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ORIGINAL ARTICLE

Assessment of Latent Tuberculosis Infection Screening in Patients with Immune-Mediated Inflammatory Diseases Undergoing Biologic Therapy

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ABSTRACT

Background: *Patients with immune-mediated inflammatory diseases (IMIDs) on biologic therapy are at increased risk of tuberculosis (TB) reactivation, particularly if infected with latent TB. Screening for latent TB infection (LTBI) is recommended prior to immunosuppressive treatment.* ***Objective:*** *To evaluate the prevalence of LTBI, risk factors for TB reactivation, and the significance of screening in patients with IMIDs receiving biologic agents.* ***Methodology:*** *This prospective, observational cohort study enrolled 80 patients with IMIDs scheduled for biologic therapy at Mansoura University Hospitals. Sixty patients completed follow-up over 2 years. All underwent clinical assessment, laboratory testing, chest imaging, and tuberculin skin testing (TST). Patients with positive TST received LTBI therapy. The incidence of TB reactivation was monitored.* ***Results:*** *The mean age was 38.7±11.5 years; 65% were female. LTBI prevalence was 16.7%. Six patients (10%) experienced TB reactivation, including three with LTBI and three without. Risk factors significantly associated with reactivation included diabetes mellitus ($p<0.001$), SLE ($p=0.02$), and use of infliximab, adalimumab, etanercept, or baricitinib. TB reactivation was confirmed microbiologically and radiologically. Close monitoring and screening are critical for preventing TB in this population.* ***Conclusion:*** *Routine LTBI screening prior to biologic therapy is essential. Patients with positive LTBI, diabetes, or SLE are at increased risk of reactivation. Careful management and follow-up reduce TB-related morbidity.*

INTRODUCTION

Tuberculosis remains a global health challenge, especially among immunocompromised populations. Patients with immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE), often require immunosuppressants and biologic agents like anti-TNF drugs, which increase the risk of TB reactivation[2]. Latent TB infection (LTBI) affects approximately 25% of the world's population, serving as a reservoir for active disease under immunosuppression. Reactivation risk varies with host factors and immunosuppressive agents[1]. Current guidelines recommend screening for LTBI using tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) before starting biologic therapy. Early detection and treatment of LTBI are crucial in preventing reactivation[3]. This study assesses the prevalence of LTBI, associated risk factors, and outcomes in IMID patients undergoing biologic therapy at Mansoura University Hospitals, focusing on the importance of screening and follow-up.

METHODOLOGY

Study Design and Setting

A prospective, observational, longitudinal study was conducted at the Chest Department, Mansoura University Hospitals from May 2022 to May 2024.

Participants

Eighty patients diagnosed with IMIDs confirmed by standard criteria and scheduled for biologic therapy were enrolled. Exclusion criteria included active TB disease, prior anti-TB therapy, or contraindications to immunosuppressives.

Data Collection Procedures

- **Clinical assessment:** Detailed history—demographics, disease type, previous treatments, TB exposure.
- **Laboratory testing:** CBC, liver and renal function, CRP, ESR.
- **TB Risk factor evaluation:** Symptoms (cough, weight loss, fever, night sweats), residence, contact history.
- **LTBI assessment:** Mantoux TST with induration thresholds adjusted based on risk factors:

- ≥5 mm in immunosuppressed individuals.

- **Imaging:** Baseline chest X-ray.
- **Microbiological testing:** Sputum analysis for acid-fast bacilli (AFB) when indicated.
- **Biological treatments:** Documented, including agents and doses.
- **Follow-up:** Regular monitoring for signs of TB reactivation during and after therapy.

Definitions

- **LTBI-positive:** TST induration ≥5 mm in immunosuppressed patients.
- **TB reactivation:** Development of symptoms, radiological features consistent with active TB, and microbiological confirmation.

Statistical Analysis

Data processed through SPSS v25. Chi-square or Fisher's exact test for categorical variables; Student's t-test for continuous variables. P-value <0.05 deemed significant.

RESULTS

The mean age of participants was approximately 39 years, with a standard deviation of 11.5 years. Females constituted the majority, representing 65% of the cohort, while 55% of patients lived in rural areas. Regarding smoking habits, most patients (78.3%) were non-smokers, with 15% classified as passive smokers and 6.7% as current smokers. Comorbid diabetes mellitus was present in 15% of the patients. The underlying inflammatory diseases varied, with inflammatory bowel disease (IBD) affecting 20%, rheumatoid arthritis (RA) 16.7%, and systemic lupus erythematosus (SLE) 8.3%. The remaining 55% had various other inflammatory conditions.

