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Performance of 4 methods for screening of latent tuberculosis infection in patients with chronic inflammatory arthritis under TNFα inhibitors: a 24-month prospective study

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Abstract

Background: The reactivation rate of tuberculosis in patients with chronic inflammatory arthritis (CIA) on TNFα inhibitors (TNFi) and baseline negative screening for latent tuberculosis infection (LTBI) is higher than in the general population.

Aim: To compare the performance of tuberculin skin test (TST), TST-Booster, ELISPOT (T-SPOT.TB) and QuantiFERON-TB Gold in tube (QFT-IT) to detect LTBI in patients with CIA on TNFi.

Patients and methods: A total of 102 patients with CIA [rheumatoid arthritis (RA), n = 40; ankylosing spondylitis (AS), n = 35; psoriatic arthritis (PsA), n = 7; and juvenile idiopathic arthritis (JIA), n = 20] were prospectively followed-up for 24 months to identify incident LTBI cases. Epidemiologic data, TST, T-SPOT.TB, QFT-IT and a chest X-ray were performed at baseline and after 6 months of LTBI treatment.

Results: Thirty six percent (37/102) of patients had positive TST or Interferon Gamma Release Assays (IGRAs) tests. Agreement among TST and IGRAs was moderate (k = 0.475; $p = 0.001$), but high between T-SPOT.TB and QFT-IT (k = 0.785; $p < 0.001$). During the 24-Month follow-up, 15 (18.5%) incident cases of LTBI were identified. In comparison to TST, the IGRAs increased the LTBI diagnosis power in 8.5% (95% CI 3.16–17.49). TST-Booster did not add any value in patients with negative TST at baseline. After 6-Month isoniazid therapy, IGRAs results did not change significantly.

Conclusions: Almost 20% of CIA patients had some evidence of LTBI, suggesting higher conversion rate after exposition to TNFi. TST was effective in identifying new cases of LTBI, but IGRAs added diagnostic power in this scenario. Our findings did not support the repetition of IGRAs after 6-Month isoniazid therapy and this approach was effective to mitigate active TB in 2 years of follow-up.

Keywords: Latent tuberculosis infection, Chronic inflammatory arthritis, TNFα inhibitors, IGRAs, Prospective cohort, Non-interventional trial

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Introduction

TNFα inhibitors are important therapeutic agents used for the management of pain, inflammation, quality of life and function in patients with chronic inflammatory arthritis (CIA), including rheumatoid arthritis (RA) [1], psoriatic arthritis (PsA) [2], ankylosing spondylitis (AS) [3] and juvenile idiopathic arthritis (JIA) [4]. However,

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these drugs, particularly the monoclonal inhibitors, are associated with an increased risk of reactivation of latent tuberculosis infection (LTBI) [5]. In this context, the clinical presentation of active tuberculosis (TB) occurs in the first 12 months of treatment with biolological drugs and some TB cases are severe, including extrapulmonary and miliary forms, which limit the clinical management of the underlying disease [6]. The pathophysiological mechanism is related to granuloma disorganization after TNFα inhibition in patients with latent forms or after re-exposure to *Mycobacterium tuberculosis* (*M. tuberculosis*) [6].

The incidence of active TB is approximately 3–9 times higher in patients on TNFα inhibitors than in the general population (86.9 cases per 100,000 person-years vs. 35.8 cases per 100,000 person-years, respectively) [7]. Therefore, different strategies have been developed to minimize the risk. Several guidelines have recommended to use tuberculin skin test (TST), as well as to assess epidemiological background and chest X-ray for diagnosing LTBI. If LTBI is identified, treatment is recommended. The LTBI treatment with isoniazid for 6 months was valid, safe, and efficient in patients with RA [8].

Moreover, active TB cases have been identified in patients with negative baseline LTBI test, particularly among those with AS [7]. Therefore, additional strategies, including the interferon gamma release assays (IGRAs), are necessary to better identify high-risk patients and to minimize the impact of incident TB cases. These tests were developed after the recognition of crucial role of IFN-gamma on cellular response against the *M. tuberculosis*, by specific targeting the peptides ESAT-6 and CFP-10, which are not present in the bacillus Calmette–Guérin (BCG) vaccine neither in most of the other non-tuberculous mycobacteria [9].

