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Original Article

Latent Tuberculosis Infection in Inflammatory Rheumatic Diseases Before Biological and Synthetic DMARD Treatment: Results from Three Rheumatology Centers in Different Regions of Türkiye

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Abstract

OBJECTIVE: The objective of this study was to investigate the prevalence of latent tuberculosis (TB) infection (LTBI) and its associated factors in patients with inflammatory rheumatic diseases (IRDs) prior to the administration of biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs/tsDMARDs).

MATERIAL AND METHODS: A total of 402 patients with IRDs who were receiving bDMARDs/tsDMARDs from tertiary rheumatology centers in three different geographical regions were included in the study. Demographic, clinical, and TB-related characteristics were documented. The patients were divided into two groups, namely those with LTBI and non-LTBI, and their data were subjected to comparative analysis. The impact of various factors on LTBI was evaluated by regression analysis.

RESULTS: The prevalence of LTBI was 50.7% (204/402) before bDMARD/tsDMARD therapy. The proportion of male patients [108 (52.9%) vs. 84 (42.3%); $P = 0.03$] and the prevalence of smoking [102 (50.0%) vs. 64 (32.3%); $P = 0.001$] were statistically higher in the LTBI group. The preference for adalimumab was statistically lower in patients with LTBI (30.4%, 62/204 vs. 45.9%, 91/198; $P = 0.021$). Smoking [odds ratio (OR) 95% confidence interval (CI): 1.46 (1.16-1.65); $P = 0.007$], and duration of bDMARD use [OR 95% CI: 1.10 (1.03-1.17); $P = 0.013$] were significantly associated with LTBI. Isoniazid was used as the prophylactic agent in 96.45% (190/204) of patients, whereas there were no cases of TB reactivation among the three cohorts.

CONCLUSION: The present study demonstrated that more than half of patients with IRDs undergoing advanced therapies have LTBI, with this infection being associated with male sex, smoking status, and duration of bDMARD use. Furthermore, this study indicates that appropriate screening and treatment of LTBI in patients with rheumatic diseases are associated with favorable clinical outcomes.

KEYWORDS: Latent tuberculosis infection, interferon-gamma release tests, rheumatic disease, epidemiology, biologic disease-modifying antirheumatic drugs, targeted-specific synthetic disease-modifying antirheumatic drugs

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INTRODUCTION

Tuberculosis (TB) is an infectious disease that represents a significant public health concern.[1] Latent TB infection (LTBI) is defined as a persistent immune response to tubercle bacilli that does not manifest clinically.[2] Although dormant tubercle bacillus may remain asymptomatic in the lungs for years, they may cause active TB in approximately 10% of cases.[1] Over the past two decades, the rise in immunosuppressive therapies has increased the risk of TB reactivation in individuals with LTBI.[1,2]

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Biologic disease-modifying antirheumatic drugs (bDMARDs) and target-specific synthetic disease-modifying antirheumatic drugs (tsDMARDs) utilized in the treatment of inflammatory rheumatic diseases (IRDs) exert immunosuppressive effects through disparate mechanisms, including anticytokine, co-stimulator, and antibody blockade.[3] In the context of TB infection, in which a T cell-mediated response is of significance, the reactivation of LTBI may be observed as a consequence of these drugs.[3,4]

The World Health Organization has identified early recognition and treatment of LTBI as a crucial strategy for controlling reactivation TB in patients with IRDs who are immunosuppressed.[2] It is estimated that approximately one-quarter of the global population will be infected with LTBI.[5] For this reason, both clinical practice and guidelines recommend that LTBI screening be performed before bDMARD and tsDMARD therapies.[1,4] Furthermore, patients should undergo clinical evaluation for TB at 3-month intervals after the commencement of treatment.[2,6,7]

The prevalence of LTBI in IRD may vary according to demographic characteristics, such as regional differences, and various clinical features, such as differences in immune mechanisms in rheumatic diseases.[4,8] In addition, a comparative presentation of the results of latent TB diagnosis, treatment, and follow-up among patients from different rheumatology centers will provide important information on the management of LTBI.[7]

Accordingly, in this study, we aimed to reveal the frequency of LTBI and related factors in patients with rheumatic diseases prior to bDMARD/tsDMARD therapy in tertiary rheumatology centers located in three different regions of Türkiye.