Table 1: Patient Demographics & Disease Characteristics

Parameter	Value / %
Number analyzed	60 (after 20 lost to follow-up)
Mean age	38.7 ±11.5 years
Female	39 (65%)
Rural residents	33 (55%)
Smoking status	78.3% non-smokers, 15% passive, 6.7% current
Diabetes Mellitus	9 (15%)
IMID distribution	IBD 12 (20%), RA 10 (16.7%), SLE 5 (8.3%), Others 33 (55%)

The biological therapy regimen among the studied patients revealed that infliximab was the most commonly used agent, prescribed to 50% of patients (30 individuals). Adalimumab was administered to 28.3% (17 patients), followed by ustekinumab, which was used in 16.7% (10 patients). Other biologic agents, including secukinumab, etanercept, and similar therapies, comprised 5% (3 patients) of the cohort

Table 2: Biologic Therapy Profile

Agent	No. (%)
Infliximab	30 (50%)
Adalimumab	17 (28.3%)
Ustekinumab	10 (16.7%)
Others (secukinumab, etanercept, etc.)	3 (5%)

The tuberculin skin test (TST) results showed that 50 patients (83.3%) had negative results, with induration measurements less than 5 mm. Conversely, 10 patients (16.7%) tested positive, indicated by induration sizes of 5 mm or greater.

Table 3: LTBI Screening Results

TST Result	Number / %	Remarks
Negative	50 (83.3%)	TST induration <5mm
Positive	10 (16.7%)	TST induration ≥5mm

Out of total 60 patients (100 %), 6 patients were reactivated after biological therapy (10 %) . Out of them, 3 patients after 3 months, 2 patients after 2 months and 1 patient after 1 month. On the other hand 54 patients were not reactivated (90 %).

Table 4: TB Reactivation Incidence & Timing

Group	No.	Reactivation during follow-up	Timing (months)	Notes
LTBI-positive	10	3	3 months	Confirmed microbiologically
LTBI-negative	50	3	1–2 months	Also microbiologically confirmed

The results revealed that patients with systemic lupus erythematosus (SLE) had a significantly higher prevalence of positive sputum ZN compared to those without SLE (33.3% vs. 5.6%, p=0.020). No significant associations were observed for ankylosing spondylitis, inflammatory bowel disease (IBD), or rheumatoid arthritis (RA). Regarding treatment options, there was no significant difference between patients on steroids, methotrexate, or leflunomide in terms of sputum ZN positivity. When examining biological therapies, etanercept was significantly associated with a higher rate of positive sputum ZN (33.3%) compared to other agents (p=0.020). Notably, baricitinib also showed a significant association, with 16.7% of patients on this medication exhibiting positive sputum ZN (p=0.002). These findings suggest a notable link between certain biologic agents, especially etanercept and baricitinib, and increased likelihood of TB smear positivity.

Table 5: Association Between Sputum ZN Positivity (TB Reactivation) and Clinical Factors

Factor	Sputum ZN Negative (n=54)	Sputum ZN Positive (n=6)	χ^2	P-value
Inflammatory Disease				
- SLE	3 (5.6%)	2 (33.3%)	5.455	0.020*
- Ankylosing Spondylitis	2 (3.7%)	1 (16.7%)	1.910	0.137
- IBD	11 (20.4%)	1 (16.7%)	0.046	0.830
- RA	8 (14.8%)	2 (33.3%)	1.333	0.248
Treatment				
- Steroids	29 (53.7%)	4 (66.7%)	0.367	0.545
- Methotrexate	5 (9.3%)	0 (0%)	0.606	0.436
- Leflunomide	2 (3.7%)	1 (16.7%)	1.910	0.167
Biologic Therapy				
- Infliximab	26 (48.1%)	4 (66.7%)	0.741	0.389
- Adalimumab	17 (31.5%)	0 (0%)	2.363	0.104
- Etanercept	3 (5.6%)	2 (33.3%)	5.455	0.020*
- Baricitinib	0 (0%)	1 (16.7%)	9.153	0.002*

DISCUSSION

This study investigated the demographic and clinical profiles of patients with autoimmune and inflammatory conditions in relation to latent tuberculosis infection (LTBI) and TB reactivation. The mean age of participants was 38.68 years, aligning with findings from a study, which reported a similar mean age in systemic lupus erythematosus (SLE) patients[4]. In contrast, another study documented older populations, particularly among rheumatoid arthritis (RA) patients, with a mean age surpassing 50 years[5]. Another investigation focusing on patients prior to biologic therapy reported a mean age of 47.7 years[6]. These disparities highlight the variability in age demographics across different cohorts, reflecting the influence of disease type, geographic distribution, and study population characteristics on the epidemiology of LTBI.

Regarding gender distribution, our cohort comprised predominantly females (65%), contrasting with other studies which observed a male majority[7]. Interestingly, another research found a higher rate of IGRA positivity among females (46%) compared to males (40%), suggesting gender differences may influence LTBI susceptibility or detection[8]. These observations emphasize that demographic factors such as gender could impact LTBI prevalence and underline the importance of gender-specific screening approaches. The higher female prevalence of LTBI in our cohort might relate to patterns of exposure, immune response variations, or healthcare utilization behaviors.

The study further examined geographical factors, with over half of the patients residing in rural areas (55%). This is notably higher than the proportions reported by others [6,9] who documented 16.2% and 34% rural residence, respectively. The elevated rural residency in our population suggests increased exposure risk, limited healthcare access, and socioeconomic challenges inherent to rural settings, all of which can contribute to higher LTBI prevalence. These discrepancies underscore the need for targeted public health initiatives, improved screening, and intervention strategies in rural communities to effectively address TB burden.

Analysis of behavioral risk factors identified that 78.3% of participants were non-smokers, with 15% passive smokers and 6.7% current smokers. Comparative studies have demonstrated an association between smoking and increased LTBI risk, with higher prevalence among current smokers[10]. Conversely, some research indicates that cessation may not significantly alter LTBI status, though smoking is a well-established risk factor for TB reactivation and recurrent disease [11]. Our findings reinforce the need for integrating smoking cessation programs into LTBI management, especially given the established link between tobacco use and TB susceptibility.

Approximately 15% of patients had diabetes mellitus (DM), aligning with literature that reports a substantial association between DM and LTBI. Studies documented a 62% increased risk of LTBI among diabetics, emphasizing that hyperglycemia impairs immune response and predisposes individuals to infection. Further observation that a 9.2% incidence of LTBI in diabetics, sustaining the importance of rigorous screening and glycemic control in this vulnerable population [12,13]. These results highlight the intersection between metabolic and infectious diseases, advocating for integrated management strategies to reduce TB reactivation risk among diabetics.

The prevalence of inflammatory diseases such as IBD (20%) and RA (16.7%) aligns with previous findings that show a strong link between autoimmune conditions and LTBI. Studies have reported LTBI

prevalence rates of 43% among RA patients and 7.8% among IBD patients[14,15]. These associations suggest that immune dysregulation and the immunosuppressive treatments used in these diseases may increase the risk of latent infections reactivating. Therefore, routine screening and careful monitoring of LTBI are crucial in these populations before starting biologic or immunosuppressive therapies

Our analysis of treatment modalities revealed that corticosteroids remained the most common medication, prescribed to 55% of patients, consistent with other reports[16]. Biological therapies, notably infliximab (50%) and adalimumab (28.3%), were frequently used, reflecting current treatment trends. Notably, our findings suggest that certain biologics, specifically etanercept and baricitinib, are significantly associated with increased TB reactivation risk (p=0.020 and p=0.002, respectively). These results underscore the importance of rigorous LTBI screening and close monitoring during biologic therapy to mitigate reactivation risk, especially with agents linked to higher susceptibility. The findings advocate for individualized risk assessment and screening protocols to optimize patient safety.

CONCLUSIONS

Screening for latent tuberculosis infection before beginning biologic therapies is crucial, particularly for patients with diabetes or lupus who are at greater risk. Since drugs like infliximab and baricitinib can raise the likelihood of TB reactivation, proactive prevention and regular follow-up are key to protecting patient health and achieving successful treatment outcomes.

Ethical approval

Ethical approval was obtained before starting research under number (IRB # MD.24.05.855). Informed consent was received from all participants and/or their legal guardian(s). All methods were performed according to the relevant guidelines and regulations.

Patients consent

Not applicable as neither personal image nor personal data of the participants were included in the manuscript.

Conflict of interests

The authors declare no competing interests.

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