The aim of this study was to compare the performance of three methods for detecting LTBI, including TST, QuantiFERON-TB Gold in tube (QFT-IT) test and ELISPOT (T-SPOT.TB), in patients with active CIA on anti-TNFα therapy. In addition, we aimed to evaluate the TST-Booster phenomenon effectiveness in diagnosing LTBI, as well as to verify incident cases of mycobacterial infection in a 24-Month follow-up and to test the IGRA positivity after treatment with isoniazid for 6 months.

Patients and methods

A total of 102 patients with CIA classified according to classification criteria as RA [1], PsA [2], AS [3] and JIA [4] were selected and consecutively screened from Rheumatology and Paediatric Rheumatology Outpatients Clinic of the Federal University of São Paulo, Paulista School of Medicine (Universidade Federal de São Paulo/ Escola Paulista de Medicina, Unifesp/ EPM). All of them were on TNFα inhibitors for at least 6 months. However, 21

patients had previous positive TST and had been treated for LTBI according to local standard guidelines. Therefore, this study included 81 patients who were negative TST before starting TNFα inhibitors and were followed up for 24 months. Patients with active TB, previous neoplasms or other current infections were excluded.

Demographic data, medical history and concomitant medications were recorded. Disease activity was assessed using the Disease Activity Score (DAS28) [10] for RA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS [11], the Psoriasis Area Severity Index (PASI) [12] for PsA and the Wallace criteria [13] for JIA. All participants answered a questionnaire about TB disease symptoms, including cough, weight loss, fever and sweating. Epidemiological data regarding personal, professional and family contact with TB, as well as BCG vaccination were also recorded. Chest X-rays were evaluated by a radiologist and by a rheumatologist, and tomography was performed, in case of disagreement between specialists. TST and IGRAs were conducted performed in this group of 81 patients with previous negative TST test before starting TNFα inhibitors.

TST was conducted via an intradermal inoculation of 0.1 mL (2 UT) of PPD-RT-23 (Statens Serum Institute, Denmark) on the left forearm, approximately 8 cm below the elbow crease. The results were read 72 h after inoculation by a trained nurse. TST was considered positive if the measured area of induration had a diameter larger than or equal to 5 mm. In case of negative results, a TST-Booster was performed, which consisted in repeating the TST in the contralateral forearm within 3 weeks after the first reading. TST-Booster was considered positive when the total area of induration was larger than 10 mm or whether the induration was 6 mm greater than the first TST measurement [14].

Blood samples were collected in the same visit along with TST and IGRAs. A 7 mL blood sample was collected from each patient: 3 mL were transferred to specific test tubes for use in the third generation QFT-IT system (Cellestis, Carnegie, Australia), and the remaining 4 mL were transferred to heparinized tubes for T-SPOT. TB (Oxford Immunitec, Abingdon, UK). All assays were performed according to the manufacturer's instructions.

In case of current contact with TB, chest X-ray suggestive alterations or positivity for TST, T-SPOT.TB or QFT-IT, but without evidence of active TB detected, patients were treated with isoniazid (10 mg/kg/day, maximum of 300 mg/day) for 6 months. After that, TST, T-SPOT.TB or QFT-IT were repeated and the patients were monitored for signs and symptoms of active TB during 24 months. Medical appointments occurred monthly during the first 6 months and quarterly thereafter. In addition, the LTBI tests (TST and IGRAs) were defined as modified if

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the status became from negative to positive or vice-versa after 6-Month of isoniazid treatment. In addition, the remaining 21 patients were clinically prospectively followed for 24 months to evaluate the active tuberculosis incidence.

Statistical analysis

Descriptive analyses were performed with demographic, anthropometric and clinical data for each CIA. Both baseline and current LTBI tests (after exposition to TNFα inhibitors), including TST, chest X-ray and epidemiology, were compared. The Kolmogorov–Smirnov test and Levine's test were used to test the normal data distribution. Categorical variables were compared using chi-square test and Fisher's exact test, when appropriate. Continuous variables with a non-normal distribution were compared using the Mann–Whitney test, whereas continuous variables with a normal distribution were compared using analysis of variance (ANOVA). The agreement between the tests was assessed using the kappa test. The qualitative results of the tests before and after the treatment of LTBI were compared using McNemar's test. The

increment rate was calculated considering the percentage of cases detected by IGRAs methods (T-SPOT.TB or QFT-IT) but not by TST. All statistical analyses were performed using SPSS version 20.0 (IBM, USA). p value was set as 0.05.

