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Original Article

Tuberculin test conversion in patients with chronic inflammatory arthritis receiving biological therapy

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Abstract

Objective: The blockade of inflammatory mediators produced by biological therapies is associated with an increased risk of opportunistic infections, as for example *Mycobacterium tuberculosis* (MT). Given the endemic situation of tuberculosis (TB) in some countries and immunosuppression/anergy of patients with chronic inflammatory arthritis, we wonder whether it is necessary to monitor the MT infection after starting the biological treatment. To evaluate the frequency of the tuberculin skin test (TST) conversion and its association with an active TB infection and other disease variables.

Methods: Patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and spondyloarthritis (SpA) receiving treatment with anti-TNF, tocilizumab, and/or abatacept agents were included into the study. Patients had to have a negative TST (<5 mm) at the baseline, and a second TST was performed 2-22 months after the initiation of biologic therapy. The TST conversion was considered as a variation ≥5 mm between the two TSTs performed within an interval between 2 months and 2 years.

Results: A total of 85 patients were included into the study, and 78.8% were women, with a median schooling duration of 12 years. A total of 74.1% of patients had RA, 16.5% psoriatic arthritis, and 4.7% AIJ and ankylosing spondylitis. Regarding treatment, 75.3% received anti-TNF therapy (31.8% etanercept, 21.2% adalimumab, 17.6% infliximab, 3.5% golimumab, and 1.2% certolizumab), 15.3% tocilizumab, and 9.4% abatacept. Eight patients (9.4%) developed a TST conversion. The shift was more frequent in men (62.5%) than in women (37.5%) (p=0.009), and in those with a prolonged disease duration (X 226±109 vs X130±105 [p=0.017]). This association remained after adjusting for other variables. All patients who developed a TST conversion received prophylactic isoniazid, and only one patient with other risk factors developed active TB.

Conclusion: The frequency of a TST conversion in patients with chronic inflammatory arthritis was low and was associated with male gender and longer disease duration.

Keywords: Rheumatoid arthritis, TST conversion, tuberculosis, biological therapy

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Introduction

Chronic inflammatory arthritis is a disabling condition that requires early and appropriate treatment. The introduction of biological therapies has improved the treatment of this disease. These medications have an acceptable safety profile, although increasing the risk of opportunistic infections (1, 2). Tumor necrosis alpha (TNF-α) inhibitors (TNFi) were the first ones to be introduced and presently are used most frequently. TNF-α plays a key role in the formation and maintenance of granulomas responsible for containing intracellular pathogens, such as Mycobacterium Tuberculosis (MT). A fourfold increased risk of tuberculosis (TB) has been reported in patients under anti-TNF treatment (3, 4). Argentina is a country with an average TB incidence. In 2011, a total of 10,618 cases were reported to the National Program (incidence rate, 26/100,000), and 640 people died from TB during 2010 (5).

The Mantoux test or TST was developed in the XIX century and is still in use. It is the only widely available method to detect latent TB. Despite of its long history, some aspects of its interpretation are still controversial (7, 8). The cutoff value to determine infection depends on the epidemiology of the region and the patient type. In our country, the TB Argentine Consensus that took place in 2009 determined a cut/off value for the general population of ≥10 mm and ≥5 mm (9) for immunocompromized patients and high-risk contacts.

Table 1. Sociodemographic, clinical, and therapeutic characteristics

Variable	n=85
Male sex n (%)	18 (21.2)
Disease:	
Rheumatoid arthritis n (%)	63 (74.1)
Psoriatic arthritis n (%)	14 (16.5)
Juvenile idiopathic arthritis n (%)	4 (4.7)
Ankylosing spondylitis n (%)	4 (4.7)
Poverty n (%)	7 (8.2)
Overcrowding n (%)	11 (12.9)
Occupation	
Housewife n (%)	26 (30.6)
Professional n (%)	13 (15.3)
Retired n (%)	11 (12.9)
Administrative n (%)	10 (11)
Trader n (%)	8 (9.4)
Construction worker n (%)	3 (3.5)
Health professional n (%)	2 (2.4)
Student n (%)	1 (1.2)
Unemployed n (%)	10 (11.8)
Risk factor (in 14 patients)	14 (16.5)
Type 2 diabetes n (%)	9 (10.6)
Alcoholism n (%)	1 (1.2)
History of TBC with complete treatment n (%)	5 (5.9)
Contact with TB n (%)	2 (2.4)
Concomitant DMARD treatment	
Methotrexate n (%)	72 (84.7)
Leflunomide n (%)	18 (21.2)
Hydroxycloroquine n (%)	6 (7.1)
Sulfazalasin n (%)	1 (1.2)
Biologic treatment	
Etanercept n (%)	27 (31.8)
Adalimumab n (%)	18 (21.2)
Infliximab n (%)	15 (17.6)
Certolizumab n (%)	1 (1.2)
Golimumab n (%)	3 (3.5)
Abatacept n (%)	8 (9.4)
Tocilizumab n (%)	13 (15.3)
Steroid therapy n (%)	42 (49.4)
Prednisone >10 mg/day n (%)	16 (18.8)

TB: tuberculosis, DMARD: disease-modifying anti-rheumatic drug

TST evaluates delayed hypersensitivity (mediated by T lymphocytes) to MT proteins. The reaction occurs in case of the exposure to bacillary proteins, the BCG vaccination, or mycobacterial infection. A negative test means that there is no hypersensitivity, and it is commonly interpreted as the absence of previous contact. However, two situations may occur:

People may lose responsiveness in time. This may be seen in elderly patients, infected or vaccinated after the age of 15 and who had no posterior infection (10).