Main Points

- Latent tuberculosis (TB) infection (LTBI) occurs in more than half of patients with inflammatory rheumatic diseases (IRDs) scheduled for biologic disease-modifying antirheumatic drugs/target-specific synthetic disease-modifying antirheumatic drugs (bDMARD/tsDMARD) therapy.
- Smoking, male gender, and duration of bDMARD use are associated with LTBI.
- In patients with LTBI in whom adalimumab was less preferred, no TB reactivation was detected in any patient in the three centers, despite a longer duration of bDMARD use.
- Prior to commencing bDMARD/tsDMARD therapy, the TB skin test was performed to screen for LTBI in >85% of patients, with >95% of LTBI patients with IRD receiving full-dose isoniazid.
- The present study indicates that appropriate screening and treatment of LTBI in patients with rheumatoid arthritis are associated with favorable clinical outcomes.

MATERIAL AND METHODS

Patients and Rheumatology Centers

The study included 402 patients with IRDs [ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, familial Mediterranean fever (FMF), Behçet's disease, juvenile idiopathic arthritis, large vessel vasculitis (LVV) and deficiency of adenosine deaminase 2 disease] who were to be started on biologic or targeted DMARD therapy. Patients were recruited from tertiary rheumatology centers across different regions. Rheumatology centers were selected from different geographical regions in Türkiye, with consideration given to the potential for variations in the prevalence of latent TB between regions. The selected regions were the West Black Sea region (Kastamonu), the East Anatolia region (Erzurum), and the Marmara region (İstanbul), which ranged from rural to urban (from low to high population density). Patients aged below 18 years with multiple concurrent rheumatic diseases, solid or hematologic malignancies, using immunosuppressive drugs for non-rheumatic indications, on drugs causing pulmonary toxicity and with active TB infection before the start of bDMARDs/tsDMARDs therapy were excluded from the study.

Data on patients between 2010 and 2024 were retrospectively obtained from the hospital electronic records. Informed consent was not obtained from the patients because of the retrospective study design.

The patient data set comprised demographic data (age, gender, weight, height) and clinical data, including diagnosis, disease duration, smoking status, comorbidities, medications, duration of medication use, and clinical measurements of the diagnosis and treatment of LTBI. The study protocol was approved by the Karabük University Faculty of Medicine Ethics Committee for Clinical Research (protocol number: 2024/1863; date: 10.09.2024). The study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice.

Biological and Synthetic DMARD Therapy

The current utilization of bDMARDs, including adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, secukinumab, ixekizumab, ustekinumab, tocilizumab, abatacept, anakinra, and canakinumab, and tsDMARDs, including tofacitinib, baricitinib, and upadacitinib, were recorded. The duration of use and concomitant administration of glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and/or immunosuppressive agents, including azathioprine, mycophenolate, and cyclophosphamide, were also documented.

Latent Tuberculosis Diagnosis, Treatment, and Reactivation

In accordance with national and global guidelines, a diagnosis of LTBI was made when a patient exhibited a TB skin test (TST) result of 5 mm or greater and/or a positive interferon gamma release assay (IGRA) test [T-SPOT.TB test (T-SPOT), Oxford Immunotec Ltd., Oxford, UK or QuantiFERON-TB (QFT, Cellestis Ltd., Carnegie, Australia or Qiagen, Hilden, Germany)] without any signs or symptoms.[9,10]

Rheumatic patients with LTBI are referred to the TB dispensaries (the primary health center where patients are seen for follow-up and treatment of TB), which are widely distributed throughout Türkiye and provide a nine-month course of isoniazid (INH)

treatment.[9] Rifampicin (RIF) is used as monotherapy for a period of four months when INH is contraindicated. The use of INH for 9 months or RIF for 4 months in LTBI prophylaxis is expressed as the full dose.[9,11] Conversely, the administration of these agents for periods shorter than the aforementioned durations is classified as an insufficient dose.[9,11]

Follow-up of patients with LTBI is conducted at TB dispensaries in collaboration with tertiary rheumatology centers. The medication used for LTBI, duration of treatment, and any drug-related adverse effects are documented. Patients who experience reactivation of TB during rheumatology follow-up are also recorded.

Statistical Analysis

The statistical analyses were conducted using IBM Statistical Package for the Social Sciences statistics 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to ascertain data normality. The mean±standard deviation was used to represent average distribution values for numerical data that exhibited a normal distribution. The median and minimum-maximum values for the non-normally distributed variable, as well as the frequencies for the categorical data, are presented. A comparison of the LTBI and non-LTBI groups was conducted using the independent *T*-test to assess differences in numerical variables with a normal distribution, the chi-square test, and Fisher's exact test to compare categorical data. In the case of numeric variables lacking a normal distribution, the Mann-Whitney U test was used for analysis. Univariate and multivariate logistic regression analysis were utilized to assess the association between LTBI (the dependent variable) and other variables. Odds ratios (ORs) with 95% confidence intervals (CI) for LTBI were calculated. The threshold for statistical significance was set at $P < 0.05$.

RESULTS

Of the 402 patients included in the study, 204 (50.7%) were diagnosed with LTBI, whereas 198 (49.3%) did not. The mean age of patients with LTBI was 47.9 (±12.5) years, while the mean age of patients without LTBI was 46.1 (±14.5) years. The proportion of male patients was significantly higher in the LTBI group (52.9%) than in the non-LTBI group (42.3%) ($P = 0.03$). No significant differences were observed in mean weight, height, or disease duration between the two groups. Additionally, a higher prevalence of smoking was observed in the LTBI group [102 (50.0%) vs. 64 (32.3%); $P = 0.001$].

When the frequency of LTBI was compared according to the rheumatology centers, it was similar in all 3 centers ($P = 0.32$). Although not statistically significant, the prevalence of LTBI was higher in the Marmara region (55.0%) than in the Eastern Anatolia region (53.9%) and the Western Black Sea region (47.0%) from more populated to less populated areas.

Regarding the frequency of LTBI according to diagnosis, no significant difference was found for any disease diagnosis ($P > 0.05$) (Table 1). When patients with and without LTBI were compared according to medical treatments, the duration of biologic drug use was significantly longer in the LTBI group than in the non-LTBI group [3.0 (0.25-18.0) vs. 1.5 (0.25-14.0); $P = 0.008$, respectively] (Table 1).

Table 2 illustrates the comparative frequency of rheumatic drug selection between patients with and without LTBI. Adalimumab was significantly more preferred in the non-LTBI group than in the LTBI group (45.9%, 91/198 vs. 30.4%, 62/204; $P = 0.021$). Except for adalimumab, all drug use preferences were similar between the groups.

In patients with IRD, TST (175; 85.8%) was the most frequently used method for diagnosing LTBI before treatment. This was followed by the QuantiFERON and T-SPOT tests, which were used in (21; 10.3%) and (8; 3.9%) of the cases, respectively (Figure 1). The majority of patients (190; 96.45%) received the full dose of INH for LTBI prophylaxis, 5 patients (2.54%) received an insufficient dose of INH, and 2 patients (1.02%) developed INH-related adverse effects (hepatotoxicity in two patients). Additionally, 8 patients (80%) received full-dose prophylaxis for RIF, 1 patient (10%) received an insufficient dose, and 1 patient (10%) developed RIF-related side effects (cutaneous reaction in a patient) (Figure 2). Notably, there were no cases of reactivation of TBIs among the 402 patients receiving biologic or tsDMARD therapy.

The effects of various factors on LTBI was assessed by univariable and multivariable regression analysis. The univariate analysis indicated that cigarette smoking [OR=1.48 (1.25-1.64); $P < 0.001$], male gender [OR=1.35 (1.03-1.56); $P = 0.035$], and duration of bDMARD use [OR=1.11 (1.04-1.18); $P = 0.001$] were independent factors that increased the frequency of LTBI. In the multivariable model, cigarette smoking [OR=1.46 (1.16-1.65); $P = 0.007$] and duration of bDMARD use [OR=1.10 (1.03-1.17); $P = 0.013$] remained significantly associated with LTBI, whereas gender, disease duration, and glucocorticoid dose were not significantly related with LTBI (Table 3).

