-TNF drug	TNFi–TB duration (months)	Infection
1	PsA	M	45	Salesman	Household contact, Smoking	pos	ADA	20.6	Pleural
2	PsA	M	69	Retired	DM, Schistosomiasis	neg	INFLIXI	3.7	Peritoneal
3	PsA	M	55	Unknown	None	neg	INFLIXI	15.5	Pulmonary
4	PsA	F	52	Unknown	DM, Smoking	pos	INFLIXI	32.4	Pulmonary
5	AS	M	36	Mechanic	None	neg	ADA	22.2	Pulmonary
6	AS	M	53	Retired	DM	neg	ADA	42.8	Pulmonary
7	AS	M	59	Retired	None	neg	INFLIXI	7.0	Pulmonary
8	AS	M	46	Unknown	Drug addiction, Alcoholism	pos	ADA	2.3	Pleural
9	AS	M	37	Physician	Occupational exposure	pos	ADA	8.8	Pleural
10	AS	M	36	Hairdresser	DM, Obesity	neg	ETA	23.3	Spondylodiscitis
11	AS	M	21	Student	None	neg	INFLIXI	14.2	Pulmonary

TB, tuberculosis; LTBI, latent tuberculosis infection; PsA, psoriatic arthritis; AS, ankylosing spondylitis; ADA, adalimumab; INFLIXI, infliximab; ETA, etanercept; DM, diabetes mellitus; neg, negative; pos, positive.

months after initiating anti-TNF therapy. Fifty percent of the patients received INH previously; one of these patients had a confirmed report of irregular use of INH. More prolonged therapy was observed in most patients (8/12, 66.7%), with a median duration of 22.8 (IQR, 17.7-27.2) months, including the patient with two events. Considering the seven patients, the median duration was 21.9 (IQR, 14.2-42.8) months. Two (28%) of these patients were LTBI-positive and treated with INH as recommended. The frequency of extra-pulmonary TB was 25% (2/8) among the patients with TB diagnosed after 12 months and 75% (3/4) among those diagnosed up to 1 year under anti-TNF therapy.

Table 4 describes the active TB cases with their respective risk factors. The majority of the patients (7/11, 64%) had identifiable isolated or concomitant risk factors: diabetes mellitus (n=4); smoking (n=2); occupational exposure (n=1); drug addiction (n=1); schistosomiasis (n=1); alcoholism (n=1); household contact (n=1); and obesity (n=1).

DISCUSSION

In this study, we provided novel evidence that known re-exposure is the most critical risk factor for incident TB in patients with SpA under long-term anti-TNF therapy.

Brazil is among the 30 high-TB-burden countries prioritized by the World Health Organization, encompassing 80% of the global TB cases. The risk for TB among patients with inflammatory arthritis is higher than that among the general population, varying according to the region or country of the study (1,2). However, no study has yet been performed on the incidence of TB among patients with SpA in Brazil.

The great advantage of this study is the consistent and complete LTBI screening for all patients using a standard protocol recommended by Brazilian guidelines (11) and the national recommendation for TB control (12,13). The non-homogeneous use of an LTBI screening protocol in previous studies hampers the interpretation of their findings on the relevance of each risk factor. A screening limited to a few parameters was reported by Shobha et al. (15), and a low adherence to screening was also observed in the Brazilian registry (16).

A long-term follow-up was also essential for this evaluation, as TB re-exposure is considered after at least 12 months (17,18), and it has already been shown that the risk remains throughout the treatment (19). The lack of information regarding the treatment duration (3,16,20) precludes an accurate evaluation of the importance of re-exposure in the context of incident TB. In addition, all but one study (21) evaluated SpA associated with other rheumatic diseases (17,22-24) without clear discrimination of the TB risk among each disorder. Unbalanced intrinsic disease features, such as age, occupational exposure, and glucocorticoid and DMARD use, in different illnesses are relevant confounding variables in the evaluation of risk factors (1,9). Moreover, the report focusing on AS is an extensive case-control study in Korea, analyzing solely the incidence of TB related to the use of anti-TNF drugs (21).