Results

A total of 102 patients including 82 adults with CIA (40 with RA, 35 with AS and 7 with PsA) and 20 children with JIA were enrolled in this 24-month prospective study. RA patients had a predominance of women, while AS and PsA group had male predominance. The demographic and clinical data, including concomitant medication (conventional disease-modifying antirheumatic drugs [cDMARDs] and TNFα inhibitors) are shown in Table 1. Also, all tests to detect LTBI were performed before, as a recommended screening protocol by the Brazilian health authorities, and after TNFα inhibitors exposition, as research protocol design. The mean time interval since the introduction of these agents can be found in Table 1.

Table 1 Demographic and clinical data of patients treated with TNFα inhibitors

Parameter	JIA (n = 20)	RA (n = 40)	AS (n = 35)	PsA (n = 7)	*p* value
Age (years)	14.2 ± 7.2[a]	55.5 ± 9.3[c]	42.8 ± 9.9[b]	54.3 ± 6.7[c]	0.001
Female sex	12 (60%)	36 (90%)	10 (28.5%)	3 (42.9%)	0.001
Length of disease (years)	5.6 ± 3.3[a]	14.8 ± 8.2[b]	12.5 ± 7.7[b]	18.0 ± 7.9	0.001
Disease activity					
BASDAI			1.76 ± 1.51		
DAS28		2.86 ± 0.8			
PASI				2.68 ± 4.12	
Current medications					
Concomitant					
GC	1 (5%)	11 (27.5%)	0	0	0.001
Methotrexate	7 (35%)	17 (42.5%)	3 (8.6%)	5 (71.4%)	0.001
Leflunomide	7 (35%)	20 (50%)	0	1 (14.3%)	0.001
Sulfasalazine	0	0	4 (11.4%)	0	0.079
NSAIDs	2 (10%)	0	12 (34.3%)	0	0.001
CG	1 (5%)	11 (27.5%)	0	0	0.001
Cyclosporine	1 (5%)	0	0	0	0.267
Mesalazine	2 (10%)	0	0	0	0.07
Length of TNFi use to TNF inhibitorsα (years)	1.4 ± 1.1[a]	2.4 ± 1.9[a]	3.5 ± 1.6[b]	3.9 ± 1.9[b]	0.001
TNFα inhibitors					0.057
Adalimumab	5 (25%)	11 (27.5%)	7 (20%)	4 (57.2%)	
Etanercept	9 (45%)	22 (55%)	14 (40%)	0	
Infliximab	6 (30%)	7 (17.5%)	14 (40%)	3 (42.8%)	

Student's *t*-test, ANOVA; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DAS-28, Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; PASI, Psoriasis Area Severity Index; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, TNF inhibitors; GC, glucocorticosteroids; (a) and (b) had different means according to Duncan's multiple comparison test (age and period of exposure) or (c) Dunnet's test at an overall level of significance of 5%

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Despite living in an endemic country for TB, only twelve (11.8%) patients had consistent positive epidemiology. Three patients had chest X-ray abnormalities, including two with a calcified nodule (patient with RA, but negative for TST and IGRAs and another patient with AS, but positive for TST and IGRAs) and one with pulmonary fibrosis (patient with RA and negative for TST and IGRAs). RA, AS, PsA and JIA patients did not differ concerning to epidemiological data and chest X-ray findings. Regarding BCG, all children and adolescents with JIA had vaccine scar and BCG recorded on vaccination card. Although no adult patient had BCG vaccine recorded, a BCG scar was observed in more than 70% of patients with PsA and AS and 47% of RA patients (Table 2).