The absence of reaction was described in patients with autoimmune diseases with compromised Th1 response (11).

Other situations unrelated to the patient's responsiveness in which the TST response can be modified also exist. These include differences in the administration of the derivative and/or mode of reading or "booster" phenomenon. A TST conversion represents latent or recent infection.

The purpose of our study was to evaluate the frequency of a TST conversion in patients with autoimmune arthropathies receiving biological therapy. Furthermore, we aimed to investigate the association between the TST shift and an active MT infection and to explore other variables that could affect the TST conversion.

Methods

A multicenter, observational study including patients with chronic inflammatory arthritis was performed. Three rheumatologic centers participated, two from the Autonomous City of Buenos Aires (Instituto de Rehabilitación Psicofísica and Hospital de Agudos General Enrique Tornú) and one from La Plata City (Hospital San Martín de La Plata). Outpatients with rheumatoid arthritis (RA) according to the ACR 1987 (12) and ACR/EULAR 2010 (13) criteria; juvenile idiopathic arthritis (JIA) according to the ILAR criteria (14); spondyloarthritis (SpA) by the ASAS axial criteria (15) or peripheric SpA criteria (16); and psoriatic arthritis (PsA) according to the CASPAR criteria (17) were included into the study. Patients receiving biological therapy with TNF inhibitors (TNFi) (etanercept, adalimumab, infliximab, certolizumab, golimumab), interleukin 6 (IL-6) inhibitor (tocilizumab), or inhibitor of the T-lymphocyte CTLA4 co stimulatory signal (abatacept) were included. All the patients had to have a previous negative TST test (≤5 mm) prior to the beginning of the first biological treatment. Subsequently, a second TST test was performed in all patients within a time interval between 2 and 22 months from the first one, and without there being any change in the biological agent. This time interval was established to avoid the "booster" phenomenon and the loss of the antigenic stimuli (6-8). The TST test consisted of injecting 0.1 mL of TST (equivalent to 2 tuberculin units), followed by a 48-72-hour papule measurement by trained blind readers. Positivity was defined as a variation in the diameter of the papule greater than 5 mm compared to the first TST test (9).

Patients with a history of active or latent TB, or patients who had two TST tests performed outside the established interval time, and patients with acute or chronic infections that could interfere with the result were excluded from the study. All patients provided written consent to participate in the study. Sociodemographic data (age, sex, type of residency and education) were collected. Certain pathological conditions associated with an increased risk of contracting TB were especially collected, including the following:

Overcrowding, which according to the World Health Organization (WHO) means three or more people per bedroom.

Low weight, which according to the WHO means protein caloric deficiency that results in a body mass index (BMI) <18.5.

Alcoholism, which according to the WHO means daily alcohol intake greater than 20-40 grams in women and 40-60 grams in men (18).

Poverty, which according to the National Institute of Statistics and Census in Argentina (19) means monthly income less than $1500 (Argentinean pesos) for a family with three children (August, 2013), and this date coincided with our study.

Variables related to the disease such as its duration, comorbidities, and treatments received were investigated by direct interview with the patient and from medical records. High steroid use was considered as prednisone or equivalent ≥10 mg/day or three or more injectable corticosteroids in 1 year. The type and dose of disease-modifying anti-rheumatic drug (DMARD) and biologic treatment were noted.

Disease activity was assessed using RAPID 3 (20) and DAS28 (21) for RA and PsA, while BASDAI (22) was used for patients with axial SpA (axSpA). Functional capacity was evaluated by means of HAQ (23) and BASFI (14).

Table 2. Characteristics of the eight patients with TST conversion

Patient	Disease	Sex	Occupation	Poverty	Overcrowding	DBT	TB history	Steroid use	Use of Concomitant cDMARD	Type of bDMARD Used	Time of Chest X-Ray	TST Conversion	Isoniazid Treatment	Active TB
1	PsA	M	Professional	No	No	No	No	No	No	Adalimumab	Normal	22 months	Yes	No
2	RA	F	Housewife	No	No	No	No	No	Yes	etanercept	Normal	8 months	Yes	No
3	RA	F	Unemployed	No	No	No	No	No	Yes	etanercept	Normal	12 months	Yes	No
4	PsA	M	Trader	No	Yes	No	No	No	Yes	adalimumab	Normal	7 months	Yes	No
5	RA	F	Trader	No	No	No	No	Yes	Yes	etanercept	Normal	9 meses	Yes	No
6	RA	M	Trader	No	No	No	No	No	No	tocilizumab	Normal	17 meses	Yes	No
7	RA	M	Construction worker	No	No	Yes	Yes	Yes	Yes	adalimumab	Abnormal	20 meses	TB treatment	Yes
8	PsA	M	Trader	No	No	No	Yes	No	Yes	etanercept	Normal	8 meses	Yes	No

