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# QuantiFERON-TB Gold Test Results in Patients with Psoriasis Receiving Biologic Therapy

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## ABSTRACT

**Background:** Psoriasis is a chronic inflammatory disease of the skin, and to a lesser extent of the nails and joints, and has recently been recognized as a complex disease with systemic comorbidities. Recent breakthroughs in the treatment of psoriasis have led to significant improvements in the Psoriasis Area and Severity Index response and Dermatology Life Quality Index, but long-term survival and safety remain controversial. Although the risk of biological agents activating latent tuberculosis (TB) is low, it should not be ignored. This is especially important in Turkey where migration traffic is intense due to its geographical location. The aim of this study was to investigate the safety of biological agents in terms of latent TB infection during the initiation and follow-up of treatment in patients with moderate to severe psoriasis.

**Materials and Methods:** This retrospective, cross-sectional, single-center, hospital-based study included patients admitted to our department between 24.08.2017 and 24.12.2021 who were started on biological agents.

**Results:** The study included 187 patients. The mean age was 42.45±12.48 (16-74) years. Patients had a mean disease duration of 12.66 (3-32) years and 88.8% (n=166) were diagnosed with chronic plaque type psoriasis, 10.7% (n=20) with plaque + nail psoriasis, and 0.5% (n=1) patient with palmoplantar type psoriasis. Psoriatic arthritis was present in 17.6% of patients. Adalimumab was used as a biologic agent in 10.7%, ixekizumab in 35.3%, secukinumab in 31.6%, and ustekinumab in 22.5% of the patients. The mean duration of biologic agent use was 36.56 (12-61) months. Among the patients included in the study, 78.6% (n=147) had used methotrexate, 25.1% (n=47) cyclosporine and 15.55% (n=29) acitretin as conventional treatment agents. While the rate of patients with positive QuantiFERON test at baseline was 42.2% (n=79), the rates of those who became positive and negative during follow-up were 5.3% (n=4) and 11.8% (n=9), respectively. In two patients, the QuantiFERON-TB Gold (QFT) first became positive and then became negative again. The rate of patients with positive initial QFT test results was 42.2%, while the rate of patients who became negative during follow-up was 11.8%. There were no active TB cases. Of the 79 patients with positive QFT test results, 27.8% (n=22) had a negative QFT test result over time.

**Conclusion:** It could not be clarified whether this result of patients who became positive during follow-up but whose initial QFT test result was negative was due to false negativity due to previous immunosuppressive conventional treatment or due to the biological agent used. Recently, there are some confusing results regarding the reliability of QFT test results in latent TB infection screening. It should also be taken into account that seroreversion may be due to false QFT test positivity and that negativity during follow-up may be due both to this cause and to decreased QFT test sensitivity in isoniazid treated individuals.

**Keywords:** Quantiferon, Tuberculosis, Psoriasis, Biological agents, LTBI

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## Introduction

Psoriasis is a chronic inflammatory disease of the skin and to a lesser extent of the nails and joints [1]. The incidence of psoriasis varies in relation to age, gender, geographic region, ethnicity, genetic and environmental factors. The prevalence of the disease ranges from 0.27% to 11.4%. Epidemiological studies reported a latent tuberculosis infection (LTBI) prevalence rate of 5-22% in Italy, 10% in United Kingdom, 11% in Taiwan, and 20-29% in Spain, respectively, in psoriatic patients screened for tuberculosis (TB) [2,3].

Moderate to severe psoriasis has recently been recognized as a systemic disease due to its association with systemic comorbidities. It causes a great deal of psychosocial pressure in patients and has a negative effect on Dermatology Life Quality Index. Due to all these features, groundbreaking options have recently emerged in the treatment of the disease. The recent increase in the use of biological therapies is an example of this. Their use is more effective and safe in patients with moderate to severe psoriasis who do not respond to conventional treatments or for whom conventional treatments are contraindicated. Although biologic agents are target-oriented, their immunosuppressive effects should not be ignored. The risk of infectious diseases and TB activation should not be underestimated due to immunosuppressive effects. Patients who are candidates for biologic therapy, especially anti-tumor necrosis factor (TNF) agents, should be routinely evaluated for infections and TB before and during treatment [4]. Screening for TB infection should include a detailed medical history, chest radiography and tuberculin skin test or QuantiFERON-TB Gold (QFT) tests.

It is estimated that one-third of the world's population is infected with LTBI [5]. Although LTBI individuals are not infective, they may play a reservoir role in increasing the number of future TB incidence [6]. QFT test should be the first choice for LTBI screening in psoriasis patients for whom anti-TNF and other biologic agent therapy is indicated [4]. QFT test is more specific for LTBI screening and is not affected by Bacillus Calmette-Guerin vaccination or other atypical mycobacterial variants [7].

## Materials and Method

### Patients and Study Design

We retrospectively reviewed the electronic medical records of 187 patients who were admitted to our department between October 2016 and December 2022 and started biological agent treatments (adalimumab, ustekinumab, secukinumab, ixekizumab). Patients with active infection, premalignancy or malignancy and patients who did not meet the age criteria were excluded.

Demographic characteristics such as age, gender, personal medical history, disease duration, presence of psoriatic arthritis (PsA) and duration of drug exposure were reviewed. Conventional therapies [methotrexate (MTX), cyclosporine (CYC) or acitretin] used by the patients before the initiation of biologic therapy were recorded.

QFT test results were defined as baseline and follow-up QFT results during biological therapies; patients with positive QFT test or those who became positive later (seroconversion) were consulted to the pulmonology department, and isoniazid (INH) prophylaxis was started for 9 months after checking the results of chest radiography and thorax computer tomography. Biological treatment was stopped during the first month of INH treatment in patients with seroconversion.

This study protocol was reviewed and approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Research Ethics Committee (decision number: 749867, date: 15.11.2022).

### Statistical Analysis

SPSS v.21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were presented as mean ± standard deviation and median (interquartile range), categorical variables were presented with frequency and percentage. The variables were investigated using visual (histograms, Q-Q plots) and analytical methods (Shapiro-Wilk or Kolmogorov-Smirnov test) to determine whether or not they are normally distrubuted. Comparisons of the groups for continuous variables were made by one-way ANOVA or Kruskal-Wallis test. Chi-squared test was used to analyze categorical variables. Post-hoc analyzes were performed to test significance differences for multiple comparisons. All tests are two-sided and significance level was accepted as $p<0.05$.

## Results

The study included 187 randomly selected patients, 75 females and 112 males. The mean age of the patients was 42.45±12.48 years. Patients had a mean disease duration of 12.66 (3-32) years and 88.8% (n=166) were diagnosed with chronic plaque type psoriasis, 10.7% (n=20) with plaque + nail psoriasis, and 0.5% (n=1) patient with palmoplantar type psoriasis. An additional 17.6% (n=9) of patients had PsA (Table 1).

Adalimumab was used as a biologic agent in 10.7% (n=20), ixekizumab in 35.3% (n=66), secukinumab in 31.6% (n=59) and ustekinumab in 22.5% (n=42) of the patients. The mean duration of biologic agent use was 36.56 (12-61) months. