Original Article

Screening for Latent Tuberculosis Infection at a Rheumatology and Medical Rehabilitation Center in Duhok City, Iraq

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Abstract

Background: Patients with rheumatoid diseases are at increased risk of infection due to a combination of inherent energy or immunomodulating drugs used for its treatment. The study aimed to screen for latent tuberculosis infection (LTBI) among patients with rheumatologic diseases. **Materials and Methods:** In the present prospective cross-sectional study, a total of 149 patients diagnosed with different types of rheumatoid diseases were included. The rheumatic diseases were diagnosed based on the American College of Rheumatology criteria for rheumatoid arthritis (RA) or the European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. The patients were screened by interferon-gamma release assay and tuberculin skin tests using purified protein derivative. **Results:** The mean age of the patients was 39.91. The most common types of diseases were ankylosing spondylitis (37.6%) and RA (34.9%). The prevalence rate of LTBI was 12.1% among rheumatic patients. The patients with positive LTBI had significantly longer therapy duration (4.51 vs. 2.81 years, $P < 0.001$) and were older (48.61 vs. 38.72 years, $P = 0.005$), respectively. There was no statistically significant association between the disease types and LTBI positivity ($P = 0.512$). However, LTBI positive was more prevalent in patients who received rituximab (16.7%; $P = 0.035$) and those patients with past medical history (20.9% vs. 8.5%, respectively; $P = 0.035$) and those did not receive the bacillus Calmette–Guérin vaccination (36.4% vs. 10.1%; $P = 0.029$). **Conclusions:** This study suggests that patients with rheumatoid diseases and treated with anti-tumor necrosis factor therapies are at an increased risk of tuberculosis infection.

Keywords: Anti-tumor necrosis factor therapy, screening, tuberculosis

Introduction

The advent of biologic agents has made the revolution in the treatment of several immune-mediated inflammatory diseases. These agents decrease the symptoms and prevent radiological progression.[1] However, these agents increase the risk of reactivation of latent tuberculosis (TB) infection (LTBI) in patients previously exposed to TB bacilli.[2,3] Anti-cytokine therapies are associated with an increased incidence of bacterial infections. Anti-tumor necrosis factor (TNF) therapies (e.g., infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol) are used for the treatment of rheumatoid arthritis (RA), Crohn's disease, and other chronic noninfectious inflammatory diseases.[4]

Patients with rheumatic diseases should be screened for active or LTBI before therapy.[5] Active TB should be treated properly before launching therapy with anti-TNF agents. Furthermore, these patients should receive the proper treatment for LTBI before initiation of anti-TNF therapy.[6] Both tocilizumab (a humanized anti-interleukin 6 [IL-6] receptor monoclonal antibody) and rituximab (a B-cell-depleting anti-CD20 monoclonal antibody) are used to treat rheumatic diseases carry Food and Drug Administration boxed warnings regarding the risk of serious infection. The latter has specific to progressive multifocal leukoencephalopathy. Both abatacept (an inhibitor of T-cell co-stimulation) and anakinra (a recombinant human IL-1 receptor antagonist) have also been associated with serious infections.[7] The risk of TB reactivation is increasing after the introduction of biological therapies. This reactivation is the outcome of reactivation of LTBI.[8]

The study aimed to screen for TB infection among patients with rheumatologic disease in a region where TB is endemic.

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Materials and Methods

Study design and patients

In this cross-sectional study, a total of 149 patients diagnosed with different types of RA who were taking anti-cytokine therapies were included. The patients attending the rheumatology and medical rehabilitation center in Duhok city in 2019 were screened clinically for the inclusion and exclusion criteria. The mentioned setting is a specialized center health-care facility dealing with all rheumatologic diseases such as RA, spondyloarthropathy, systemic sclerosis, and systemic lupus erythematosus.

Inclusion and exclusion criteria

The patients who were diagnosed with RAs by a rheumatologist and were receiving biological therapies were eligible to include in this study. The patients were adult males and females. The rheumatic diseases included in this study were RA, ankylosing spondylitis (AS), and psoriatic arthritis.

