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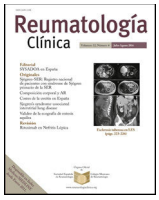

Original Article

How many patients with rheumatic diseases and TNF inhibitors treatment have latent tuberculosis?

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ABSTRACT

Objectives: Spanish clinical guidelines recommend screening patients for tuberculosis (TB) before TNF inhibitors (TNFi) treatment. Our objective was to estimate the prevalence of TST seroconversion as an estimation of the prevalence of latent TB in patients with rheumatic diseases and TNFi treatment that have already been screened for tuberculosis.
Methods: TST, booster and chest x-ray were performed to patients with rheumatic diseases, TNFi treatment, negative tuberculin skin tests before treatment and that were attending the rheumatology Department of three different hospitals in Barcelona. According to the Spanish Society Rheumatology guidelines, these patients had not received TB prophylaxis treatment.
Results: One hundred and forty patients were included in the study. The tuberculin skin test was positive in 4.28% (n=6) of the patients. 50% of the patients were undergoing TNFi $\leq$ 2 years, being two of the patients only one year on the TNFi when a positive TST was detected. This shows that a conversion of the TST can occur even few months or years after the TNFi is started.
Conclusions: The present study observed that 4.28% of patients with rheumatic diseases on TNFi who did not have performed a pre-treatment TB prophylaxis, had a conversion of the TST. Moreover, the conversion of the TST had been within the first two years of treatment in half of the patients of our cohort. In spite of these results, false TST positives in the diagnosis of latent TB cannot be excluded as an explanation for our results.

¿Cuántos pacientes con enfermedades reumáticas en tratamiento con anti-TNF alfa tienen tuberculosis latente?

Palabras clave:
Tuberculosis
Tratamiento anti-TNF
Enfermedades reumáticas

RESUMEN

Objetivos: Las guías de la Sociedad Española de Reumatología recomiendan el cribaje de tuberculosis (TB) antes del tratamiento con inhibidores del TNF (TNFi). El objetivo de este estudio fue estimar la prevalencia de seroconversión de la PT como estimación de la prevalencia de TB latente en pacientes con enfermedades reumáticas y tratamiento con TNFi a los que ya se había realizado el cribaje de TB previo al tratamiento.

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Métodos: Se realizó un cribado de TB a los pacientes con enfermedades reumáticas en tratamiento con TNFi, con un screening pre-tratamiento negativo, que acudían al servicio de reumatología de tres hospitales de Barcelona. De acuerdo a las guías, estos pacientes no habían recibido tratamiento profiláctico para la TB.
Resultados: Se incluyeron a 140 pacientes. La PT fue positiva en 4,28% (n=6) de los pacientes. El 50% de los pacientes estaban en tratamiento con TNFi por $\leq$ 2 años y había dos pacientes que solo llevaban un año con TNFi. Esto muestra que la seroconversión de la PT puede ocurrir incluso poco tiempo después de iniciado el tratamiento con TNFi.
Conclusiones: Se observó que un 4,28% de los pacientes con enfermedades reumáticas en tratamiento con TNFi y que no habían realizado una profilaxis para TB previa al tratamiento tenían una seroconversión de la PT. Esta seroconversión había tenido lugar durante los dos años siguientes al inicio del tratamiento, en la mitad de los pacientes de la cohorte estudiada. A pesar de estos resultados, no se pueden excluir falsos positivos a la PT.

Introduction

Most of the patients with rheumatoid arthritis will develop radiological, functional and social damage within the course of their disease. The early treatment with disease modifying antirheumatic drugs (DMARD) has shown efficacy in reducing this damage. However, conventional DMARD are not helpful enough in roughly a third of these patients.