DISCUSSION

The findings of this study indicate that the prevalence of LTBI among patients with IRD undergoing advanced rheumatic therapies (bDMARD/tsDMARD) is higher in males, with a higher prevalence of smoking among these patients and a longer duration of bDMARD use. Additionally, this study revealed that adalimumab, a monoclonal tumor necrosis factor (TNF) antibody, was less frequently selected as a drug for the treatment of patients with LTBI.

TB has the potential to reactivate in patients undergoing treatment with bDMARDs or tsDMARDs in the presence of LTBI. The management of TB in patients with rheumatoid arthritis may vary depending on the specific rheumatoid disease and treatment regimen involved. Additionally, local recommendations from countries and recommendation sets from international organizations and associations serve as valuable resources in clinical practice.[9,12] It is recommended that clinical assessment along with one of the TST or IGRA tests and chest radiography be performed in every patient who is considered to start bDMARD or tsDMARD treatment for screening LTBI.[12]

In addition to the general recommendations, it is important to consider the epidemiological and demographic differences associated with TB infection. The present study revealed a higher

Table 1. Clinical and demographic characteristics of rheumatic patients with and without LTBI

	All patients from three centers (n=402)	Patients with LTBI (n=204)	Patients without LTBI (n=198)	*P* value
Age, year, mean (±SD)	47.0 (±13.5)	47.9 (±12.5)	46.1 (±14.5)	0.18[β]
Sex (male; %)	210 (52.1%)	108 (52.9%)	84 (42.3%)	**0.03**[γ]
Weight, kg, mean (±SD)	74.1 (±12.4)	74.9 (±11.1)	73.2 (±13.5)	0.19[β]
Height, cm, mean (±SD)	166.4 (±9.6)	167.5 (±8.8)	165.1 (±10.3)	0.14[β]
Disease duration, year, mean (±SD)	11.3 (±8.4)	12.1 (±8.3)	10.6 (±8.4)	0.09[β]
Smoking	168 (41.3%)	102 (50.0%)	64 (32.3%)	**0.001**[γ]
Diabetes mellitus	50 (12.5%)	26 (12.7%)	24 (12.1%)	0.86[γ]
Hypertension	96 (23.9%)	49 (24.0%)	47 (23.7%)	0.94[γ]
CKD	11 (2.7%)	4 (1.9%)	7 (3.5%)	0.33[γ]
COPD	12 (3.0%)	6 (2.9%)	6 (3.0%)	0.95[γ]
Rheumatology center				
West Black Sea region (Kastamonu)	200 (49.7%)	94 (47.0%)	106 (53.0%)	
The Eastern Anatolia region (Erzurum)	102 (25.3%)	55 (53.9%)	47 (46.1%)	0.32[γ]
Marmara region (İstanbul)	100 (24.9%)	55 (55.0%)	45 (45.0%)	
Diagnosis				
AS	227 (56.4%)	122 (59.8%)	105 (53.0%)	0.17[γ]
RA	115 (28.5%)	55 (26.9%)	60 (30.0%)	0.45[γ]
PsA	36 (8.9%)	14 (6.9%)	22 (11.1%)	0.13[γ]
FMF	8 (2.1%)	3 (1.5%)	5 (2.5%)	0.49[δ]
Behçet's disease	6 (1.5%)	4 (1.9%)	2 (1.0%)	0.68[δ]
JIA	5 (1.2%)	2 (1.0%)	3 (1.5%)	0.68[δ]
LVV	4 (1.0%)	3 (1.5%)	1 (0.5%)	0.62[δ]
DADA2	1 (0.2%)	1 (0.5%)	-	-
Medications				
NSAID	165 (41.0%)	85 (41.6%)	80 (40.4%)	0.79[γ]
csDMARDs	146 (36.3%)	70 (34.3%)	76 (38.3%)	0.39[γ]
bDMARDs	369 (91.8%)	185 (90.7%)	184 (92.9%)	0.86[γ]
Duration of current bDMARD therapy (years), median (min-max)	2.0 (0.25-18.0)	3.0 (0.25-18.0)	1.5 (0.25-14.0)	**0.008**[α]
tsDMARDs	33 (8.2%)	19 (9.3%)	14 (7.1%)	0.40[γ]
Duration of current tsDMARD therapy: year, median (min-max)	0.5 (0.25-6.0)	0.5 (0.25-6.0)	0.5 (0.25-3.0)	0.24[α]
Glucocorticoid dose, milligrams, mean (±SD)	1.09 (±2.07)	0.89 (±1.76)	1.29 (±2.34)	0.053[β]
Immunosuppressive	8 (2.0%)	5 (2.4%)	3 (1.5%)	0.72[δ]