Diagnosis and measurement criteria

The following general information was collected in a predesigned questionnaire: age, gender, smoking, alcohol consumption, past medical history, disease types, and their duration, and treatment types and their duration. The rheumatic diseases were diagnosed based on the American College of Rheumatology criteria for RA[9] or the European Spondyloarthropathy Study Group (ESSG) preliminary criteria for the classification of spondyloarthropathy.[10]

Medical tests

The patients were screened by interferon-gamma release assay (IGRA) and tuberculin skin tests (TSTs) using purified protein derivative (PPD) according to the specification of the variables of the ESSG criteria.[10]

Interferon-gamma release assay

The patients included in the study were screened using the T-SPOT.TB kit (Oxford Immunotec Ltd., Oxford, United Kingdom) at baseline. Shortly after that, gamma-interferon-precoated enzyme-linked immunosorbent spot (ELISPOT) assay plate is feed with 2.5 × 10^5 peripheral blood mononuclear cells per well. Accordingly, they were incubated with medium (as a negative control) and peptide antigens were derived from ESAT-6 or CFP-10 or phytohemagglutinin (as a positive control) in a 5% CO2 atmosphere at 37°C for 16–24 h. The result of the T-SPOT.TB assay was considered to be positive if panels had more than six or more spots than the negative control and this number was at least two times greater than the number of spots in the negative controls. The spots were read using an ELISPOT assay plate reader (AID GmbH, Germany). The results were double-checked by other laboratory workers and, if necessary, corrected by manual counting.[11,12] The laboratory procedures were performed by an expert in Central Laboratory in Duhok city.

Tuberculin skin tests

TST was carried out, using the Mantoux technique on the volar surface of a forearm, with five tuberculin units of tuberculin PPD RT23. Accordingly, the results were read by one individual. Tests were read at 48–72 h, and the results were measured with a ruler as induration diameters along and across the arm. The results were negative if the TST induration was 10 mm in diameter. It was considered positive if the reaction was more than 10 mm in diameter or there was blistering.[13]

Statistical analysis

The descriptive purposes of the study were displayed in frequency distribution whether in mean and standard deviation or frequency and percentage. The rate of LTBI positive was determined in number and percentage. The difference in disease and treatment duration and age between the patients diagnosed with positive LTBI and negative LTBI was examined in independent *t*-tests. The difference in the incidence of LTBI in patients with different clinical and medical characteristics was examined in Chi-square or Fisher's exact tests. The null hypothesis was rejected in $P < 0.05$. The statistical calculations were performed in the Statistical Package for the Social Sciences version 25 (SPSS, IBM Company, Chicago, IL 60606, USA).

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The ethical approval of the present study was taken from the ethical committee of the Iraqi Board for Medical Specialties in Duhok city. No harmful intervention was applied to patients in this study.

Results

The mean age of the patients with RA was 39.91 ranging between 16 and 65 years. The patients were male (57.0%), smokers (43.6%), and alcoholic (8.1%). The patients had had a past medical history (38.9%), including ischemic heart disease, type 2 diabetes mellitus, and hypertension [Table 1].

The most common types of rheumatic diseases were AS (37.6%) and RA (34.9%). The diseases lasted for 8.37 ranging between 1 and 30 years. Moreover, the most common types of treatments were Enbrel (45.0%) and Remicade (37.6%). The average duration of treatment was 4.30 ranging between

Table 1: General information of patients

Patients' characteristics (*n*=149)	Statistics
Age (years), mean±SD (range)	39.91±12.54 (16-65)
Gender, *n* (%)	
Male	85 (57.0)
Female	64 (43.0)
Smoker, *n* (%)	65 (43.6)
Alcoholic, *n* (%)	12 (8.1)
Past medical history (IHD, DM, and HTN), n (%)	
Yes	43 (28.9)
No	106 (71.1)

SD: Standard deviation, IHD: Ischemic heart disease, DM: Diabetes mellitus, HTN: Hypertension

1 and 20 years. Furthermore, close to half of them had the experience of previous hospitalization (49.7%) [Table 2]. The study found that majority of the patients had a history of bacillus Calmette–Guérin (BCG) vaccination (92.6%). A small percentage of them (4.7%) had a previous TB. The prevalence of LTBI was 12.1% in the present investigation [Table 3].