Patients with RA had lower TST positivity (30%) than those with AS (37.1%) and PsA (42.9%) ($p = 0.017$). No patient with JIA had a positive TST. There was no significant difference regarding T-SPOT.TB and QFT-IT positivity among adult patients (31.7% and 22%, respectively). On the other hand, only one patient with JIA had a positive IGRA (T-SPOT.TB and QFT-IT). There was no association among the TNFα inhibitors and positivity of the 3 tests (TST, T-SPOT.TB and QFT-IT) (Table 3). TST-Booster was positive in only 3 patients (2 with AS and one with RA). These patients had baseline negative TST, but a positive IGRA in 2 of them (one for T-SPOT.TB and another one for QFT-IT), suggesting some agreement between TST-Booster and IGRA results. However, the TST-Booster did not add any value to identify LTBI.

Considering the 81 patients with negative TST pre-anti-TNFα screening, 10 of them (12.3%; 95% CI 6.1–21.5) became positive for TST after exposure to TNFα inhibitors. Among the remaining 71 patients, 6 had positive IGRAs [T-SPOT.TB, n = 6, 7.4% (95% CI 2.8–15.4); QFT-IT, n = 4, 4.9% (95% CI 1.4–12.1)] (Fig. 1).

Table 3 Positivity of TST, T-SPOT.TB and Quantiferon after treatment with TNFα inhibitors

LTBI tests	ADA (n = 27)	ETA (n = 45)	IFX (n = 30)	*p* value
TST	6 (22.2%)	14 (31.1%)	8 (26.7%)	0.75
T-SPOT.TB	4 (14.8%)	16 (35.6%)	7 (23.3%)	0.15
QFT-IT	3 (11.1%)	11 (24.4%)	5 (16.7%)	0.38

ADA, adalimumab; ETA, etanercept; IFX, infliximab; TST, tuberculin skin test; T-SPOT. TB, elispot; QFT-IT, quantiferon; LTBI, latent tuberculosis infection

Four of them were positive for both QFT-IT and SPOT. TB.

The remaining 65 patients were negative for the 3 LTBI screening tests. However, patients with AS had moderate agreement between TST and IGRAs (kappa = 0.697; $p < 0.01$), but 100% concordance between the T-SPOT. TB and QFT-IT. Similarly, total agreement between the T-SPOT.TB and QFT-IT was observed with JIA patients. The worst agreement was seen in patients with RA (TST and IGRAs: kappa = 0.294; T-SPOT.TB and QFT-IT: kappa = 0.632). Analysing only 35 AS patients, 22 of them had negative TST and IGRAs; 28 patients had negative QTF-IT and 25 had negative T-SPOT.TB. The Fig. 2 is showing only the 15 pacients who presented at least one positive test for LTBI. There was moderate agreement between the TST and IGRAs (kappa = 0.475; $p = 0.001$) and high agreement between T-SPOT.TB and QFT-IT (kappa = 0.785, $p < 0.001$).

In comparison to TST, IGRAs increased the diagnosis of LTBI in 8.5% (95% CI 3.16–17.49), particularly the T-SPOT.TB [8.5% for T-SPOT.TB (95% CI 3.16–7.49) vs. 5.6% (95% CI 1.56–13.8) for QFT-IT]. All patients with a positive QFT-IT test were also positive for T-SPOT.TB. In addition, all patients with a negative TST or T-SPOT. TB had also a negative QFT-IT.

Among the 81 patients who had a negative TST prior to TNFα therapy screening, 15 (18.5%) new cases of LTBI were identified after exposure to them. They were treated

Table 2 Clinical features and test results suggestive of latent tuberculosis infection in patients with chronic inflammatory arthritis after exposure to TNFα inhibitors

LTBI parameters	JIA (n = 20)	RA (n = 40)	AS (n = 35)	PsA (n = 7)	*p* value
BCG scar	20 (100%)	19 (47.5%)	27 (77.1%)	5 (71.4%)	0.001
Chest X-ray abnormalities	0	2 (5%)	1 (2.8%)	0	0.834
Positive TB epidemiology	0	7 (17.5%)	4 (11.4%)	1 (14.3%)	0.214
Positive TST	0	12 (30%)	13 (37.1%)	3 (42.9%)	0.017
Positive IGRA					
T-SPOT.TB	1 (5%)	14 (35%)	10 (28.6%)	2 (28.6%)	0.097
Quantiferon	1 (5%)	9 (22.5%)	7 (20%)	2 (28.6%)	0.277

JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; BCG, Bacillus Calmette-Guérin, TB, tuberculosis, LTBI, latent tuberculosis infection; TST, tuberculin skin test; IGRA, interferon gamma release assay; T-SPOT.TB, Elispot
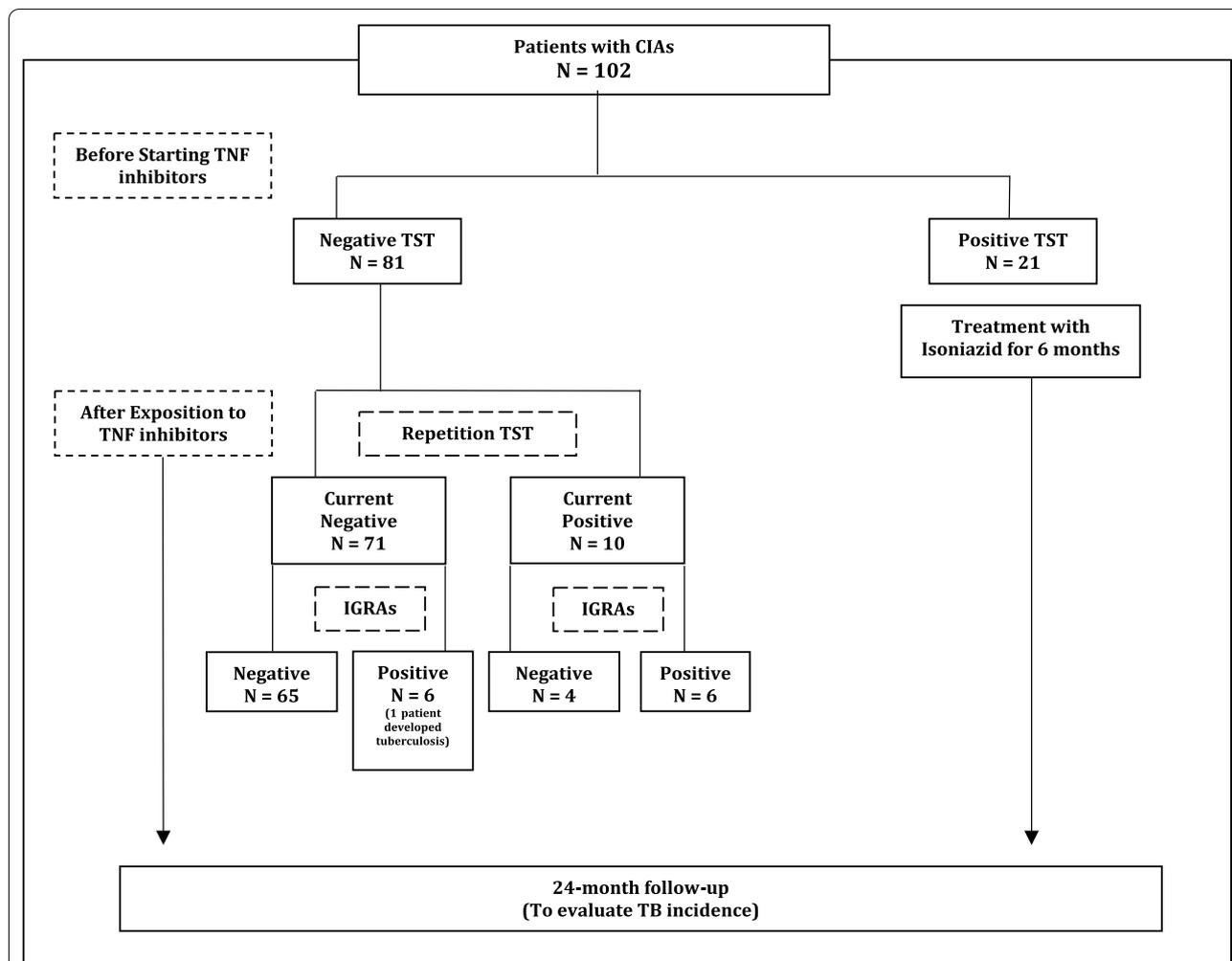
Fig. 1 Flowchart of TST and IGRAs after TNFα inhibitors introduction during a 24-Month follow-up, including a cross-sectional and other prospective phase
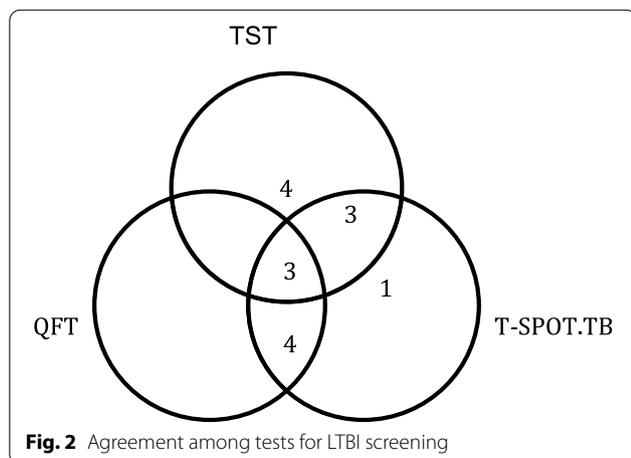