TNF inhibitors (TNFi) are the first biological therapies that were available for the treatment of rheumatic diseases. Despite their efficacy, there are some caveats regarding their safety. One of them is an increased risk to develop infections such as tuberculosis (TB)[1], especially with monoclonal antibodies.[2,3]

The lifetime risk of reactivation TB for a person with a positive TST is usually estimated to be 5 to 10 percent in the two first years and is assumed to decrease gradually for the first nine years after skin-test conversion[4], and then to continue to decrease at a rate of 10 percent per decade. However, this range substantially underestimates the risk for some patients and overestimates the risk for others, because risks vary greatly according to age, the size of the skin-test induration, and the presence or absence of specific medical conditions[5], such as TNFi treatments.

According to Horsburg et al, the lifetime risk of reactivation TB is 10 to 20 percent among most people 35 years of age or younger with induration of 15 mm or more on the tuberculin skin test who are receiving infliximab therapy or have had recent conversion of the skin test[5].

Patients with TNFi therapy are at high risk to develop TB. According to Biobadaser (a Spanish database on biologic products, launched in 2000, with the objective of monitoring the safety of such treatment), the estimated incidence of TB associated with infliximab in RA patients was 1.893 per 100.000 in the year 2000 and 1.113 per 100.000 in the year 2001. These findings represent a significant increased risk compared with background[1].

This greater incidence of tuberculosis has been seen especially with monoclonal antibodies and presenting with an infrequent pattern (extra pulmonary, disseminated TB).

Given this risk, the Spanish Society of Rheumatology established consensus guidelines to prevent active tuberculosis in patients on TNFi. [6–8] These guidelines consider mandatory to exclude TB in all patients who are about to start biologic therapy or have had recent contact with a TB patient, as well as investigating the possibility of latent TB.

The implementation of these consensus guidelines has been associated to a reduction in the risk of active TB during the treatment with TNFi.[9] However, new active TB cases keep being reported in patients on TNFi[10–13]Consensus guidelines do not establish warnings regarding tuberculosis screening after the onset of the TNFi.[7] In this sense, some authors propose repeating tuberculosis skin test periodically to identify those new latent TB patients during the treatment with TNFi.[14,15]

Our objective was to estimate the prevalence of the TST seroconversion as an estimation of the prevalence of latent TB, in patients with rheumatic diseases and TNFi treatment that have already been screened for tuberculosis.

Patients and methods

Patients

The design of the research was a cross-sectional study of a cohort of patients from three hospitals in Barcelona (Spain), two district hospitals and one tertiary hospital.

Ethical approval was obtained in each hospital and all the patients participating in the study signed an informed consent before taking part in the study.

All the patients with rheumatic diseases on TNFi attending these hospitals had undergone a pre-treatment screening test according to the guidelines of the Spanish Society of Rheumatology.

These guidelines propose that, before starting TNFi, a history of TB infection or recent contacts have to be documented, a chest x-ray be performed to rule out active TB or radiographic signs suggestive of a past infection and a TST performed, repeated after one to two weeks if the size is < 5 mm (booster). A TST or booster is considered as positive if a patient has an induration $\geq$ 5 mm, after 72 h. As it is impossible to know, whether individuals who have been vaccinated with the Calmette-Guerin bacillus have a positive TST due to the vaccination or latent TB infection, the same recommendations as those stated for non-vaccinated individuals are followed. Treatment for latent TB infection is started before the onset of biologic therapy under the following circumstances: (1) recent contact with a patient with documented TB; (2) a history of partially treated TB; (3) positive TST or booster, and (4) residual lesions seen on the chest X-ray.[6–8]

Patients with any kind of rheumatic disease who were on TNFi were included in the study. Patients with a previous positive TST were excluded. Patients who had been on TNFi less than three months were also excluded. This is because even if a TB infection would occur during the first three months after the onset of TNFi treatment, TST would not become positive until 12 weeks later.[4]

Methods

All the patients who accomplished the study criteria were contacted by telephone and given an appointment if they were willing to participate in the study.

Table 1
Characteristics of patients overall, patients with TST < 5 mm and patients with TST ≥ 5 mm.