The association of patients' characteristics with LTBI showed that the patients with positive LTBI had significantly longer biological therapy duration (4.51 vs. 2.81 years, $P < 0.0001$) and were older (48.61 vs. 38.72 years, $P = 0.005$), respectively [Table 4].

The study revealed that there is not a significant association between disease types and LTBI positivity ($P = 0.512$), while LTBI positive was more prevalent in the patients who took rituximab (16.7%) compared to those who were taking other treatment types, $P = 0.035$ [Table 5].

The study showed that LTBI positive is significantly more prevalent in patients with past medical history (20.9% vs. 8.5%, respectively; $P = 0.035$) and those did not take the BCG vaccination (36.4% vs. 10.1%; $P = 0.029$). However, the prevalence of LTBI positivity was not significantly different regarding gender ($P = 0.519$), alcohol consumption ($P = 0.162$), smoking (P = 561), previous hospitalization ($P = 0.300$), and history of TB ($P = 1.00$) [Table 6].

Discussion

The total rate of positive LTBI in this study was 12.1%. The patients with positive LTBI had significantly longer biological therapy duration and were older. The study showed that LTBI positive is significantly more prevalent in patients with rheumatic diseases who had a past medical history and those did not take the BCG vaccination.

He *et al*.[13] followed up 101 patients diagnosed with RA diseases who were candidates for biological treatments for a long-term period with an increased risk of TB infection. The results were compared with 57 healthy controls. The investigators documented the rate of conversion to IGRA positivity, the impacts of various biological agents on the risk of TB infection, and the prophylaxis in China. They found that in patients with rheumatic diseases, the rate of TST positive was 37.6% compared to 34.0% ($P > 0.05$) in healthy controls, while the rate of the T-SPOT.TB positive was 46.5% compared to 21.1% in healthy controls ($P = 0.0019$). The authors follow up the patients for between 6 and 24 months. The T-SPOT. TB-positive rate was 40.4% and 36.7% at 12-month follow-up. This rate is higher than the rate that was found in the present investigation. The reasons may back to the different follow-up periods because the authors did not find the patients and the results were not compared with any control group.

There is a possibility that some of the patients without LTBI positivity at baseline will develop the infection in the future. He *et al*.[13] did not find a significant difference in the positive rate at different time points from baseline to 12-month period.

Table 2: Diagnosis and their treatments

Disease and treatment	Statistics
Diseases, *n* (%)	
Ankylosing spondylitis	56 (37.6)
Rheumatoid arthritis	52 (34.9)
UC	4 (2.7)
Psoriatic arthritis	8 (5.4)
CD	17 (11.4)
Juvenile rheumatoid arthritis	1 (0.7)
Multidisease	1 (0.7)
Juvenile idiopathic arthritis	4 (2.7)
Enteropathic arthritis	3 (2.0)
Systemic sclerosis	2 (1.3)
SLE	1 (0.7)
Previous hospitalization, *n* (%)	74 (49.7)
Treatment type, *n* (%)	
Remicade	56 (37.6)
Enbrel	67 (45.0)
Humira	17 (11.4)
Enteropathic arthritis	7 (4.7)
Rituximab	6 (4.0)
Multidrug	3 (2.0)
Disease duration (year), mean±SD (range)	8.37±6.33 (1-3)
Therapy duration (year), mean±SD (range)	4.30±3.83 (1-20)

UC: Ulcerative colitis, CD: Crohn's disease, SLE: Systemic lupus erythematosus, SD: Standard deviation

Table 3: History of bacillus Calmette–Guérin and tuberculosis and latent tuberculosis infection diagnosis

Disease and treatment (*n*=149)	*n* (%)
History of BCG vaccination	138 (92.6)
History of TB	7 (4.7)
LTBI diagnosis	18 (12.1)