[α]: Mann-Whitney U test; [β]: Student's t-test; [γ]: Chi-square test; [δ]: Fisher's exact test.

LTBI: latent tuberculosis infection, NSAID: non-steroidal anti-inflammatory drug, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, AS: ankylosing spondylitis, RA: rheumatoid arthritis, PsA: psoriatic arthritis, FMF: familial mediterranean fever, BH: Behçet's disease, JIA: juvenile idiopathic arthritis, LVV: large vessel vasculitis, DADA2: deficiency of adenosine deaminase 2, SD: standard deviation, min-max: minimum-maximum

prevalence of LTBI in men than in women. Similarly, the prevalence of LTBI in the national TB data of Türkiye was 42.3% in women and 57.7% in men.[9] However, although male sex was found to be associated with LTBI in the univariate analysis, no such association was found in the multivariate analysis. This discrepancy can be attributed to the covariance effect, which is likely influenced by the high rate of smoking among male patients.

The prevalence of respiratory TB infection is higher in urban areas with high population density than in rural areas.[8] In this study, although no significant difference was observed between the regions, LTBI was detected more frequently (55.0%) in İstanbul (in the Marmara region), which has the highest population density, than in the other centers. In contrast, in Kastamonu (in the West Black Sea region), the most rural of the three centers, LTBI was the least frequent (47.0%).

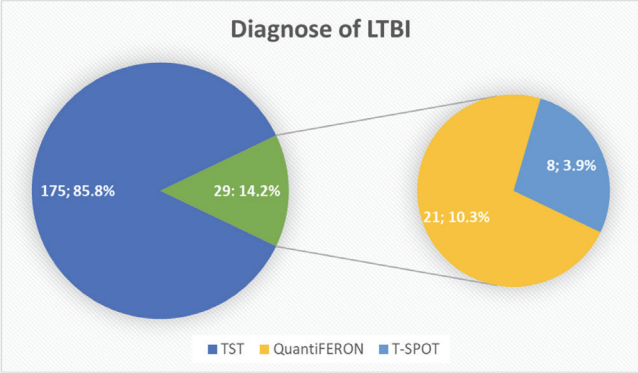

Figure 1. Frequency of tests used for LTBI diagnosis

LTBI: latent tuberculosis infection, TST: tuberculosis skin test

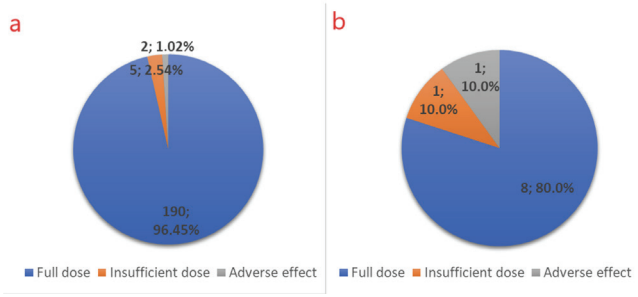

Figure 2. LTBI therapy for patients with rheumatic disease [(a) isoniazid, (b) rifampicin]

LTBI: latent tuberculosis infection

The relationship between IRDs and LTBI has been the subject of numerous studies.[13-15] The available evidence suggests that the presence of several RDs is associated with an increased prevalence of LTBI, irrespective of the pharmacological agents employed by the patients.[13-15] It has been documented in the literature that the prevalence of LTBI is higher in individuals with rheumatoid arthritis than in the general population, independent of biological therapy.[13,14] Furthermore, the risk of TB is elevated in patients with high disease activity across a range of rheumatic diseases.[7,15] However, in none of the IRDs included in this study, an increase in the frequency of LTBI was observed compared with the other IRDs. Additionally, a comparison of the results with the healthy population and an evaluation of LTBI risk according to disease activity were not conducted because they were not within the scope of this study's design.