DBT: diabetes, TB: tuberculosis, DMARD: disease-modifying anti-rheumatic drug, RA: rheumatoid arthritis, PsA: psoriatic arthritis, SD: standard deviation, Steroid use: prednisone >10 mg/day

Statistical analysis

Descriptive statistics were performed to calculate the means, standard deviations, medians, interquartile ranges (IQR), frequencies, and percentages. Continuous data were analyzed using the T-test or Mann-Whitney U test, and categorical data were analyzed with Chi^2 and Fisher's exact test. A multiple logistic regression analysis was performed using the presence of a TST conversion as the dependent variable to detect variables associated with the conversion. A p-value less than 0.05 was considered to be statistically significant.

Results

Eighty-five patients were included into the study, 63 (74.1%) with RA, 14 (16.5%) with PsA, 4 (4.7%) with JIA, and 4 (4.7%) with axSpA. Sixty-seven patients were female (78.8%). Most patients lived in urban areas (98.8%), and only one patient lived in a rural zone. Patients had a median age of 52 years (IQR 46-60), median disease duration of 11.5 years (IQR 4.8-16), and a median schooling length of 12 years (IQR 7-14). Eleven patients lived under overcrowding conditions (12.9%), and seven below the poverty line. Fourteen patients (16.5%) had TB risk factors, some of them more than one associated factor (17 factors in 14 patients): 9 (10.6%) had type 2 diabetes, 1 (1.2%) alcoholism, 2 (2.4%) had contact with TB patients, and 5 (5.9%) presented a TB history with complete treatment. Seventy-eight patients (91.8%) received concomitant biologic therapy with classic DMARDs, and 42 (49.4%) received steroids of whom 16 were under high doses (≥10 mg/day) (Table 1).

A tuberculin skin test conversion was seen in 8 (9.4%) patients, being more frequent in men than in women (62.5% vs 37.5%; p=0.009) and in those with longer disease duration (mean 226±109 months vs mean 130±105 months [p=0.017]). These associations remained significant after adjusting for age. No association was found between the TST conversion and disease activity (DAS28, RAPID3, BASDAI), disability (HAQ-A, BASFI), comorbidities, or other sociodemographic variables.

Patients with the TST conversion were further evaluated by the Infectology or Pneumonology Departments and received prophylactic isoniazid at a dose of 300 mg/day. After a median follow-up period of 14.8 months, only one patient developed active pulmonary TB. This patient suffered from type 2 diabetes, had a history of treated TB in the past, and received high-dose corticosteroid therapy, which could explain other possible risk factors (Table 2).

Discussion

Given the known increased risk of TB in patients treated with biological therapies, the present study investigated the frequency of tuberculin conversion in patients with chronic inflammatory diseases receiving biologics (17). Several European registries have reported an increased frequency of TB in patients with RA under biologic treatment (4, 24). This incidence was highest among those patients who did not perform an adequate screening for latent TB, and extrapulmonary forms are the most frequently observed (23).

A Korean study revealed that 28 out of 86 RA patients with biologic treatment had a TST conversion, encouraging annual monitoring of patients with a negative TST receiving biologics (25). Similar results were observed in Italy, where the conversion frequency was 13.6%, and no patients developed active TB (26). In our study, we observed a TST conversion in 9.4% of the studied population, more frequently among men and in those with longer disease duration. Only one patient developed active TB, although it is noteworthy that all patients with positive conversion received prophylaxis for latent TB with isoniazid.

There are reports of a greater frequency of anergy to TST in patients with chronic arthritis. In Turkey, JIA patients had more frequently a negative TST when compared to the healthy population (24% vs 6.6%) (11). Similar data were described in Perú, where 70% of RA patients had TST anergy in contrast to 26% of the general population (7).

Some limitations to our study include the lack of QuantiFERON test given its high cost. However, although some studies have shown greater sensitivity of this method compared to TST, the difference was not significant in a recent study (27). Second, all patients with a TST conversion received isoniazid, not knowing what would had happened if these patients did not receive the recommended prophylaxis. The national vaccination calendar in Argentina includes a mandatory dose of BCG vaccine to all newborns, before leaving the hospital where they were born. Since 2007, there is no longer a need for a second dose that took place at age

6, before entering primary school. For this reason, all our patients had received BCG, and its effect on TST results could not be evaluated. Finally, the study design does not clarify whether a TST test is really necessary after the initiation of a biologic therapy or whether prophylactic treatment should be given in case of a conversion.

In conclusion, in our cohort, a TST conversion in patients with chronic inflammatory diseases was low, and only one patient developed active TB. Further studies are required to establish the benefit-to-risk ratio of subsequent TST monitoring during biologic treatment and the consequent need to conduct a prophylactic treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Instituto de Rehabilitación Psicofísica (Approval Date: June 3, 2015).

Informed Consent: Written informed consent was obtained from subjects who participated in this study.

Peer-review: Externally peer-reviewed

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