Fig. 2 Agreement among tests for LTBI screening

with isoniazid for 6 months and followed monthly. Considering that none of them had any symptom related to active TB, including fever, cough, weight loss and sweating, there was no withdrawal of TNFα-inhibitors after positive TST in patients on biological therapy.

After LTBI treatment with isoniazid, we observed some modifications of 3 tests results. For TST, 2/15 patients became negative; for T-SPOT.TB, 2/13 patients became negative. On the other hand, 4/15 patients changed QFT-IT status [3 became positive and one negative]. At least one LTBI screening test was positive after 6-Month treatment with isoniazid (Table 4). The observed modifications in IGRA results did not have any clinical implication in the management of patients. None of them developed active tuberculosis in 24 months.

From the group of patients with negative IGRAs and QFT-IT negative, during 24-Month follow-up, only 1 patient with AS had pleuropulmonary tuberculosis,

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Table 4 Main outcomes and test results of new 15 patients with LTBI before and after treatment with isoniazid

Patient	Dx	TNF blocker	LT (years)	EPI	BCG	TST	Booster	ELISPOT	QFT	TST after	ELISPOT after	QFT after treatment
1	AS	ETA	3	−	+	10	NA	+	−	15	−	−
2	PsA	IFX	4	−	−	8	NA	+	+	7	+	+
3	AS	ETA	1	−	+	0	3	+	+	0	+	−
4*	AS	IFX	3	−	+	10	NA	+	+	0	+	+
5	AS	ADA	5	−	−	10	NA	+	−	10	Indet	−
6	RA	IFX	1	−	−	5	NA	+	+	20	+	+
7	RA	ETA	2	−	−	0	0	+	+	4	−	+
8	RA	ETA	1	+	+	16	NA	−	−	15	−	−
9	RA	IFX	2	−	+	9	NA	+	−	8	+	+
10	RA	ETA	3	−	+	15	NA	−	−	0	−	+
11	JIA	ETA	2	−	+	0	0	+	+	0	+	+
12	PsA	IFX	3	−	−	10	NA	−	−	8	Indet	−
13	AS	ADA	2	−	−	5	NA	−	−	5	−	−
14	RA	ETA	3	−	+	0	0	+	−	0	+	+
15	RA	ETA	1	+	+	4	10	+	+	4	+	+

* Patient diagnosed with pulmonary TB before and after treatment

RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; JIA, juvenile idiopathic arthritis; TNF, tumor necrosis factor blockers; ADA, adalimumab; IFX, infliximab; ETA, etanercept; Dx, diagnosis; LT, length of treatment (in years); EPI, epidemiology; BCG, Bacillus Calmette-Guérin; TST, tuberculin skin test (in mm); QFT, Quantiferon, NA, not available; Indet, indeterminate

despite the fact that he had negative TST twice (before and after TNF-α inhibitors exposition), as well as negative IGRAs and PPD-Booster. He was on infliximab for 3 years and developed cough, fever and radiographic abnormalities (left upper lobe consolidation). Histopathological examination of lung specimen showed chronic granulomatous pleuritis with positive acid-fast bacilli, confirming pleuropulmonary TB. The TNFα blocker was withdrawn, and he was treated with rifampicin, isoniazid, pyrazinamide and ethambutol for 6 months with good outcome. Regarding the remaining 21 patients with previous LTBI treatment before starting TNF inhibitors, none of them had active TB during 24-Month follow-up.

None of clinical, laboratory or imaging parameters had a positive predictive value for changes or conversion of the LTBI tests in patients with CIA, including epidemiological data, joint disease activity, concomitant medications, type and length of use of TNFα inhibitors and vaccination with BCG.

Discussion

This study was the first to compare the efficacy of 3 approved tests for LTBI detection in adults and children with CIA who were on TNFα inhibitors and were treated with isoniazid. Our results showed that TST was efficient in identifying LTBI in an endemic region with moderate incidence of TB [7, 8]. In addition, 15 (18.5%) incident cases of LTBI were identified after using TNFα

inhibitors and previous negative investigation, particularly in patients with RA. Interestingly, no cases of active TB were found in patients who had a positive TST and who received isoniazid before introduction of TNFα inhibitors, demonstrating high efficacy of LTBI treatment for 6 months. The positivity of LTBI screening was similar between TST and IGRAs in adult patients, regardless of CIA.

Recent meta-analysis demonstrated lower specificity and sensitivity (67% and 81%, respectively) of IGRAs in immunocompromised compared to immunocompetent patients (98.1 and 98%, respectively) when active TB diagnosis was considered as gold standard [15–18]. In contrast, we found no significant difference regarding IGRAs positivity after exposure to TNFα inhibitors.

Previous studies have highlighted that the negative predictive value for progression to TB in 2-Year follow-up was 97.8% for T-SPOT.TB and 99.8% for QFT-IT [9]. However, considering the lack of gold standard method for LTBI diagnosis and small number of active disease cases, it was not possible to calculate the specificity and sensitivity of these tests in our sampling. Besides, it is worth emphasizing that all LTBI new cases were treated with isoniazid in our study, by ethic reasons, minimizing the risk for TB disease progression. The only patient who developed active pulmonary TB over the 24-Month follow-up had negative TST and IGRAs at the time of evaluation. Interestingly, the 3 tests became positive at TB diagnosis, suggesting recent exposure to *M. tuberculosis.*

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In our prospective study, no concomitant medication (cDMARDs, GC or TNFα inhibitors) hampered the results of the four tests for LTBI, showing that the release of IFN-γ was also not impaired. These results differ from previous studies, which found low frequency of TST positivity before anti-TNFα therapy, particularly in patients with RA treated with GC and conventional DMARDs [19, 20].

Although the clinical relevance of TST conversion from negative to positive results after exposure to TNFα inhibitors is still unknown, two main hypotheses could explain positivity increment. First of all, it can be related to new recent contact ("de novo" exposition) to *M. tuberculosis*, considering that the baseline TST was negative when tested 2 years before. Secondly, it might be associated with a "less immunocompromised status" caused by reduction of cDMARDs and GC dosage or an improvement of the cell response (a less anergic condition) after TNFα antagonists [21]. Moreover, none of these patients developed active disease during the 24-Month follow-up when the protocol was correctly followed. Lastly, it is important to emphasize that the possibility of false-positive results is low. However, future studies are necessary to confirm these hypotheses.

More recently, the increasing LTBI test conversion (13% for TST, 10% for T-SPOT.TB and 7% for QFT-IT; total = 30%) after 1 year of anti-TNFα therapy was also observed by Hatzara et al. [21]. Considering that 63% of the sample had positive TB epidemiology, the authors decided to conduct treatment with isoniazid for 9 months. No cases of active TB were observed after a mean of 27-Month follow-up. In addition, the TST-Booster phenomenon was 4 times more frequent than in our sample (11% vs. 3.6%, respectively), and the only risk factor associated with higher conversion rate was the previous exposure to TB (OR 7.24; 95%CI 1.09–47.99; $p = 0.04$). Unexpectedly, infliximab had a significant protective role [21]. Our data supported for the first time that there is no need to withdraw the TNFα inhibitors after TST conversion, from negative to positive, in asymptomatic CIA patients on biological therapy, a new safety finding in this scenario.