In this study, we observed that adalimumab was less preferred in the LTBI group than in the non-LTBI group. A meta-analysis identified the highest risk of TB with monoclonal anti-TNF therapy, whereas the risk was low with etanercept and non-TNF biologic therapy.[4] Notwithstanding the elevated risk of TB reactivation, biological drugs are safely employed in rheumatic patients with suitable prophylaxis and meticulous periodic follow-up.[12] In our study, despite the LTBI group having undergone bDMARD therapy for a significantly longer duration, no cases of TB reactivation were identified.

In a study conducted in South Korea, the risk of LTBI infection in patients with rheumatoid arthritis was found to be equal between patients receiving biological therapy and those receiving JAK inhibitors (tsDMARDs).[16] Furthermore, the risk of active TB was found to be lower in patients receiving JAK inhibitors compared with those receiving biological therapy.[16] In our study, the preference for JAK inhibitors was similar between the groups with and without LTBI.

Glucocorticoids are frequently prescribed in rheumatology, yet their chronic use has been linked to an increased risk of TB.[17] The duration and dose of glucocorticoids in immunosuppression are heterogeneous. However, studies have indicated that a prednisolone equivalent of >15 mg/day for >4 weeks is a risk factor for TB.[12,18] In accordance with the literature review, this study demonstrated that the mean glucocorticoid dose was lower in the LTBI group.

The TST is a commonly employed diagnostic tool in screening for LTBI, despite inherent limitations such as measurement sensitivity and cross-reactivity with the Bacille Calmette-

Table 2. Drug selection in rheumatic patients with and without LTBI

n (%)	LTBI (n=204)	Non-LTBI (n=198)
Methotrexate	26 (12.7)	19 (9.6)
Leflunomide	20 (9.8)	28 (14.1)
Sulfasalazine	12 (5.9)	14 (7.0)
Hydroxychloroquine	2 (1.0)	2 (1.0)
Colchicine	4 (1.9)	8 (4.0)
Combination of csDMARDs	6 (2.9)	5 (2.5)
csDMARD combined with bDMARD/ tsDMARD	70 (34.3)	76 (38.3)
Azathioprine	5 (2.4)	3 (1.5)
Anti-TNFIs		
Adalimumab	62 (30.4)	91 (45.9)*
Etanercept	35 (17.1)	22 (11.1)
Infliximab	11 (5.4)	7 (3.5)
Golimumab	30 (14.7)	18 (9.0)
Certolizumab pegol	17 (8.3)	16 (8.1)
Secukinumab	11 (5.4)	10 (5.1)
Ixekizumab	1 (0.5)	3 (1.5)
Ustekinumab	1 (0.5)	3 (1.5)
Tocilizumab	13 (6.4)	6 (3.0)
Abatacept	1 (0.5)	2 (1.0)
Anakinra	0 (0)	1 (0.5)
Canakinumab	3 (1.5)	5 (2.5)
JAKinibs (tsDMARDs)	19 (9.3)	14 (7.1)
Tofacitinib	10 (4.9)	5 (2.5)
Baricitinib	2 (1.0)	4 (2.0)
Upadacitinib	7 (3.4)	5 (2.5)

*$P < 0.05$.