LTBI was seen in more than a third of the patients with SpA, a finding similar to the previously reported for

Brazilian (17), Spanish (24), South Korean (25), and Indian patients (26). We also confirmed that TST positivity was more frequent in the patients with AS than in the patients with PsA (17) possibly owing to the anergy already known in this latter arthropathy, as observed in rheumatoid arthritis (27). This distinct characteristic of PsA reinforces the relevance of exposure history screening in the evaluation of candidates for immunobiological therapy in comparison to AS.

Recent publications suggested that IGRA combined with the TST may be superior to the tests used separately (24,28-30), although the TST has already been proven useful for screening in endemic countries (3,10,12,13,27). In Brazil, owing to the unavailability of IGRA in the public health system, the TST remains the main tool for LTBI screening.

With this strict protocol and the indicated treatment of LTBI before initiating TNF blockage therapy, eleven (5%) patients developed active TB during a median follow-up of more than 5 years. This frequency is higher than that reported in other endemic countries for rheumatic diseases (15,21,31, 32). The most likely explanation is probably related to the long-term follow-up (28), biological class used (21), and concomitant analysis of distinct diseases in previous studies (15,31,32).

The analysis of the risk factors for incident TB revealed that known re-exposure is the most critical cause of this complication. It occurred in a median period of 2 years, and we confirmed the previous observation that new TB infections mostly present as a pulmonary disease (18,33,34). In contrast, TB reactivation was observed in approximately one-third of the patients with TB, and the majority of cases were extra-pulmonary with a median of 5.3 months of exposure. Non-adherence to LTBI treatment is likely the cause in this group, as half of the patients had positive screening findings. Despite the prescription and dispensing of medication and checking in each medical appointment, it is not straightforward to ensure the correct use of INH. Poor adherence to LTBI treatment is an obstacle among individuals with high-risk TB diseases. Indeed, Sandgren et al. (35) found that the proportions of individuals completing LTBI treatment may be as low as 39% for the general population and 48% for case contacts.

Host-related risk factors may have contributed to the higher incidence of TB observed in this study, as two-thirds of the patients reported at least one of the following well-known risk factors: smoking, drug addiction, alcoholism, HIV infection, malnutrition, diabetes mellitus, and chronic renalfailure(1,36). The lack of age- and sex-matched control group is a limitation and precludes the analysis of the real relevance of these factors.

Therefore, it is unquestionably necessary to reinforce the contact history and risk exposure approach as a more effective screening and preventive tool during follow-up. In addition to establishing at-risk populations that could benefit from intensive supervision of adherence to prophylaxis and periodic re-evaluation of LTBI, the preference for non-anti-TNF biological drugs, such as anti-IL-17 and anti-IL-12/23, which are not associated with an increased risk of TB (1,2), should be considered.

There was no difference found in the TB-free survival according to the type or class of anti-TNF drug used, and the small representation of ETA in our sample may account for this finding. This drug was reported to be associated with a lower incidence of TB than were other monoclonal anti-TNF antibodies in rheumatic diseases (1,2,37-39). The concomitant use of synthetic DMARDs with biological therapy was not associated herein with a higher frequency of TB, a finding similar to that reported by the CORRONA registry (40) and distinct to that observed in an Italian systematic review (41).

Brazilian guidelines do not indicate the programmed TST repetition; however, prescription of INH was essential in eight patients before the reintroduction of anti-TNF therapy after a period without medication, and active TB diagnosis was necessary in four patients with negative test findings in the baseline. These cases support the notion that re-exposure to *M. tuberculosis* remains a threat to the prevention in endemic countries and that as recommended by some guidelines (5,6,42,43), LTBI re-evaluation may identify patients at a higher risk of developing active TB in a long-term follow-up.

Despite the previously defined LTBI screening protocol, a retrospective analysis was conducted in this study, which limits some results and conclusions, such as those for the risk factors. Further, the unavailability of other tests (IGRA, QuantiFERON-TB Gold In-Tube test, and T-SPOT.TB assay) impaired the comparison with the TST.

Herein, we provided new data demonstrating that known re-exposure is the most crucial factor for incident TB cases in patients with SpA under anti-TNF therapy, despite the screening and treatment of LTBI before initiating TNF blockage therapy. We also confirmed some distinct features in AS and PsA LTBI screening. Annual risk reassessment taking into consideration these peculiar features and including the TST should then be recommended for these patients in endemic countries.

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