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ORIGINAL ARTICLE

Tuberculosis infection in rheumatic patients with infliximab therapy: experience with 157 patients

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Abstract It is recommended to evaluate the presence of latent tuberculosis infection (LTBI) prior to the use of antitumor necrosis factor α. The aim of this study is to assess the presence of LTBI in patients with rheumatic diseases undergoing treatment with infliximab in an endemic area for tuberculosis (TB). LTBI was searched through the contact history, chest X-ray and tuberculin skin test with purified protein derivative (PPD) ≥5 mm. We studied 157 patients in the period from May 2005 to October 2008, 99 (63.1%) were women with average age of 49 years and 58 (36.9%) were men with average age of 41 years. The group comprising 90 patients (57.3%) with rheumatoid arthritis (RA), 54 (34.4%) with ankylosing spondylitis (AS) and 13 (8.3%) with psoriatic arthritis (PsA) had PPD reactor 13.4% (21/157), being prevented by isoniazid (INH) in these patients. There are dissimilar responsiveness to the PPD between the three pathologies, and the reactivity was lower in RA (RA × AS: $\chi^2 = 12$; $P = 0.0004$; and RA × PsA: χ^2 with Yates' correction $= 3.6$; $P = 0.05$). No significant difference between the reactivity of the PPD and the use of immunosuppressive drugs ($P = 0.81$) is observed. The immunoprophylaxis with INH showed an efficacy of 95% (20/21); three (1.9%) patients developed active TB (spondylodiscitis, meningitis and lymphadenopathy) after the use of infliximab, reaffirming extrapulmonary involvement. These results suggest that PPD has a low sensitivity for detection of LTBI in RA and that the previous use of immunosuppressive drugs does not affect the response to PPD.

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Introduction

Substantial evidence shows a risk of reactivation of tuberculosis (TB) five to ten times higher after the use of anti-TNFs when compared with those of other treatments in the same population [1–3]. This risk may become even greater in emerging countries where the prevalence rate of active infection with *Mycobacterium tuberculosis* varies between 5 and 30% [4].

The World Health Organization (WHO) estimates that more than one-third of the world population is infected with *M. tuberculosis* [4], of which 95% of cases occur in the third world. Worldwide, eighty percent of the estimated cases are concentrated in 22 countries, among which is Brazil, occupying the 19th place [4]. Given the morbid mortality of this complication, research and treatment of latent tuberculosis infection (LTBI) have become essential for the initiation of therapy with anti-TNF [2].

This study aims to present the monitoring results of 157 patients with chronic rheumatic diseases, in use of infliximab in Fortaleza (Brazil), a region where tuberculosis is endemic.

Materials and methods

One hundred and fifty-seven patients followed by the Rheumatology Department of Fortaleza General Hospital (HGF) were treated with infliximab for chronic rheumatic diseases in the period from May 2005 to October 2008. All

patients fulfilled the criteria of the American College of Rheumatology (ACR) for their diagnoses. The indication of anti-TNF therapy was evaluated by an experienced specialist in rheumatology. All patients changed to the biological medication after failure of conventional therapies. Presence of LTBI was assessed by detailed history of close contact with TB in the last year, chest radiography and the PPD test, before starting therapy with infliximab. We prescribed prophylactic isoniazid (300 mg/day) for 6 months, beginning 30 days before the immunobiological treatment, for the patients identified with LTBI. All patients were informed about the risks of the therapy and signed a "free and clarified consent term" before starting the treatment and were observed at intervals of 2 months, through clinical and laboratory evaluation; supplementary radiological and histopathological studies were performed when required.

Tuberculin skin test

Two units (0.1 ml) of standard preparation of PPD RT-23 (Statens Serum Institute—Copenhagen, Denmark) were injected in the intradermal region of the forearm volar surface (Mantoux method). The reaction was read at 72 h with the transverse diameter in millimeters of induration. The cutoff for a positive skin test was accepted as an area greater than or equal to 5 mm in diameter.

Statistical analysis

Statistical analysis was performed by Epi Info 6 version 6.04d. For comparison studies between strata, we used the chi-square (χ^2) test of dissimilarity between strata, calculating the *odds ratio* (OR) with confidence intervals (CI) of 95%. We considered the significance level of 5% ($P \leq 0.05$). When needed, we used the χ^2 with Yates' correction and Fisher's exact probability to compare groups with small sample sizes.