LTBI: latent tuberculosis infection, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, Anti-TNFIs: anti-tumor necrosis factor inhibitor

Table 3. Univariable and multivariable regression analysis results (dependent variable LTBI)

Independent variables	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age (older)	0.99 (0.97-1.01)	0.184		
Sex (male)	1.35 (1.03-1.56)	**0.035**	1.01 (0.61-1.66)	0.956
Smoking	1.48 (1.25-1.64)	**<0.001**	1.46 (1.16-1.65)	**0.007**
Disease duration	0.98 (0.96-1.00)	0.091	0.98 (0.95-1.01)	0.180
Rheumatology center	1.18 (0.94-1.50)	0.157		
Diagnosis of rheumatic disease	1.03 (0.87-1.21)	0.754		
NSAID	1.05 (0.71-1.56)	0.797		
csDMARD	0.84 (0.56-1.26)	0.396		
bDMARD	0.98 (0.91-1.05)	0.600		
Duration of current bDMARD therapy	1.11 (1.04-1.17)	**0.001**	1.10 (1.03-1.17)	**0.013**
tsDMARD	0.91 (0.65-1.28)	0.606		
Duration of current tsDMARD therapy	0.65 (0.34-1.26)	0.202		
Glucocorticoid dose (low)	1.10 (0.99-1.21)	0.053	1.05 (0.94-1.17)	0.361

Bold values indicate $P < 0.05$.
LTBI: latent tuberculosis infection, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, OR: odds ratio, CI: confidence interval, NSAID: non-steroidal anti-inflammatory drug

Guérin vaccine.[19] As the test was commonly employed in the Tuberculosis Dispensaries and hospitals in Türkiye, the TST was identified as the most frequently utilized test in this study. IGRA tests do not suffer from the aforementioned limitations, and there are two main types of IGRA tests. These are the T-SPOT. TB and QuantiFERON-TB tests.[10] The tests have been employed with increasing frequency in our country, particularly in recent years, and have been used exclusively in tertiary care centers, as evidenced by their use in 14.9% of patients in this study. The TST test is the primary recommendation for LTBI screening in accordance with the National Tuberculosis Diagnosis and Treatment Guidelines. In immunosuppressive patient groups (chronic renal failure, chemotherapy planned due to hematological malignancy, rheumatic patients before bDMARD treatment, before long-term steroid use of 15 mg/day and before transplantation), one of the IGRA tests is recommended in conjunction with a negative two-step TST test and clinically highly suspected TB infection.[9,20]

The American Thoracic Society has established a series of treatment protocols for the management of LTBI.[11,21] The National Tuberculosis Guideline in Türkiye recommends INH treatment (300 mg/day) for 9 months as the first-line treatment. In patients who cannot tolerate INH or who have resistance, RIF treatment is provided for 4 months.[9] In this retrospective study, >95% of patients with LTBI received INH prophylaxis, whereas only 8 patients received full-dose RIF therapy.

This study has several potential limitations. The first limitation is that disease activation could not be evaluated due to its retrospective nature. Second, the relatively small number of patients in the study sample with less advanced therapies in the treatment protocol (FMF, Behçet's disease, etc.) and rarer rheumatic diseases (LVV, etc.) represents a limitation. On the other hand, the study's multicentre design, comparison of different geographical regions and high sample size represent its main strengths.

CONCLUSION

A recent study indicated that more than half of patients with rheumatic diseases prior to bDMARD/tsDMARD therapies is diagnosed with LTBI. Furthermore, the findings revealed that smoking and male gender were significant factors associated with LTBI. In patients with LTBI in whom adalimumab was less preferred, no TB reactivation was detected in any patient in the three centers, despite a longer duration of bDMARD use. It can be argued that the periodic follow-up of patients for LTBI and high rates of full-dose LTBI prophylaxis led to favorable clinical outcomes. These results provide valuable insight into the management of LTBI in patients with rheumatic diseases undergoing advanced therapy in rheumatology centers across Türkiye.

Ethics

Ethics Committee Approval: The study protocol was approved by the Karabük University Faculty of Medicine Ethics Committee for Clinical Research (protocol number: 2024/1863, date: 10.09.2024).

Informed Consent: Informed consent was not obligated from patients due to retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., C.A., S.B., Concept: A.K., C.A., S.B., Design: A.K., C.A., S.B., Data Collection or Processing: A.K., C.A., S.B., Analysis or Interpretation: A.K.,

C.A., S.B., Literature Search: A.K., Critical Review: C.A., S.B., Writing: A.K.

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