The percentages of BCG, TB history, and LTBI prevalence were calculated in 149 cases.
BCG: Bacillus Calmette–Guérin, TB: Tuberculosis, LTBI: Latent TB infection

Table 4: Association of patients' characteristics with latent tuberculosis infection

Patients' characteristics	LTBI positive (*n*=18)	LTBI negative (*n*=131)	*P* (two-sided)
Duration of disease	8.50±5.98	8.35±6.40	0.921
Therapy duration	4.51±4.02	2.81±1.23	<0.000
Age	48.61±12.59	38.72±12.10	0.005

An independent *t*-test was performed for statistical analyses. The bold numbers show a significant difference. TB: Tuberculosis, LTBI: Latent TB infection

He *et al*.[13] examined the risk of infection during biological treatment and found a positive conversion in the biologic treatment group only with a positive conversion rate of 11.2%. This rate is so similar to the rate reported in the current study. Besides, they did not find active TB in patients with negative T-SPOT.TB at follow-up.

Table 5: Association of latent tuberculosis infection with disease and treatment types

Patients' characteristics (n=149)	LTBI		P (two-sided)
	Positive, F (%)	Negative, F (%)	
Type of disease			
Ankylosing spondylitis	4 (7.1)	52 (92.9)	0.512**
Rheumatoid arthritis	11 (21.2)	41 (78.8)	
UC	1 (25.0)	3 (75.0)	
Psoriatic arthritis	1 (12.5)	7 (87.5)	
CD	1 (5.9)	16 (94.1)	
Juvenile rheumatoid arthritis	0 (0.0)	1 (100)	
Multidisease	0 (0.0)	1 (100)	
Juvenile idiopathic arthritis	0 (0.0)	4 (100)	
Enteropathic arthritis	0 (0.0)	3 (100)	
Systemic sclerosis	0 (0.0)	2 (100)	
SLE	0 (0.0)	1 (100)	
Therapy type			
Remicade	7 (12.5)	49 (87.5)	0.035*
Enbrel	8 (11.9)	59 (88.1)	
Humira	2 (11.8)	15 (88.2)	
Rituximab	1 (16.7)	5 (83.3)	
Multidrug	0 (0.0)	3 (100)	

*Chi-square and Fisher's exact tests were performed for statistical analyses. UC: Ulcerative colitis, CD: Crohn's disease, SLE: Systemic lupus erythematosus, SD: Standard deviation, TB: Tuberculosis, LTBI: Latent TB infection

Table 6: Association of latent tuberculosis infection with patients' characteristics

Patients' characteristics (n=149)	LTBI		P (two-sided)
	Positive, F (%)	Negative, F (%)	
Past medical history			
Yes	9 (20.9)	34 (79.1)	0.035*
No	9 (8.5)	97 (91.5)	
Sex			
Male	9 (10.6)	76 (89.4)	0.519*
Female	9 (14.1)	55 (85.9)	
Smoking			
Yes	9 (13.8)	56 (86.2)	0.561*
No	9 (10.7)	75 (89.3)	
Alcoholic			
Yes	3 (25.0)	9 (75.0)	0.162**
No	15 (10.9)	122 (89.1)	
Previous hospitalization			
Yes	11 (14.9)	63 (85.1)	0.300*
No	7 (9.3)	68 (90.7)	
History of BCG			
Yes	14 (10.1)	124 (89.9)	0.029**
No	4 (36.4)	7 (63.6)	
History of TB			
Yes	1 (14.3)	6 (85.7)	1.000**
No	17 (12.0)	125 (88.0)	

*Chi-square and **Fisher's exact tests were performed for statistical analyses. The bold numbers show a significant difference. TB: Tuberculosis, LTBI: Latent TB infection, BCG: Bacillus Calmette–Guérin

The rate of infection may be different according to the genetic differences. For instance, African American ethnicity has a six-fold higher risk of TB infection compared to White patients who are treated with anti-TNF therapy.[14]

The present study found that older patients and those taking the treatment for a longer period were more likely to develop LTBI. In addition, the patients on rituximab drugs were more likely to develop LTBI compared to enteropathic arthritis, Remicade, and others. The risk of TB has been reported to be higher in patients taking anti-TNF antibody therapy (infliximab).[14,15] However, this is important that the risk of TB in patients with RA is significantly increased following anti-TNF therapy. The researchers did not find any positive LTBI in patients who were taking multidrug for the RA. This is one of the most important points in the present study that needs to be investigated more in future studies.

We found 69 cases of TB among patients treated for RA (n = 40), spondylarthritides (n = 18), inflammatory colitis (n = 9), psoriasis (n = 1), and Behcet's disease (n = 1) treated with infliximab (n = 36), adalimumab (n = 28), and etanercept (n = 5). The authors found that the standardized incidence rate was 12.2%. This rate is similar to the rate reported in the present study. They found that the rate was higher in patients treated with infliximab and adalimumab than those treated with etanercept 18.6% and 29.3% versus 1.8%. The older patients were more likely to develop LTBI positive compared to younger patients. Moreover, it was found to be the second predictor of LTBI positivity in the patients in this study. The same finding has been reported in other studies as well.[14,15]

The strong point of the present investigation must be traced in the diagnostic test of LTBI because IGRAs are superior to TST to identify LTBI in immunosuppressed and BCG-vaccinated populations. However, the patients' information was not compared with a control group in this study. The rate of LTBI was measured at one point in time without following the patients for some time.

Conclusions

This study found that patients with RA and treated with anti-TNF therapies are at an increased risk of TB infection. The older patients and those who did not receive the BCG vaccination are more to be affected by the TB infection. We recommend that the patients who take the biological drugs for chronic inflammatory diseases be followed up for possible other infections and diseases. The periodical screening could be performed for these kinds of patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: A medical revolution. Postgrad Med J 2007;83:251-60.
2. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor α–neutralizing agent. N Engl J Med 2001;345:1098-104.
3. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis Rheum 2003;48:2122-7.
4. Daniel TM, Bates JH, Downes KA. History of tuberculosis. In: Bloom B, editor. Tuberculosis: pathogenesis, protection and control. Washington D.C.: American Society for Microbiology Press; 2006. p. 13-24.
5. Graham J, Kearns A, Magee J, El-Sheikh M, Hudson M, Manas D, *et al*. Tuberculosis transmitted through transplantation. J Infect 2001;43:251-4.
6. Donald PR, Marais BJ, Barry CE. Age and the epidemiology and pathogenesis of tuberculosis. Lancet 2010;375:1852-4.
7. MacMicking JD, Taylor GA, McKinney JD. Immune control of tuberculosis by IFN-γ-inducible LRG-47. Science 2003;302:654-9.
8. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev 2007;8:107-17.
9. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
10. Dougados M, Linden SV, Juhlin R, Huitfeldt B, Amor B, Calin A, *et al*. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218-27.
11. Jiang W, Shao L, Zhang Y, Zhang S, Meng C, Xu Y, *et al*. High-sensitive and rapid detection of *Mycobacterium tuberculosis* infection by IFN-γ release assay among HIV-infected individuals in BCG-vaccinated area. BMC Immunol 2009;10:31.
12. Zhang S, Shao L, Mo L, Chen J, Wang F, Meng C, *et al*. Evaluation of gamma interferon release assays using *Mycobacterium tuberculosis* antigens for diagnosis of latent and active tuberculosis in Mycobacterium bovis BCG-vaccinated populations. Clin Vaccine Immunol 2010;17:1985-90.
13. He D, Bai F, Zhang S, Jiang T, Shen J, Zhu Q, *et al*. High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. Clin Vaccine Immunol 2013;20:842-7.
14. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, *et al*. Risk of tuberculosis is higher with anti–tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective french research axed on tolerance of biotherapies registry. Arthritis Rheum 2009;60:1884-94.
15. Dixon W, Hyrich K, Watson K, Lunt M, Galloway J, Ustianowski A, *et al*. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522-8.