Results

The demographic characteristics of patients selected for this study are described in Table 1. The immunosuppressant drugs administered concurrently with infliximab were corticosteroids and/or DMARDs (disease-modifying antirheumatic drugs). The LTBI prevalence prior to the use of infliximab was 13.4% (21/157). Our patients had a negative history of contacts and chest X-ray negative for TB, with all cases being diagnosed by the result of PPD reactor greater than or equal to five millimeters. Among 21 patients subjected to INH prophylaxis, one (5%) developed active TB after 11 months of infliximab use. The reactivity to PPD by pathology group (Table 2) did not appear homogeneous, being estimated at 4% among patients with RA, 23% among patients with PsA and 26% among patients with AS. The chances of reactivity to PPD in RA accounted for 13% of the chances of reactivity between patients with AS (OR: 0.13; CI: 0.03–0.47; χ^2: 12; $P = 0.0004$) and 16% of the chances of reactivity of PsA, presenting the latter with borderline difference to the significance level of 5% (OR: 0.16; CI: 0.02–1.04; χ^2 with Yates' correction: 3.6; Fisher's exact $P = 0.05$) (Table 3). The analysis of PPD prevalence in the use of immunosuppressive therapy prior to treatment with infliximab in 157 patients showed no statistically significant differences ($P > 0.05$). The RA subgroup, where PPD reactor prevalence was even lower, on the sample was insufficient for a conclusive analysis. During the monitoring period of patients using infliximab, active TB was diagnosed in 3/157 (1.9%) of patients, all extrapulmonary (spondylodiscitis, meningitis and lymph nodes), with an appearance average of clinical manifestations of 12 months after starting the treatment. The clinical and demographic characteristics of these patients are shown in Table 4.

Table 1 Patient characteristics

Features	Study group ($n = 157$), n (%)
Sex	
Male	58 (36.9)
Female	99 (63.1)
Age (years)*	47 ± 14.7
Male	41.1 ± 12.7
Female	49.1 ± 15.1
Primary disease	
RA	90 (57.3)
AS	54 (34.4)
PsA	13 (8.3)
Concomitant immunosuppression	
Yes	119 (76)
No	38 (24)
PPD results	
Reactor	21 (13.4)
No reactor	136 (86.6)
Negative close contacts of TB	157 (100)
Normal chest X-ray	157 (100)

n number, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *PsA* psoriatic arthritis, *PPD* tuberculin skin test with purified protein derivative, *TB* tuberculosis

* Mean ± standard deviation

Table 2 PPD status according to primary disease

Group	PPD				Total	χ^2	*P*	OR	CI (95%)
	≥5 mm		<5 mm						
	n	(%)	*n*	(%)	*n*				
RA	4	4	86	96	90	–	–	–	–
AS	14	26	40	74	54	12	0.0004	0.13	0.03–0.47
PsA	3	23	10	77	13	3.6*	0.05**	0.16	0.02–1.04

PPD tuberculin skin test with purified protein derivative, *mm* millimeter, χ^2 chi square, *P* statistical significance *OR* Odds ratio, *CI* confidence intervals, *n* number, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *PsA* psoriatic arthritis

* χ^2 with Yates' correction; ** Fisher's exact probability

Table 3 PPD status according to the usage of immunosuppressive therapy

Group	Immunosuppression	PPD				Total	χ^2	*P*	OR	CI (95%)
		≥5 mm		<5 mm						
		n	(%)	*n*	(%)	*n*				
Total ($n = 157$)	Yes	16	13.4	103	86.6	119	0.05*	0.81**	1.03	0.32–3.49
	No	5	13.2	33	86.8	38				
RA ($n = 90$)	Yes	3	4.4	65	95.6	68	0.32*	0.68**	0.97	0.08–25.56
	No	1	4.5	21	95.5	22				

PPD tuberculin skin test with purified protein derivative, *mm* millimeter, χ^2 chi square, *P* statistical significance, *OR* odds ratio, *CI* confidence intervals, *n* number, *RA* rheumatoid arthritis

* χ^2 with Yates' correction; ** Fisher's exact probability

Table 4 Patient characteristics of active tuberculosis receiving anti-TNF therapy during the study

Case	Age (years)	Sex	Disease	DD (years)	PPD	Prophylaxis INH	Infliximab (months)	Site of TB
1	48	F	RA	15	NR	No	17	Lymph nodes
2	40	M	AS	20	15 mm	3 months	11	Meningitis
3	51	F	RA	8	NR	No	8	Bone