Our initial hypothesis was that the TST-Booster could promote stimulation of cellular response and optimize the identification of more LTBI cases, which had not been identified by initial TST, related to attenuation of response due to disease activity itself or concomitant medication [14]. However, we could not confirm this hypothesis, due to the low rate of positive TST-Booster and an increment of TST positivity over time.

All these aspects contribute to the discussion regarding the best strategy for monitoring TB in patients exposed to TNFα antagonists. The latest recommendation from the American College of Rheumatology (ACR) has emphasized that patients with baseline negative TST or IGRA should perform them annually to identify new cases after exposition to TNFα inhibitors, even without evidence from robust randomized studies to support this decision [22]. In Brazil and other endemic areas, these recommendations should be applied because the exposure to mycobacteria is very common. In addition, considering the high TST positivity rate following exposure to TNFα inhibitors and the fact that the epidemiological data over time added little value to LTBI diagnosis, our data do not suggest the retesting of patients with negative initial screening for TST or IGRA could help to protect against active TB incident cases. Considering the 10%-increment in LTBI diagnosis with IGRAs, and the possibility of severe active TB disease development [7], we advise that, whenever possible, IGRAs might be performed. However, it is important to take into account the costs and availability of them in each epidemiological scenario, particularly after TNFα inhibitors exposition over time.

Furthermore, we found some interesting IGRA changes after treatment of LTBI with isoniazid. However, no patient with negative TST or SPOT.TB test became positive in 6-Month follow-up, which could suggest higher risk of TB disease. Surprisingly, the QFT-IT retest had an increment of positivity in 3 patients after the LTBI treatment, but without clinical relevance in 2-Year follow up. In contrast to Johnson et al. who found no significant differences in the qualitative and quantitative results of QFT-IT after treatment of LTBI in healthy subjects in South Africa, we observed some patients became positive for QFT-IT [23]. Moreover, a recent Brazilian study found no qualitative difference regarding IGRAs results in healthy children after LTBI treatment [24]. In Gambia, another study conducted in healthy subjects who had had contact with TB patients did not find quantitative or qualitative changes in T-SPOT.TB after LTBI treatment [25]. These data highlight that the repetition of IGRAs tests after the completion of therapy with isoniazid is not necessary for CIA patients treated with TNFα inhibitors.

Considering the prospective design and the requirement for patients to come to several appointments, it is worth mentioning that we obtained an excellent compliance, highlighting the main strength of our study. Another relevant question is the correct ethically management because all patients with some positive LTBI tests were treated with isoniazid and did not develop TB during 24-Month follow-up.

Our study has some limitations, particularly the lack of IGRA testing before starting TNFα blockers to better understand the conversion of LTBI tests after treatment. Also, we used the third generation QFT-IT system; using

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the now available fourth generation QFT-IT system, QFT results might be even better. Therefore, future studies are necessary to identify new biomarkers, including the ability to diagnose LTBI, greater power to predict the risk of active disease over time, as well as to differentiate active from latent disease and to indicate a favourable response to a specific treatment for mycobacteria.

Conclusion

Our results demonstrated as the main finding that approximately 20% of patients with CIAs had at least one positive test for LTBI during exposure to TNFα inhibitors. In adults, the TST was effective in identifying new cases of LTBI and the IGRAs added almost 10%-diagnostic power in this scenario. The TST-Booster did not provide additional information compared to the other 3 methods. Given the high risk of TB in Brazil, our results suggest that in patients with CIA on TNFα inhibitors and with negative TST, the IGRAs may be a good strategy to identify LTBI cases and to minimize the likelyhood of active disease during exposure to TNFα inhibitors.

Authors' contributions
CMFG performed the sample collection and processing, data analysis and drafted the manuscript. MTT participated in the design of the study, helped to data analysis and in drafting of the manuscript. MIdM-P participated in the design of the study, helped to data analysis and in drafting of the manuscript. MMP participated in the design of the study, helped to data analysis and in drafting of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
All data and materials used in this research are available for consultation and monitoring.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Research. Subjects were included in the study after signing an informed consent form.

Consent for publication
All patients gave consent for anonymous data publication, in accordance with the Declaration of Helsinki.

Competing interests
The authors declare no disclosures or any conflict of interest for this manuscript.

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