	Overall (n = 140)	Patients with TST < 5 mm (n = 134)	Patients with TST ≥ 5 mm (n = 6)
Age (years), mean ± SD	49.9 ± 12.9	49.8 ± 13.1	53.5 ± 7.9
Gender n (%)			
Male	57 (40.7)	54 (40)	3 (50)
Female	83 (59.3)	80 (59)	3 (50)
Diagnosis n (%)			
Rheumatoid arthritis	63 (44.7)	59 (44)	4 (66.7)
Psoriatic arthritis	40 (28.4)	39 (29.1)	1 (16.7)
Ankylosing spondylitis	22 (15.6)	22 (16.4)	0 (0)
Undifferentiated SpA	10 (7)	9 (6.7)	1 (16.7)
Idiopatic juvenile arthritis	4 (2.8)	4 (3)	0
Still disease	1 (0.7)	1 (0.7)	0
Age at diagnosis (years) mean (±SD)	36.4 ± 13.3	36.3 ± 13	38 ± 20.2
Duration of disease (years), mean (±SD)	13.9 ± 10.3	13.8 ± 9.8	15.5 ± 19.0
Disease activity, mean (±SD)			
DAS 28	3.0 ± 2.8	3.0 ± 2.8	3.4 ± 1.5
HAQ	0.77 ± 1.1	0.77 ± 1.1	0.72 ± 0.3
BASDAI	14.4 ± 21.8	14.5 ± 22.0	6.9
BASFI	14.5 ± 21.2	14.7 ± 21.4	4.1
Medical therapy, n (%)			
Prednisone	37 (26.4)	36 (26.9)	1 (16.7)
Methotrexate	68 (48.6)	63 (47)	5 (83.3)
Leflunomide	16 (11.4)	15 (11.2)	1 (16.7)
Sulfasalazine	2 (1.3)	2 (1.5)	0 (0)
Anti-TNF treatment, n (%)			
Infliximab	47 (32.8)	44 (32.8)	3 (50)
Etamercept	41 (29.3)	39 (29.1)	2 (33.3)
Adalimumab	48 (34.3)	47 (35.1)	1 (16.7)
Duration of anti-TNF therapy (years), mean (±SD)	4.9 ± 2.9	4.9 ± 2.9	4.2 ± 3.5
Lab values, mean (SD)			
ESR, mm/h	19.6 ± 18.7	19.7 ± 18.7	17 ± 19.7
CRP mean, mg%	2.1 ± 4.8	2.1 ± 4.9	1.4 ± 1.4
Chest radiograph			
Normal, *n* (%)	127 (91)	122 (91)	5 (83.3)
Non informed, *n* (%)	13 (9.3)	12 (8.9)	1 (16.7)

SD, standard deviation; SpA, spondyloarthropathy; DAS28, disease activity score; HAQ, health assessment questionnaire; BASDAI, bath ankylosing spondilytis disease activity index; BASFI, bath ankylosing spondilytis functional index; ESR, erytrocite sedimentation rate; CRP, C-reactive protein.

Table 2
Characteristics of patients with TST ≥ 5 mm.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	63	45	58	58	54	43
Gender	M	F	F	F	M	M
Diagnosis	RA	PsA	SpA	RA	RA	RA
Age at diagnosis (years)	52	34	51	53	44	38
Duration of disease (years)	11	11	7	5	10	5
Disease activity						
DAS 28	3.25	3.99		5.61	1.54	2.87
HAQ	0.25	1		1	0.5	0.875
BASDAI			6.9			
BASFI			4.15			
Medical therapy (dose)	MTX (20 mg)	MTX (15 mg)	MTX (15 mg)	Leflunomide (4 mg)	MTX (25 mg)	MTX (15 mg)
Prednisone (dose)	N	N	N	Y	N	N
Anti-TNF treatment	I	E	A	I	E	I
Duration of anti-TNF therapy (years)	1	8	2	1	9	4
Lab values						
ESR, mm/h	57	8	13	9	9	6
CRP, mg%	1.95	0.27	3.5	0	0.4	2.1
Chest radiograph	N	N	N	N	N	N
Size of the tuberculin reaction (in mm)	20 x 19	10 x 12	12 x 19	10 x 15	9 x 5	19 x 17

DAS, disease activity score; HAQ, health assessment questionnaire; BASDAI, bath ankylosing spondilytis disease activity index; BASFI, bath ankylosing spondilytis functional index; M, male; F, female; RA, rheumatoid arthritis; PsA, psoriatic arthritis; SpA, spondyloarthropathy; I, infliximab; E, etanercept; A, adalimumab; MTX, methotrexate; N, normal.

In this appointment, they signed a written consent to participate in the study and have a new TST and a new chest x-ray. History of TB symptoms, recent contacts or trips to endemic areas was documented. A second TST (booster) was performed if the first TST was negative.

TST was performed on the patient forearm according to the Mantoux method and was assessed 3 days later. The test was considered positive if it was more or equal to 5 mm size. A new latent TB Infection was considered if the TST was positive and/or there were typical TB chest lesions on the x-ray. The new latent TB patients diagnosed were given treatment for latent TB with Isoniazid 300 mg a day during 9 months as established in the Spanish guidelines. The TNFi treatment was not stopped during this period.

Clinical data were collected regarding the patient, the disease and the treatment.

Results

One hundred and forty patients (83 women and 57 men) were included in the study. Their mean age was 49.95 ± 12.89. Of them, 63 (45%) had rheumatoid arthritis, 40 (28.57%) had psoriatic arthritis, 22 (15.71%) had ankylosing spondylitis, 10 (7.14%) had undifferentiated spondyloarthropathy, four (2.85%) had idiopathic juvenile arthritis and one (0.71%) had a Still's disease.

Characteristics of the patients are summarized in Table 1.

The TST was positive in 4.28% (n=6) (95% confidence interval 0.98%-7.58%) of the patients (three men and three women). The conversion was detected in the first tuberculin skin test in four patients and in the booster in two patients. The characteristics of the patients with a positive tuberculin skin test are shown in Table 2. They did not have prior contacts with patients with TB, nor have travelled to a TB endemic area and none had respiratory symptoms. All of them were taking DMARD and only one of them was taking corticosteroids (at a low dose). Four of them were on their first TNFi while two were on the second TNFi treatment. The mean period time on anti-TNF therapy, in the six patients with a positive TST, was 4.88 ± 2.95 years. Two of the patients had been on TNFi treatment less than one year, one patient between one and two years and three patients for more than two years (for 4, 8 and 9 years). This shows that a conversion of the TST can be detected even only few months or years after the TNFi is started.

Discussion

The main finding in the study is that, despite the pre-treatment screening, up to 4.28% of rheumatic patients on TNFi had a positive TST and had not received prophylaxis. These patients with a positive TST could be patients with a false negative TST in the pre-treatment screening or could be new cases of latent TB or they could be a false positive in this second screening. In the first two cases, they would have a latent TB and they would be at high risk to develop TB infection. This risk is further increased by the TNFi treatment. Moreover, the conversion of the TST had been within the first two years of treatment in half of the patients of our cohort. Horsburg et al al[5] defined recent conversion as positive TST in persons who were known to have had a negative test within the previous two years. On the other hand, there were three patients who had a conversion and were on TNFi for 4, 8 and 9 years. As this was a cross sectional study, we do not know for how long those patients have been positive until they have been re-tested.

Although the TST has been used as a surrogate of the diagnosis of latent TB, neither of the patients in this study with a positive TST had been in contact with a patient with active TB, nor had travelled to endemic TB areas, nor had respiratory symptoms or a chest x-ray with TB changes. Therefore, a false positive of the TST technique cannot be excluded.

In addition to the pre-treatment screening before starting TNFi, there are some authors that recommend repeating the tuberculin skin test periodically to detect recent conversion of patients on TNFi.

Fuchs et al.[14] evaluated forty patients with rheumatic diseases on TNFi. They found a 20% ($n = 8$) of patients had a conversion during TNFi treatment, with four patients having an increase of the TST of 10 mm or more. This study was performed in Israel where the diagnosis of latent tuberculosis infection is a matter of debate: while for some a TST > 5 mm is diagnostic for latent tuberculosis, it is widely accepted to diagnose latent tuberculosis infection only if TST reading is greater than 10 mm. In another study, Elbek et al.[15] included 240 patients on TNFi of whom five presented TST conversion during the 12-month follow-up. None of them developed active TB. Of note, most of the patients in this study (74%) had BCG scars and the TST values of patients at admission were 10.7 ± 7.0 mm.

The results of these two studies were performed in populations with a higher incidence of active TB and a higher frequency of BCG vaccinated patients than the incidence of TB and the frequency of BCG vaccinated patients in our population, as well as different cut-off of the TST, thus a comparison with the present study is difficult to establish.

In contrast, in a recent study[16] with 726 patients with immune mediated inflammatory diseases did not recommend a systematic periodic retesting of patients with a negative screening result at baseline. In this study, 542 patients on at least one course of TNFi are reported with a median observation of 5.47 years. Four patients of this cohort (0.6%) developed active TB: three receiving TNFi treatment and one had not ever been on TNFi. At the two-year follow-up, comparison of the incidence of active TB between the exposed and non-exposed to TNFi found no significant differences. Moreover, no TB cases occurred beyond the first 12 months of TNFi therapy.

There are studies performed in the same geographical area than the present to assess the prevalence of latent TB by using a TST in the general population. In a study performed in 2003, in 8202 adults between 20 and 54 years old, a 22.36% of positive TST was observed.[17] In another study performed in 2011, in 2179 people who worked in a university hospital in a risk TB area, 25.7% of positive TST was observed.[18]

Regarding the percentage of TST conversion in rheumatic patients on TNFi, there is a study published in 2006,[19] performed in 61 patients treated with infliximab due to rheumatic diseases, that describes 48 patients with a negative TST at the onset of treatment. After 54 weeks, three patients initially negative had a positive TST. This is a similar percentage (6.25%) of TST conversion to the percentage observed in the present study.

In spite of the percentages of TST conversion described, the incidence of active TB seems to be similar in patients on TNFi than in patients without TNFi if the pre-treatment screening for latent TB is performed correctly. In this sense, Biobadaser[20] describes that after the implementation of the pre-treatment screening for latent TB in clinical practice, the incidence of active TB decreased and among the patients with rheumatoid arthritis reached the Estudio de Morbilidad y Expresión Clínica de la artritis reumatoide (EMECAR) rate (a cohort of patients with rheumatoid arthritis who were not treated with TNFi and were followed for 5 years). In another study,[16] in 726 patients with immune-mediated inflammatory diseases on TNFi followed for a median observation of 5.47 years, four patients (0.6%) developed active TB. In this study, the incidence of active TB in patients exposed and non-exposed to TNFi was similar, at the 2 year follow-up. Of note, the cases of active TB described were observed within the first 2 years of follow-up. This is quite similar to the present study, in which half of the patients diagnosed with latent TB were patients on TNFi for less than two years.

Our study has some limitations. One of them is the sample size. As the sample of patients with a positive TST in this cohort was small, a statistical analysis to compare demographic and clinical characteristics between positive and negative TST patients could not be performed.

In the last few years, the ex-vivo interferon-ϒ release assay (IGRAs) has been used in some hospitals and studies for the diagnosis of latent TB infection. However, in many hospitals this test is not available due to its high cost and could not be used in the present study. As mentioned above, a false positive of the TST technique could not be excluded.

In conclusion, the present study observed that 4.28% of patients with rheumatic diseases on TNFi and that had not had pretreatment TB prophylaxis, had a conversion of the TST. Moreover, the conversion of the TST had been within the first two years of treatment in half of the patients of our cohort. In spite of these results, a false positive of the technique used to diagnose a latent TB cannot be excluded in the present study. A prospective study would have obtained more accurate results, as well as a bigger sample size and the performance of IGRA to complete the assessment of the patients studied.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Right to privacy and informed consent. The authors must have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence must be in possession of this document.

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Conflict of interests

The authors declare no conflict of interest.

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