DD disease duration, *PPD* tuberculin skin test with purified protein derivative, *INH* isoniazid, *TB* tuberculosis, *F* female, *M* male, *RA* rheumatoid arthritis, *NR* non-reactive, *AS* ankylosing spondylitis, *mm* millimeter

Images from the appearance of bone TB (spondylodiscitis) are shown in Figs. 1 and 2. Patient 2 (Table 4), after the diagnosis of active TB, admitted that he did not complete the prophylaxis regimen with INH for 6 months despite the information on the risk of anti-TNF therapy. Infliximab was discontinued in three patients who developed active TB, and then, antituberculosis therapy was performed. The patients remain in follow-up, showing good clinical progress, and there were no deaths.

Discussion

It is known that the prevalence of LTBI and active TB depends on the population studied. In this study of 157 patients treated with infliximab at HGF, 13.4% were diagnosed with LTBI, and 1.9% (three patients) developed active TB. Prophylaxis with INH failed in only one case that was justified by the absence of INH use after the third month of the biological, when the patient stopped the medication omitting this information in subsequent clinical reassessments, developing active infection 11 months after the use of infliximab. The other two patients showed PPD non-reactor prior to treatment. Although our LTBI prevalence is much lower than that found in Turkey in a population of 192 patients treated with anti-TNFs (67.2%), the occurrence of active TB was similar to our study, three patients, who also did not use INH [3]. Two patients were PPD non-reactor, and one with positive test of 14 mm also refused to take prophylactic medication. These findings

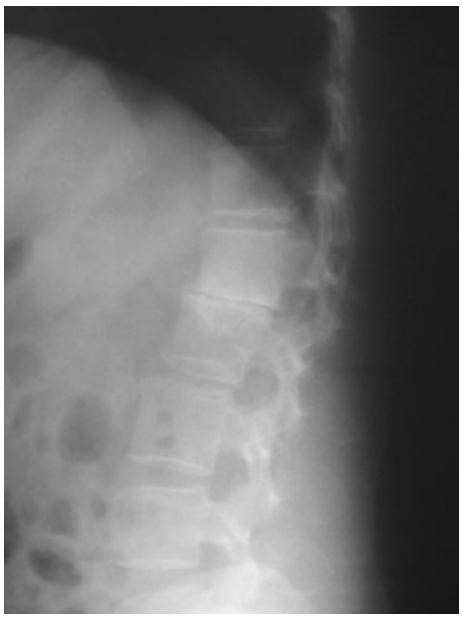

Fig. 1 X-ray of patient 3 showing spondylodiscitis in L1 and L2

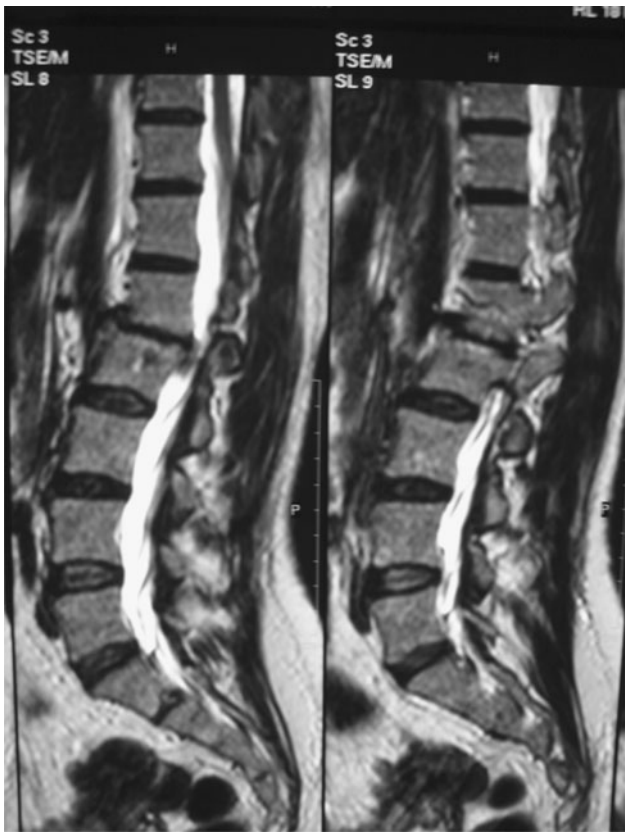

Fig. 2 Resonance of patient 3 showing spondylodiscitis in L1 and L2

strengthen the concern about prescription and adherence to INH prophylaxis in these two sets of patients, with results similar to other studies with follow-up for 17–18 months [5, 6].

The prevalence of 1.9% of active TB in this study was very high when compared with the Brazilian normal population with 58 cases/100,000 inhabitants [7], presenting a patient's chance of developing TB corresponding to 21 times the odds of the general population of Fortaleza (OR: 20.7; CI: 16.8, −25.6; χ^2: 1,663; *P*: 0.0000000) and 34 times the odds of the Brazilian general population (OR: 33.6; CI: 25.7–44.0; χ^2: 1,761; *P*: 0.0000000) for the use of infliximab in patients immunosuppressed by their disease and/or by immunosuppressive treatment prior to the use of anti-TNF in Fortaleza. The Ministry of Health estimates that the national incidence of infection is in 41/100.000 inhabitants, with 72,000 new cases reported in 2007 [4]. In the city of Fortaleza, Façanha et al. [8] reported 18.5% of TB underreporting in the period from 2000 to 2002. During this period, the municipality average prevalence was 94.28/100,000 inhabitants, 62.5% higher than the national prevalence. Some studies in developing countries, such as Korea, are in line with our data, which indicate a risk 30 times greater of active tuberculosis in RA patients on anti-TNF compared to the general population [9].

The appearance of extrapulmonary active infection supports the literature assertion that there is a greater propensity of this kind of manifestation after the use of immunobiologicals, giving greater morbidity and diagnostic difficulty, and may often evolve in an unfavorable way [1]. In the general population, only 17.5% of TB cases are extrapulmonary [7, 10]. Studies in patients subjected to therapy with infliximab have shown rates around 57% [1]. The average time for clinical manifestations of active tuberculosis infection at HGF was 12 months, pointing to later manifestation when compared to previous studies where the average interval from the start of infliximab therapy until the development of active TB was 2–8 months [11]. Oligosymptomatic extrapulmonary manifestation in the three cases of this study should have also contributed to delay the diagnosis of active TB. In the series of cases in Turkey [3], mentioned above, one of the patients with intestinal TB was diagnosed after 30 months of anti-TNF use.

In our study, 13.4% of patients had PPD reagent. Evaluation by disease subgroup showed that the occurrence of positive results was not homogeneous, being significantly lower in RA (4%) when compared to AS and PsA with 26 and 23%, respectively. These results corroborate the statements of the limitations of this test in patients with RA in which regulatory T cells (TReg) (CD4+CD25+), which have a fundamental role in the prevention of autoimmunity and are directly related to the magnitude of PPD, show a decrease in number and function [5]. These abnormalities of cellular function decrease the responsiveness of peripheral blood mononuclear cells, leading to

a loss of delayed skin hypersensitivity and antigen recognition [12–15]. Two recent Brazilian studies have also shown an attenuated response to PPD in RA patients who are applicants for immunobiological therapy [16, 17]. In a study conducted in Recife, the prevalence of PPD reactor was 14.6% in RA, which was statistically significant ($P = 0.034$) among healthy adults selected as controls (33.3%) than had a history of BCG vaccination in infancy, and some are health professionals who worked in the local rheumatology clinic [16]. Laurindo et al. [17] demonstrated in São Paulo that the frequency of PPD reactive was significantly lower ($P < 0.0001$) in RA patients (27%) compared to the control group (58.6%) composed by healthy individuals, with an average age of 34 years, who are employees of the administrative area of the hospital. However, it is evident that these two national studies have factors that increase the population frequency of PPD reactor, as previous vaccination [18] and/or health care workers included in control groups [19, 20], favoring the statistical differences reported between groups for comparison. In a study conducted in Peru [6], where TB is endemic and BCG vaccination of the population sample tested was greater than 80%, a 74% positivity of PPD was identified in an immunocompetent volunteers group matched for age and sex, compared with 29% in RA group, concluding that the tuberculin test was not appropriate to diagnose LTBI in RA. In Turkey, an area where TB prevalence is relatively high and the presence of BCG scar was identified in 90% of the universe of study, a low positivity of PPD in RA was found (29.8%) compared with patients with AS (65.9%), gouty arthritis (68.8%) and osteoarthritis (63%) [21]. Conversely, another study from Turkey [3] showed no statistical difference regarding PPD positivity in RA and AS patients who have been subjected to anti-TNF therapy.

