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# Evaluation of patients receiving anti-TNF alpha therapy in terms of tuberculosis and hepatitis

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**Abstract**

Rheumatic diseases and inflammatory bowel disease (IBD) are chronic inflammatory diseases for which biological therapies are widely used; however, these treatments may increase the risk of tuberculosis (TB) infection and Hepatitis B and C viruses (HBV, HCV) reactivation. This study aimed to evaluate tuberculosis infection and viral hepatitis screening and follow-up practices in patients with rheumatic diseases and IBD receiving biological therapy at a tertiary university hospital. Patients diagnosed with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Behçet's syndrome (BS), ulcerative colitis (UC), or Crohn's disease (CD) who initiated biological therapy between January 2015 and March 2022 were included. Tuberculin skin test (TST) results, QuantiFERON-TB Gold (QFT-G) results, hepatitis serology, and infections during follow-up were evaluated. A total of 131 patients were analyzed (78 females; mean age 45.1 ± 14.5 years). Diagnoses included RA (49; 37.4%), AS (52; 39.7%), CD (5; 3.8%), and UC (3; 2.3%). Mean duration of biological therapy was 2.1 ± 1.3 years. Latent TB infection (LTBI) was detected in 30 patients (22.9%), but concordance between TST (≥ 5 mm) and QFT-G was low ($\kappa = 0.308$; $p = 0.180$). Thirty-five patients (26.7%) received isoniazid prophylaxis. One patient (0.8%) developed tuberculous peritonitis on adalimumab. No HBV or HCV reactivation occurred during follow-up. Biological therapies are effective for RA and IBD, but careful screening and prophylaxis for TB and viral hepatitis are crucial to minimize infection risk and maximize patient safety.

**Keywords:** Biological therapy; tuberculosis; interferon-gamma release tests; tuberculin test; hepatitis B

## Introduction

Tumor necrosis factor-alpha (TNF-α) is a major mediator involved in the pathogenesis of several inflammatory disorders, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and inflammatory bowel disease (IBD) [1]. Accordingly, anti-TNF-α (TNFi) therapy has emerged as an effective therapeutic approach for these diseases, as it alleviates clinical symptoms and limits bone erosions, thereby contributing to a more favorable prognosis [2].

Tuberculosis (TB), caused by Mycobacterium tuberculosis, predominantly involves the lungs, although extrapulmonary manifestations may also occur. It is estimated that approximately one-third of the world's population has been exposed to M. tuberculosis, and more than eight million active TB cases are reported annually, with an estimated 1.3–2 million deaths each year [3]. TNF-α is essential for effective host defense against TB, contributing to macrophage activation, acting synergistically with interferon-γ, and preserving granuloma integrity, thereby limiting the dissemination of mycobacteria [4]. Consequently,

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inhibition of TNF-mediated immune responses by TNFi therapy has been consistently associated with an increased risk of TB, potentially due to disruption of T-cell activity and cytokine signaling pathways that are required for maintaining granuloma-mediated protection [5].

Clinical trials and real-world evidence have demonstrated that currently available biologic therapies may increase the risk of reactivation of latent tuberculosis (LTBI) and viral hepatitis, including Hepatitis B and C viruses (HBV, HCV). Although uncommon, HBV or HCV reactivation can manifest as fibrosing cholestatic hepatitis. In addition, HBV reactivation has been documented in individuals with previous HBV exposure and resolved infection who subsequently receive immunosuppressive therapy [6].

This study evaluated tuberculosis infection and viral hepatitis screening and follow-up practices among patients with rheumatic diseases and IBD receiving TNFi and non-TNFi biologic therapies at a tertiary university hospital.

## Material and Methods

Patients diagnosed with RA, AS, PsA, Behçet's syndrome (BS), ulcerative colitis (UC) or Crohn's Disease (CH) who initiated biological therapy for the first time between January 2015 and March 2022 in our clinic were included. Patients with a TB infection history were excluded from the study as they might have caused Tuberculin skin test (TST) positivity regardless of Bacillus Calmette–Guérin (BCG) vaccination. Patients with active TB, those who had previously received biological therapy at other clinics, and those under the age of 18 were excluded from the study. All patients who met the eligibility criteria and had none of the predefined exclusion criteria were included in the study.

