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Incidence of latent tuberculosis in rheumatic diseases after taking immunesuppressive drugs

Alemeh Doostdar[1], Zeinab Saremi[2*], Elham Atatbati[3], Gholamreza Sharifzadeh[4]

[1] Department of Internal Medicine, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran. [2] Department of Internal Medicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran. [3] Department of Internal Medicine, Clinical Research and Development Unit, Valiasr Hospital, Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran. [4] Department of Epidemiology and Biostatistics, School of Health, Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran.

Tuberculosis remains a serious public health concern. Comorbidity in immunocompromised patients makes its diagnosis more difficult. The present study was conducted to assess the prevalence of positive tuberculin skin test and Chest X-ray changes in patients with rheumatologic diseases treated with immunosuppressive medications in the city of Birjand, Iran. The present prospective study was conducted in 2020 in the city of Birjand, Iran on 40 patients with rheumatologic diseases and 40 healthy people. Inclusion criteria were patients with the diagnosed rheumatic disease under treatment with immunosuppressive drugs. Exclusion criteria were active tuberculosis and changes in chest X-ray in favor of tuberculosis. Purified protein derivative solution was used to carry out a tuberculin skin test and screen both groups for latent tuberculosis and Chest X-ray to ascertain the presence or absence of the radiographic signs of old tuberculosis in the patients' group at the initiation of treatment and six months after. The collected data were recorded in a checklist and then analyzed in SPSS-22 using descriptive and statistical tests. Mean age was 47.32 ± 13.61 years in the case group and 46.40 ± 14.19 years in the control. Also, 7.5% of the case group patients taking immunosuppressive medications were tuberculin skin test positive, but no significant difference was observed between the case and control groups (*P value* = 0.24). In the positive tuberculin skin test group, 66.6% had spondyloarthritis of whom, 100% were taking Cinnora (Adalimumab). The emergence of latent tuberculosis in rheumatic patients after taking immunosuppressive medications is likely, and clinicians should be aware of its risk.

Keywords: Tuberculosis; Mycobacterium Tuberculosis; Tuberculin skin test; Rheumatic disease; Immunosuppressive medication

Introduction

Patients with the rheumatic disease are at risk of infection due to the immunosuppressive effect of the drug and immune system dysfunction as a result of the disease [1]. Over the past two decades, there has been a greater use of synthetic and biologic Disease Modifying Anti Rheumatic Drugs (DMARDs) to control rheumatic diseases. Elevated risk of infection is a significant side effect of thesedrugs, of which tuberculosis (TB) is

*Corresponding Author: Zeinab Saremi, Department of Internal Medicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran. Email: zsaremi@bums.ac.ir

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one of the most important [2].

According to the guidelines, Tuberculin Skin Test (TST) should be carried out before starting treatment with anti-tumor necrosis factor (TNF), but other DMARDs such as methotrexate or cyclophosphamide are not mentioned before starting the treatment. Based on available data, approved csDMARDs increase the risk of TB reactivation, but screening of latent TB is not advised for these drugs [3].

TB is a highly contagious infectious disease that spreads globally [4]. According to the World Health Organization estimate in 2016, almost a quarter of the world's population is infected with Mycobacterium tuberculosis [5]and, one and half million people worldwide lost their lives to this disease [6]. The majority of TB patients live in 22 Asian and African countries including Iran's eastern neighbors Afghanistan and Pakistan. Department of Tuberculosis and Leprosy Control of the Center for Disease Management of the Ministry of Health reported that 14.4 people per 100,000 in Iran are infected with tuberculosis every year. The incidence of tuberculosis is not evenly spread across Iran, and the prevalence is higher in the marginal regions of the country such as Sistan and Baluchestan, Khorasan, Gorgan and East Azarbaijan and Khuzestan [7].

TB infection can be reactivated during different stages and even kill the host. These processes include old age, HIV infection and use of immunosuppressive medications. Although biological and immunosuppressive medications have greatly transformed the treatment of autoimmune diseases (especially by improving symptoms), one of their important side effects is the reactivation of latent TB.

The diagnosis and treatment assessment of TB is difficult in patients taking immunosuppressive medications, and if undiagnosed and untreated, it can even lead to the patient's death [8, 9]. Therefore, before initiating some immunosuppressive medications, screening or latent or active TB is recommended [10]. Although the incidence of TB is uncommon during the treatment of patients taking immunosuppressive medications, clinicians should constantly be aware of the risk during the treatment, in spite of a negative initial screening [11]. This study aimed to evaluate the rate of positive TST in patients with a history of rheumatic disease who were treated with immunosuppressive drugs in Birjand, Iran.

Materials and Methods

The present prospective study was conducted in January and August 2020 on 40 patients with rheumatologic diseases attending the rheumatology clinic of Birjand University of Medical Sciences. In addition, 40 healthy people were selected by convenient sampling from healthy people in Birjand city, which is an endemic region for TB.

The study was conducted after obtaning the permission of the Research Ethics Committee of Birjand University of Medical Sciences (Code: IR.BUMS.REC.1398.313) and a letter of introduction from the university authorities and explaining the study objectives. The inclusion criteria for the case group were: age between 18 and 70 years, being diagnosed with a rheumatic disease, a candidate for receiving immunosuppressive medications (the diagnosis of the rheumatic disease based on diagnostic criteria and by a rheumatologist) and living in the city of Birjand. Rheumatic diseases included in this study were rheumatoid arthritis, Sjogren's syndrome, scleroderma, vasculitis, and spondyloarthritis. Immunosuppressive drugs were Anti TNF, cyclophosphamide, mycophenolate mofetil, azathioprine, prednisolone at daily doses > 10 mg and methotrexate at a dose ≥ 20 mg per week**.** The exclusion criteria were: active TB receiving anti-TB medication, Chest X-ray (CXR) patients with changes in favor of the old TB at the treatment initiation, positive TST patients at the initiation of immunosuppressive therapy, those having to terminate medication during therapy due to other side-effects, those with hepatic or renal failure, patients with acquired immune deficiency syndrome (AIDS), and those in contact with active TB patients over the past year. The inclusion criteria for the control group were: healthy people with no underlying diseases or contact with TB patients, and living within the Birjand city zone. The study objectives and method were fully explained for the participants. After obtaining written consent forms from those willing to take part, the researcher completed the questionnaire relating to demographic and disease details.

For the case group, demographic and disease-related details (medication type, dose, and duration of taking it), TST results (based on predetermined positive or negative values) and CXR (based on the presence or absence of lung involvement in favor of TB) were recorded in a researcher-made checklist. A total of 40 patients were selected according to the inclusion and exclusion criteria. The rheumatologic diseases were diagnosed according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) criteria for each disease and by a rheumatology subspecialty based on the clinical symptoms, physical examination, and radiologic and laboratory signs. The participants' TST was controlled before treatment and at least six months afterwards. To this end, one-tenth of milliliter of purified protein derivative (PPD) solution was administered intra-dermally and read 48 to 72 hours later. Induration > 5mm was considered positive for the immunocompromised patients, ≥ 15mm for the control and healthy group, and < 5mm for all participants in both groups was negative. If the TST value was between 5 to 15 mm in the healthy control group, they were excluded from the study. CXR was also assessed in patients before therapy and at least six months afterwards. Changes in CXR in favor of latent TB included calcified and non-calcified nodules or fibrotic lesions and pleural thickening. CXR and TST were interpreted by the internal medicine PA. Given the TB endemicity of the region, the control group included 40 people from the normal population of Birjand selected according to the inclusion and exclusion criteria who were covered by the comprehensive health centers of Birjand. PPD was checked twice over six months, and induration < 5mm was taken as negative. TST was interpreted by the internal medicine PA.

Based on the data from a similar study by Paluch-Oles et al. [12], the sample size was determined 28 people per group, which was raised to 40, given a possible withdrawal of 40%. The data were analyzed in SPSS-22 using descriptive statistics to find central tendency and dispersion for the quantitative variables, qualitative data with the number (%) and Chi-squared, Fisher's exact and Mann-Whitney tests to compare the frequency of TST and changes in CXR in rheumaic patients treated with immunosuppressive medications in terms of age, gender, and duration of taking medication. Statistical significance was set at *P value* < 0.05.

Results

The present study was conducted on 40 patients with rheumatic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, scleroderma, vasculitis, and spondyloarthritis receiving immunosuppressive medications including anti-TNF, cyclophosphamide, mycophenolate mofetil, azathioprine, prednisolone at daily doses > 10 mg and methotrexate at a dose ≥ 20 mg per week. The study subjects matched in terms of age and gender (Table 1).

Table 1. Mean age and gender and Frequency distribution of TST cases in case and control groups

Group/age	**Case** **Mean Ñ SD**	**Control** **Mean Ñ SD**	***P value***
Age (years)	47.32±13.61	46.40±14.90	p=0.76*
Gender	Case Number (%)	Control Number (%)	*P value*
Male	10 (25)	12 (30)	p=0.61 **
Female	30 (75)	28 (70)	
Positive TST	3 (7.5)	0 (0)	P=0.24*
TST negative	40 (100)	37 (92.5)	

*Independent T-Test results
**fisher exact test

Fisher's exact test showed no significant difference between the two groups in terms of the frequency of positive TST cases after taking medication (*P value* = 0.56). Moreover, this test showed no significant difference across genders in terms of the frequency of positive TST (*P value* = 0.61) (Table

1). None of the subjects in the control group were TST positive. In the patients' group, it was positive in 3 people. The mean duration of the positive TST in these 3 patients was 7.6 ± 0.8 months.

No changes in CXR in favor of TB were observed in any of the case group patients before and at least six months after taking immunosuppressive medications.

In the positive TST group, 33.3% of patients had rheumatoid arthritis and 66.6% had spondyloarthritis. Also, 100% of the patients with positive TST used Cinnora (Adalimumab) and 33.3% took prednisolone and MTX (Table 2). In addition, the mean duration of using immunosuppressive medication was 14.0 ± 4.0 months in the positive TST group and 16.9 ± 12.2 months in the negative TST group, and the Mann-Whitney U test showed no significant difference between these groups (*P value* = 0.84) (Table 3).

Table 2. Frequency distribution of TST cases in terms of type of rheumatologic disease and immunosuppressive medications

TST cases/rheumatologic disease	Positive TST (n=3)	Negative TST (n=37)
Systemic lupus erythematosus (SLE)	0 (0)	10 (27.02)
Rheumatoid Arthritis	1 (33.3)	15 (40.54)
Scleroderma	0 (0)	2 (5.40)
Sjogren's syndrome	0 (0)	3 (8.10)
Vasculitis	0 (0)	1 (2.70)
spondyloarthritis *	2 (66.6)	8 (21.62)
** Immunosuppressive medication		
Cinnora (Adalimumab)***	3 (100)	11 (29.72)
Altebrel (Etanercept)	0 (0)	9 (24.32)
Remicade (infliximab)	0 (0)	1 (2.70)
Cyclophosphamide	0 (0)	4 (10.81)
Cellcept (Mycophenolate Mofetil)	0 (0)	6 (16.21)
Azathioprine	0 (0)	6 (16.21)
Prednisolone	1 (33.3)	14 (37.83)
MTX*	1 (33.3)	4 (10.81)

Number (%)
*Of those with negative TST, two patients had two concomitant rheumatologic diseases
** Some of the patients with negative TST used more than one medication
*** All three patients with positive TST used Cinnora, and as well as Cinnora, one of them used methotrexate, and another prednisolone

Table 3. Mean duration of taking immunosuppressive medication in the case group in terms of TST status

TST cases/duration of taking immunosuppressive	Positive TST (n=3) Mean ± SD	Negative TST (n=37) Mean ± SD	*P value*
Duration (months)	14.0±4.0	16.9±12.2	P=0.84*

*Mann-Whitney test results

According to the above table and the Mann-Whitney U test, no significant difference was observed between the positive TST and negative TST groups in terms of the mean duration of taking immunosuppressive medications (*P value* = 0.84).

Discussion

The results showed that 7.5% of patients with rheumatic diseases were TST positive after using immunosuppressive medications, and Fisher's exact test showed no significant difference between the case and control groups in terms of the requency of positive TST cases (P value = 0.24). No CXR changes in favor of TB was observed in any of the case group patients before and at least six months after using immunosuppressive medications.

In a study by Lee et al. [13], the activation of latent TB was assessed in 702 patients with rheumatoid arthritis, ankylosing spondylitis and Crohn's disease, treated with Anti-TNF, during which, latent TB turned into active TB in six patients. In a study by Perifanou et al. [14], 70.6% of patients with autoimmune diseases receiving immunosuppressive medications had positive TST and 22.8% had CXR changes in

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