In São Paulo, Pinheiro et al. [22] reported the positivity of PPD in children and adults with chronic inflammatory joint diseases and indications for the use of anti-TNF therapy, with frequencies of 12.8, 37.6, 18.8 and 6.8% in patients with RA, AS, PsA, and juvenile idiopathic arthritis, respectively. The discrepancy of PPD reactor frequency in the Brazilian studies mentioned could lead to several questions, involving socioeconomic, genetic and epidemiological aspects of these population samples. PPD reactor prevalence in Brazilian studies was always much lower than those found in Turkey [3, 21] and Peru [6], countries considered as having TB epidemiological conditions similar to Brazil. The high prevalence of PPD reactor in Turkey could be explained by the intradermal BCG vaccination policy, which induces persistent response to PPD [3]; the revaccination is used in all schoolchildren, regardless of vaccination scar or PPD reactor [23]. Peru revaccinated schoolchildren until 1995 [24], which would explain the high rates of PPD reactor in the study of Ponce de Leon et al. [6], in 2005, where the controls and RA patients had an average age of 55 years. Although the HGF study does not provide data on vaccination history, we can attest, as the patients are above 30 years of age, that those individuals were born before 1976, the time when the official replacement of oral BCG vaccine in Brazil, which does not induce reactivity to PPD, for intradermal BCG vaccine was started [18]. It can be acknowledged that these HGF patients' positive responses to PPD showed only the presence of tuberculosis infection, not being vaccine presensitization.

We did not find any association between the use of immunosuppressive therapy prior to treatment with infliximab and the response of tuberculin tests. These results are similar to findings of national [16, 17] and international previous studies [3, 6].

Although widely accepted, the procedure to screen for LTBI before the use of anti-TNF has been criticized, because in several situations, it is not able to identify the disease. Among the problems described herein, we have the possible uncertainty about the patient's medical history of TB, the lack of specific radiographic signs of LTBI, besides the difficulties in PPD use [16]. Provenzano et al. [25] evaluated 69 patients with chronic joint inflammatory disease, who would be subjected to anti-TNF treatment. During screening for LTBI, we found 2.9% of patients with a previous history of treated TB, 8.7% of positive PPD and radiographic changes compatible with TB sequel in 20.3%, demonstrating the PPD failure to identify all patients with LTBI. Enzymatic assays based on the detection of interferon gamma secreted by memory T lymphocytes (T-SPOT.TB), less prone to cross-react with BCG vaccination and other microbacteria infections, are very useful in patients with a LTBI diagnosis by indirect evaluations of *M. tuberculosis* infection (clinical history and presence of radiological signs consistent with TB) but do not solve the cases of false-negative PPD in RA, widely reported in the literature [26, 27] and identified in two patients of this study. The sensitivity of T-SPOT.TB was equivalent to the gold standard for diagnosis of LTBI in the first Brazilian study developed with this technique in RA patients [28].

Monitoring the presence of tuberculosis infection in patients who are on infliximab will be of key importance for further evaluation of these results, especially in RA patients. The active and strict control to ensure adherence to INH prophylaxis in patients with PPD reactors can also minimize the risks of anti-TNF therapy. Recognizing the importance of vulnerability to TB increased by Anti-TNF, especially in false-negative PPD patients, we emphasize the need for an expansion of a proportional protection, namely a safer epidemiological clinical screening, with a

review of the history of exposure to TB patients, screening through a more precise chest X-ray.

Facing the challenges and difficulties to prevent LTBI, through PPD examination in our environment, the execution of sensitized PPD test could increase the TB diagnosis of candidate patients or using immunobiological drugs [29]. The CDC does not recommend periodic repetition of the PPD test in patients using anti-TNF for lack of scientific documentation, but clarifications online [30] mentions some papers, among them that of Cooray et al. [31], which revealed PPD conversions in 18 (7.8%) patients after the use of anti-TNF therapy in a set of 411 patients in the United States. The test was positive at different times (test annual reproduction from two to five times), and although the patients are clinically asymptomatic, all patients received prophylaxis with INH, being recommended by the authors to repeat the PPD yearly. In Israel, Fuchs et al. [32] concluded that PPD in series identifies patients with reactivation of LTBI or exposed to microbacteria after 3 months of immunobiological therapy use in a set of 40 patients with 20% conversion of PPD. Currently, the CDC recommends repeating the PPD in case of re-exposure or risk, and it should be considered when there is a biological agent change or when the patient travels or belongs to high-risk populations [30].

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