### LTBI Screening and Follow-Up

The algorithm created by the Turkish Society for Rheumatology and the Turkish Thoracic Society in 2005 was mandated for LTBI screening and treatment before biological therapy. According to these guidelines, 9 months of isoniazid treatment was recommended for patients who did not have active tuberculosis, had a positive TST (5 mm) and/or suspicious fibrotic/calcific lesions on chest x-rays, had active tuberculosis in the previous year, healthcare personnel at high risk of contracting tuberculosis, and patients with a history of close contact with TB. Even if these criteria were not met, isoniazid (INH) prophylaxis was initiated if the treating physician considered that the TB risk was high.

BCG vaccines were routinely administered in Türkiye until 2006. The number of BCG scars was determined by examining the patients' deltoid region. TST was performed by injecting five tuberculin units of purified protein derivative at a bioequivalent dose of 0.1 ml into the inner surface of the forearm. An experienced nurse or physician measured the transverse diameter of the induration 48-72 hours after injection. Study analyses were performed for two cut-off points, ≥ 5 and ≥ 10 mm, for TST positivity. The QuantiFERON-TB Gold (QTF-G) test was used in conjunction with TST in some patients at the start of biological therapy.

Furthermore, the frequency of completing 9 months of INH treatment, the reasons for quitting, and the incidence of tuberculosis in INH users and non-users were evaluated. The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were routinely measured before starting isoniazid therapy and at regular intervals thereafter. Patients were also monitored for other side effects. As recommended in the guidelines, INH was discontinued if transaminase levels increased ≥ 3 times the upper normal limit in symptomatic cases and ≥ 5 times the upper normal limit in asymptomatic cases. In patients whose transaminase levels had returned to normal, INH was reinitiated. In case of relapse, INH was completely discontinued. Rifampicin was started in these patients based on the time of biological therapy onset, duration of INH use, and TB risk factors. Screening and treatment recommendations for LTBI were developed in accordance with international guideline, and the Turkish Thoracic Society's (TTD) and Turkish Society for Rheumatology's (TRD) Joint Consensus Report on Biological Agent Therapy and Tuberculosis [7,8].

### Screening and Follow-Up for Viral Hepatitis

Before beginning treatment, all patients' hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), total hepatitis B core antibody (Anti-HBc), hepatitis B e antigen (HBe-Ag), hepatitis B e antibody (Anti-HBe), hepatitis C virus antibody (Anti-HCV), human immunodeficiency virus antibody (Anti-HIV), complete blood count, AST, ALT, and hepatitis B virus DNA (HBV-DNA) results were evaluated. Recommendations for viral hepatitis screening, prophylaxis, and treatment of patients were arranged in accordance with the 2016 guideline by Karadağ et al. [9].

### Sample Size Calculation

The minimum required sample size was estimated using the finite population correction method. Assuming a total accessible population of 150 patients, an expected prevalence of 50% due to the lack of reliable prior estimates, a 95% confidence level, and a 5% absolute margin of error, the minimum required sample size was calculated as 109 patients.

### Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 14 (Ostend, Belgium). Normality was assessed using the Shapiro–Wilk test and variance homogeneity using Levene's test. Quantitative variables were compared using the independent-samples t-test or Mann–Whitney U test, as appropriate. Categorical variables were analyzed using Pearson's chi-square or Fisher's exact test. Diagnostic performance was evaluated

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using receiver operating characteristic (ROC) curve analysis. Logistic regression analysis with the backward method was used to identify independent risk factors. Agreement between the TST and QFT-G was assessed using Cohen's kappa. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), and categorical variables as number (percentage). A p value < 0.05 was considered statistically significant.

### Ethical Approval and Consent to participate

This study was approved by the Clinical Research Ethics Committee of Sanko University (Approval No: 2022/09, 01 Date: 26/05/2022). Written informed consent was obtained from all participants prior to inclusion in the study.

## Results

A total of 131 patients, 78 (59.5%) of whom were female, with a mean age of 45.07 (14.49) years, were included in our study. All patients were receiving TNFi or non-TNFi biological therapy. The diabetes mellitus (DM) frequency was found to be 12.2% and the frequency of HT 11.5%. While HBsAg (+) was detected in 2 (1.5) of the patients, Anti-HBs (+) was detected in 44 (33.6%). While anti-Hbc (+) was detected in 30 (22.9%) patients, HBe-AG and HBV-DNA positivity was not detected in any patient. While Anti-HCV (+) was detected in 3 (2.3%) of the patients during follow-up, hepatitis C virus RNA (HCV-RNA) (+) was not detected in the follow-ups. Anti-HIV (+) was found in 1 (0.8%) patient in the study, and the patient's care was transferred to an infectious diseases clinic (Table 1).

**Table 1.** Demographic findings

| Characteristics | | Mean (SD) |
|---|---|---|
| **Age (year)** | | 45.07 (14.49) |
| **BMI (kg/m²)** | | 25.25 (3.04) |
| **Duration of therapy (year)** | | 2.14 (1.33) |
| **Tuberculin skin test (mm)** | | 5.58 (4.73) |
| | | **n (%)** |
| **Sex, Female** | | 78 (59.5) |
| **Rheumatic disease** | **Rheumatoid arthritis** | 49 (37.4) |
| | **Ankylosing spondylitis** | 52 (39.7) |
| | **Psoriatic arthritis** | 9 (6.9) |
| | **Psoriasis vulgaris** | 9 (6.9) |
| | **Crohn's disease** | 5 (3.8) |
| | **Ulcerative colitis** | 3 (2.3) |
| | **FMF** | 3 (2.3) |
| | **Behçet's syndrome** | 1 (0.8) |
| **Co-morbidity** | **Diabetes mellitus** | 16 (12.2) |
| | **Hypertension** | 15 (11.5) |
| | **Cardiovascular disease** | 1 (0.8) |
| | **None** | 99 (75.6) |
| **Carrying hepatitis / reactivation** | **HBsAg (+)** | 2 (1.5) |
| | **Anti HBs (+)** | 44 (33.6) |
| | **HBeAg (+)** | 0 (0) |
| | **Anti-Hbc (+)** | 30 (22.9) |
| | **HBV-DNA (+)** | 0 (0) |
| | **Hepatitis B prophylaxis (+)** | 21 (16) |
| | **Hepatitis B reactivation (+)** | 0 (0) |
| | **Anti HCV (+)** | 3 (2.3) |
| | **Anti-HIV (+)** | 1 (0.8) |
| **Carrying tuberculosis / reactivation** | **TST (mm) (≥ 5mm) (n = 24)** | 15 (62.5) |
| | **QuantiFERON-TB Gold (+)** | 30 (22.9) |
| | **Involvement in lungs (+)** | 0 (0) |
| | **Tuberculosis prophylaxis (+)** | 35 (26.7) |
| | **Latent TBI (+)** | 30 (22.9) |
| | **Active TBI (+)** | 1 (0.8) |

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; anti-HCV, hepatitis C virus antibody; anti-HIV, human immunodeficiency virus antibody; BMI, body mass index; FMF, familial Mediterranean fever; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus DNA; mm, millimeter; n, number; SD, standard deviation; TBI, tuberculosis infection; TST, tuberculin skin test.

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The mean duration with respect to the use of biological therapies was 2.14 ± 1.33 years. Of the patients, 49 (37.4%) were diagnosed with RA and 52 (39.7%) with AS. Among the patients in our study, 5 (3.8%) had CD and 3 (2.3%) had UC. In addition, 3 (2.3%) of the patients were diagnosed with familial Mediterranean fever (FMF) and 1 (0.8%) with Behçet's Syndrome (Table 1).

Of the patients, 93 (71%) were using TNFi, while 38 (29%) patients were using non-TNFi biological drug therapy. The most commonly administered TNFi treatments were adalimumab (n = 53, 57%) and sertolizumab (n = 14, 25.8%), while the most commonly administered non-TNFi treatments were secukinumab (n = 21, 53%) and tocilizumab (n = 6, 15.8%).

### Evaluation of QFT-G and TST Results

While QFT-G (+) was found in 30 (22.9%) of the patients, A TST was performed in 24 (18.3%). An induration diameter of ≥ 5 mm was found in 15 (62.5%) of the patients who had undergone TST. TB prophylaxis was given to 35 (26.7%) of the patients (Table 2).

**Table 2.** Evaluation of QFT-G and TST results

| Characteristics | QuantiFERON-gold test | | p |
|---|---|---|---|
| | Negative (n = 101) | Positive (n = 30) | |
| **Age (years), mean (SD)** | 44.45 (14.31) | 47.17 (15.15) | 0.366[t] |
| **Sex (Female), n (%)** | 64 (63.37) | 14 (46.67) | 0.138[c] |
| **BMI (kg/m²), mean (SD)** | 25.15 (3.13) | 25.6 (2.72) | 0.413[t] |
| **Rheumatic disease, n (%)** | | | 0.930[ff] |
| **Rheumatoid arthritis** | 38 (37.62) | 11 (36.67) | |
| **Ankylosing spondylitis** | 39 (38.61) | 13 (43.33) | |
| **Psoriatic arthritis** | 6 (5.94) | 3 (10) | |
| **Psoriasis vulgaris** | 8 (7.92) | 1 (3.33) | |
| **Crohn's disease** | 4 (3.96) | 1 (3.33) | |
| **Ulcerative colitis** | 3 (2.97) | 0 (0) | |
| **FMF** | 2 (1.98) | 1 (3.33) | |
| **Behçet's syndrome** | 1 (0.99) | 0 (0) | |
| **Tuberculin skin test (mm) (≥ 5 mm), n (%)** | 8 (50) | 7 (87.5) | 0.178[f] |
| **Tuberculin skin test (mm), median (min/max)** | 2.5 (0 / 11) | 9.5 (0 / 13) | **0.028[u]** |
| **Chest x-ray (with involvement), n (%)** | 0 (0) | 0 (0) | – |
| **Tuberculosis prophylaxis (yes), n (%)** | 5 (4.95) | 30 (100) | **<0.001[c]** |
| **Active tuberculosis disease (yes), n (%)** | 0 (0) | 1 (3.33) | – |

[t] Independent Samples t-Test (Monte Carlo), [u] Mann Whitney U Test (Monte Carlo), [f] Fishers' exact Test (Monte Carlo), [ff] Fisher Freeman Halton Test (Monte Carlo), [c] Pearson Chi-Square Test (Monte Carlo). Abbreviations: BMI, body mass index; FMF, familial Mediterranean fever; max, maximum; min, minimum; mm, millimeter; n, number; QFT-G, QuantiFERON-TB Gold test; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test.

Patients with positive QFT-G results were found to have a larger TST induration diameter and these patients received a higher rate of TB prophylaxis indication. However, it was observed that TST ≥ 5 mm (clinical positivity) was at similar rates in both groups (Table 2).

### Evaluation of Hepatitis B Screening Results

Anti-HBc (+) patients were determined to be older and to have higher body mass index (BMI) measurements (p = 0.001 and p = 0.045, respectively) (Figure 1 and Figure 2). Hepatitis B prophylaxis was given to 21 (70%) of the patients with anti-HBc (+). During the follow-up period, no patients in our study developed Hepatitis B reactivation (Table 3).

In the multiple regression analysis, when the cut-off value for age was taken as 39 years, the risk of having Anti-Hbc (+) was found to be high in patients > 39 y (OR: 10.44, CI: 1.45 – 75.31; p = 0.020). Anti-Hbc (+) frequency was found to be higher in females than males (OR: 16.703, CI: 2.99 – 93.04; p < 0.001) (Table 4).

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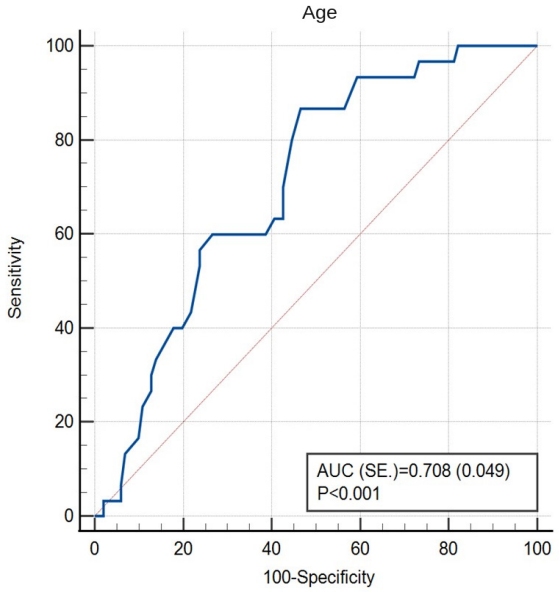


**Figure 1.** Age and Anti-HBc (+) ROC curve.Abbreviations: anti-HBc, hepatitis B core antibody; AUC, area under the curve; ROC, receiver operating characteristic; SE, standard error.

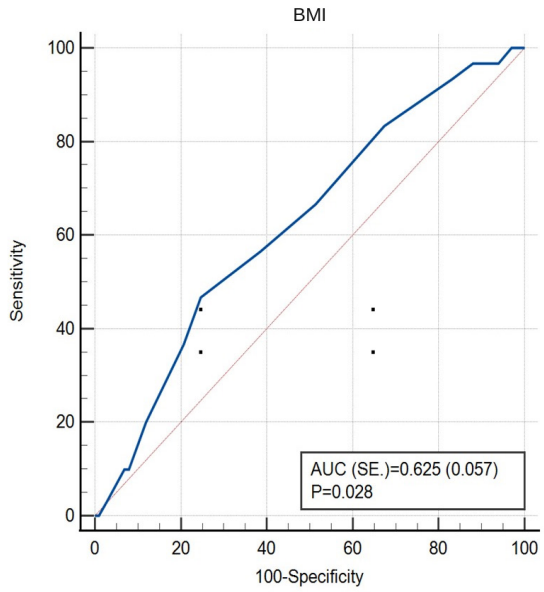


**Figure 2.** BMI and Anti-HBc (+) ROC curve. Abbreviations: anti-HBc, hepatitis B core antibody; AUC, area under the curve; BMI, body mass index; ROC, receiver operating characteristic; SE, standard error.

**Table 3.** Evaluation of hepatitis screening results

| Characteristics | Anti Hbc | | p |
|---|---|---|---|
| | Negative (n=101) | Positive (n=30) | |
| **Age (years), mean (SD)** | 42.86 (14.39) | 52.5 (12.39) | **0.001**[t] |
| **Sex (Female), n (%)** | 56 (55.45) | 22 (73.33) | 0.093[c] |
| **BMI (kg/m²), mean (SD)** | 24.97 (3.04) | 26.2 (2.86) | **0.045**[t] |
| **Duration of Treatment (years), median(min/max)** | 2 (1 / 5) | 2 (1 / 5) | 0.117[u] |
| **Rheumatic disease, n (%)** | | | 0.772[ff] |
| **Rheumatoid arthritis** | 34 (33.66) | 15 (50) | |
| **Ankylosing spondylitis** | 41 (40.59) | 11 (36.67) | |
| **Psoriatic arthritis** | 8 (7.92) | 1 (3.33) | |
| **Psoriasis vulgaris** | 8 (7.92) | 1 (3.33) | |
| **Crohn's disease** | 4 (3.96) | 1 (3.33) | |
| **Ulcerative colitis** | 3 (2.97) | 0 (0) | |
| **FMF** | 2 (1.98) | 1 (3.33) | |
| **Behçet's syndrome** | 1 (0.99) | 0 (0) | |
| **Type of TNF (Anti TNF), n (%)** | 70 (69.31) | 23 (76.67) | 0.499[c] |
| **HBs ag (positive), n (%)** | 0 (0) | 2 (6.67) | 0.051[f] |
| **Anti-HBs (positive), n (%)** | 16 (15.84) | 28 (93.33) | **< 0.001**[c] |
| **HBe ag (positive), n (%)** | 0 (0) | 0 (0) | – |
| **Anti-HCV (developed), n (%)** | 2 (1.98) | 1 (3.33) | |
| **HCV RNA (positive), n (%)** | 0 (0) | 0 (0) | – |
| **Anti-HIV (positive), n (%)** | 0 (0) | 1 (3.33) | |
| **Hepatitis B prophylaxis (given), n (%)** | 0 (0) | 21 (70) | **< 0.001**[f] |
| **Hepatitis B reactivation (developed), n (%)** | 0 (0) | 0 (0) | – |

[t] Independent Samples t-Test (Monte Carlo), [u] Mann Whitney U Test (Monte Carlo), [f] Fisher's exact Test (Monte Carlo), [ff] Fisher Freeman Halton Test (Monte Carlo), [c] Pearson Chi-Square Test (Monte Carlo), [A] Expresses significance according to the Negative Group. Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; anti-HCV, hepatitis C virus antibody; anti-HIV, human immunodeficiency virus antibody; BMI, body mass index; FMF, familial Mediterranean fever; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; max, maximum; min, minimum; n, number; RNA, ribonucleic acid; SD, standard deviation; TNF, tumor necrosis factor.

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**Table 4.** Multiple regression analysis performed for anti-Hbc (+)

| Dependent variable: Anti-Hbc<br>Reference groups: Positive | B (SE) | p-value | Odds ratio (95% CI) |
|---|---|---|---|
| **Age (> 39) (↑)** | 2.35 (1.01) | **0.020** | 10.44 [1.45 – 75.31] |
| **Sex (male) (↓)** | 2.816 (0.876) | **0.001** | 16.703 [2.998 – 93.049] |
| **Anti HBs (↑)** | 3.95 (1.09) | **< 0.001** | 51.86 [6.07 – 442.81] |
| **Accuracy rates** | **Negative: 100.0** | **Positive: 76.7** | **Overall: 94.7** |

Multiple Logistic Regression (Method = Backward Stepwise (Wald)). Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; B, regression coefficient; CI, confidence interval; SE, standard error.

### TST and QFT-G Results

In our study, LTBI was considered in 30 (22.9%) patients. 35 (26.7%) patients used INH prophylaxis for LTBI. During INH prophylaxis in 1 patient, liver function test elevation recurred twice; prophylaxis was discontinued and the patient closely monitored. During our study, 1 (0.8%) patient developed active TB (tuberculosis peritonitis) at the 48th month of adalimumab treatment. Anti-TB treatment was applied to the patient for 9 months. Active AS disease was observed 6 months after the end of treatment, and biological therapy, the IL-17A inhibitor secukinumab, was initiated (data not shown in the table).

### Evaluation of TST and QFT-G Test Compliance

In the analysis evaluating the compliance between TST (≥ 5 mm) and QFT-G tests, the kappa value was 0.308 (low) (p = 0.180) (Table 5).

**Table 5.** Evaluation of TST and QFT-G test compliance

| Test | | QuantiFERON-TB Gold | | Total |
|---|---|---|---|---|
| | | Negative | Positive | |
| **Tuberculin skin test (mm)** | **< 5mm (Negative)** | 8 | 1 | 9 |
| | **≥ 5mm (Positive)** | 8 | 7 | 15 |
| **Total** | | 16 | 8 | 24 |
| **Overall compatibility (%): 62.5** | | **Kappa value: 0.308** | **Kappa Analysis p-value (Monte Carlo): 0.180** | |

Abbreviations: mm, millimeter; QFT-G, QuantiFERON-TB Gold; TST, tuberculin skin test.

## Discussion

Several guidelines have been developed to minimize the risk of tuberculosis and viral hepatitis reactivation among patients with rheumatic diseases and IBD undergoing biologic therapy. Nevertheless, variations in epidemiological characteristics and socioeconomic conditions across countries have led to differences in screening algorithms and considerable heterogeneity in reported study outcomes [10].

In our study, follow-up of patients receiving biological therapy revealed no significant increase in the frequency of infections when assessed with respect to TB infection and HBV reactivation (HBVr). Nevertheless, patients with LTBI and those with HBV infection who met the relevant clinical criteria received appropriate screening and prophylactic treatment, when indicated, in accordance with established guidelines before initiating biological therapy [7-9].

Following infection with Mycobacterium tuberculosis, the organism may persist without clinical manifestations as LTBI. Nevertheless, active TB subsequently develops in approximately 5–10% of individuals, with the highest risk occurring during the first two years following infection [11]. In the present study, the mean duration of biologic therapy was 2.14 ± 1.33 years, providing an adequate follow-up period for assessment of the risk of TB and HBV reactivation.

Meta-analyses based on long-term follow-up data from large patient populations have demonstrated that treatment with TNFi is associated with an increased risk of active tuberculosis (ATB) [12]. In particular, the risk of TB has been reported to be approximately twofold higher among patients receiving TNFi therapy. Consistent with these findings, a study conducted among patients with IBD in Türkiye reported infiltrative pulmonary tuberculosis in 3 patients (4.1%) during biological therapy; notably, two of these patients had not received LTBI chemoprophylaxis before treatment initiation [13]. Similarly, active tuberculosis was diagnosed in 4 of 330 (1.2%) IBD patients receiving anti-TNF therapy in Spain [14]. In a Korean study, active TB developed in 9 of 661 (1.4%) patients with CD who were treated with TNFi [15].

In addition to TNFi, non-TNFi biological agents, including secukinumab, rituximab, abatacept, and tocilizumab, have also been associated with an increased risk of infection. However, the

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types and frequencies of infections reported with these agents vary across treatment groups. Compared with other biological therapies, rituximab (RTX) treatment is associated with a greater expected increase in the occurrence of viral infections, particularly viral hepatitis and zoster infection [16].

The occurrence of active TB in patients receiving TNFi has been described as a biphasic pattern, particularly among those with a previous history of TB. The first phase generally occurs within 3–6 months after initiation of TNFi therapy, whereas the increased risk may persist for approximately 24 months [17,18]. Several mechanisms may account for this biphasic pattern. Early development of M. tuberculosis infection following initiation of TNFi may result from false-negative screening tests related to the immunosuppressive effects of RA or IBD, leading to failure to administer prophylaxis. In contrast, active TB emerging several months after the start of TNFi therapy may reflect the occurrence of newly acquired primary TB infection [18].

Among patients treated with TNFi, the relative risk of TB infection has been reported to range from 1.5 to 17 [19]. By interfering with the physiological TNF-mediated immunoinflammatory response, TNFi therapy can facilitate both reactivation and dissemination of M. tuberculosis [20]. The likelihood of tuberculosis infection appears to be greater with TNFi monoclonal antibodies than with soluble TNF-receptor inhibitors [21]. Supporting this distinction, a US-based study found that the risk of developing tuberculosis was more than twofold higher with infliximab than with etanercept [22].

Meta-analyses have shown that TNFi therapy is associated with an approximately fourfold increased risk of tuberculosis compared with non-exposed patients, with monoclonal antibodies posing a higher risk than TNF receptor blockers [23]. This risk may be further increased by concomitant immunosuppressive therapy, comorbid conditions, malnutrition, and advanced age. In our cohort, one patient (0.8%) developed tuberculosis peritonitis during adalimumab therapy and was successfully treated with anti-TB therapy; biologic treatment was later resumed with secukinumab [24]. The lower-than-expected incidence of active TB in our study may be attributed to early screening, isoniazid prophylaxis, and close follow-up in specialized tuberculosis dispensaries using directly observed treatment strategies

Despite widespread awareness of the need for TB screening prior to TNFi therapy, non-compliance with guidelines remains unacceptably high. Large-scale surveys report clinician compliance rates ranging from 73% to 100% [25]. Interferon-Gamma Release Assay (IGRA) demonstrates higher specificity than TST (66% for TST; 97% for QFT-G; 92% for T-SPOT. TB) [26]. Given the low specificity of TST for LTBI and its susceptibility to confounding factors, IGRA has been adopted as an alternative for diagnosing ATB and LTBI in the United States [27]. A growing preference for IGRA over TST is also observed before TNFi initiation, particularly in countries with moderate TB prevalence and mandatory BCG vaccination, such as Korea [28]. However, poor concordance between TST and IGRA has been reported across diverse populations, and multicenter, large-scale randomized comparative studies remain limited. To enhance diagnostic sensitivity in patients receiving biologic therapy, concurrent testing is recommended [29].

Patients with positive QFT-G results were found to have a larger TST induration diameter and these patients received a higher rate of TB prophylaxis indication. However, it was observed that a TST $\geq$ 5 mm (clinical positivity) was at similar rates in both groups. In addition, in the analysis evaluating the compliance between TST ($\geq$ 5 mm) and QFT-G tests, the kappa value was 0.308 (low) ($p = 0.180$). Therefore, in our study conducted on middle-aged people in Türkiye, we believe that a detailed clinical history, physical examination, QFT-G test, and careful evaluation of chest radiography is a much more effective and usable method in detecting LTBI in cases where BCG vaccination is common and TST measurement results differ. In areas where access to the QFT-G test is limited, we believe that it is appropriate to perform a TST every 6-12 months in the follow-up of patients. In patients with anergic initial TST tests, the importance of evaluating with a repeated TST (booster) test in the second week is clear in case of the absence of overt immunodeficiency and sarcoidosis [30].

Individuals infected with M. tuberculosis are generally asymptomatic during LTBI, making the assessment of tuberculosis risk challenging. Consequently, much of the available evidence is derived from nonrandomized retrospective sources, including patient registries and voluntary public health surveillance reports. These study designs have inherent limitations, and the actual risk may be underestimated because of detection bias. In other analyses, TB rates among patients receiving TNFi have been compared with national tuberculosis incidence rates or with patients with immune-mediated inflammatory diseases treated exclusively with TNFi, approaches that may introduce additional bias and lead to overestimation of the observed rates. Nevertheless, the available evidence consistently indicates that TNF-α antagonism is associated with an increased risk of TB [31].

Selection of appropriate tuberculosis screening tests should consider clinical indication, availability, and cost-effectiveness. Comparative studies of IGRAs and TSTs report variable sensitivity, specificity, and agreement. Although data on IGRA accuracy and prediction of active TB remain limited, no major deficiencies have been identified across diverse populations, and wider use is expected to further clarify their clinical utility [29].

The potential for HBV reactivation in patients with occult HBV infection undergoing TNFi therapy necessitates systematic screening and appropriate follow-up. For patients with rheumatic diseases who are candidates for anti-TNF treatment,

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screening for HBsAg and anti-HBc is recommended. Although routine antiviral prophylaxis is not generally recommended for individuals who are anti-HBc positive, careful monitoring throughout TNFi therapy remains essential. A prevalence study conducted in Türkiye reported HBV carrier and HBV exposure rates of 3.9% and 30.4%, respectively, while anti-HCV positivity was 0.9%; comparable rates were identified among patients with rheumatoid arthritis and ankylosing spondylitis [32,33]. In our study population, anti-HBc positivity was detected in 22.9% of patients. HBV prophylaxis was initiated in anti-HBc-positive patients when indicated based on individual risk assessment and shared decision-making with the patient. These patients underwent regular monitoring of HBV-DNA levels and liver function tests.

The concern surrounding viral hepatitis in patients receiving TNFi therapy is primarily related to reports of HBV and HCV reactivation during immunosuppressive treatment. Evidence from clinical studies and real-world experience, together with findings from systematic reviews and multiple investigations, demonstrates that TNFi therapy is associated with an increased risk of HBV infection or reactivation [34].

The association between TNFi therapy and HBVr has been well established over the past decade. Pérez-Alvarez et al. reported an HBVr rate of 64% in HBsAg-positive patients receiving TNFi without antiviral prophylaxis [35]. These findings indicate a substantial HBVr risk in HBsAg-positive patients without antiviral therapy. In contrast, patients with resolved HBV infection have a markedly lower risk; Lee et al. reported HBVr in only 1.7% of published cases (8/468), classifying TNFi as a low-risk therapy in this group [36]. In our study, anti-HBc–positive patients were older and had higher BMI values. Antiviral prophylaxis was administered to 70% of these patients, and no HBVr was observed during follow-up, possibly due to low baseline HBV-DNA levels.

Studies have categorized the prevalence of chronic HBV according to the epidemiological burden of the disease, distinguishing between countries with a high HBV burden (≥ 8%) and those with a low HBV burden (< 8%). Taiwan, South Korea, Thailand, and China are classified among countries with a high HBV burden, whereas Italy, France, Spain, Greece, Türkiye, and Japan are considered countries with a low HBV burden [34].

Comparison of the number of HBV cases per 1,000 patients receiving TNFi with the overall chronic HBV burden in individual countries demonstrated a more than 15-fold higher incidence of HBVr in countries with a high viral burden than in those with a low burden (65/1,000 vs. 4/1,000). This finding not only illustrates the risk of HBVr among patients receiving TNFi but also emphasizes the importance of regional epidemiological differences when assessing viral burden and the likelihood of hepatitis development [37]. Patients receiving high-dose corticosteroids (CS), TNFi, or CD20 inhibitors such as RTX without antiviral prophylaxis are considered to be at high risk for HBVr. Accordingly, HBV serological screening is recommended for almost all patients with rheumatic diseases before the initiation of immunosuppressive therapy [9]. Overall, TNFi inhibitors are associated with an increased risk of both TB and HBV infection or reactivation, contributing to a greater infectious disease burden. Further studies should investigate the factors that may modify infection risk during TNFi therapy, including comorbidities, immunization status, ethnicity, and social and health-related risk factors.

With growing concerns about the safety of TNFi agents, particularly in patients with possible LTBI, the incidence of LTBI reactivation in the general population is decreasing [38]. Mass vaccination programs, awareness of the disease, and prophylaxis in directly supervised treatment (DST) centers are all helpful. Several retrospective and observational studies have found that LTBI treatment before or during TNFi treatment effectively prevents reactivation [39].

The most important limitation of our study is its retrospective design. In some cases, there was insufficient information about BCG scar assessment, TST results, and completion of INH treatment. Another significant data that was not tested in our study was the inability to reveal interobserver variability in TST evaluation. The main limitation of the direct comparison of QTF-G and TST was the fact that not all patients had a combined QFT-G and TST.

## Conclusion

As a result, biological therapies are used as important game-changing agents in the treatment of rheumatic diseases and IBD. Considering the possibility of TB infection and viral hepatitis reactivation during these treatments, monitoring with the most appropriate screening and prophylaxis programs for the clinician provides significant clinical benefit. All patients for whom biological therapy will be initiated should be screened for LTBI and HBV. Given the rapidly changing prevalence of TB and HBV today, larger-scale studies on the long-term safety of biologics are required to improve the safety of biological therapy in clinical use.

**Ethical Approval**
*This study was approved by the Clinical Research Ethics Committee of Sanko University (Approval No: 2022/09, 01 Date: 26/05/2022).*

**Patient Consent**
*Written informed consent was obtained from all participants prior to inclusion in the study.*

**Conflict of Interest**
*The authors confirm the absence of any conflicts associated with this work.*

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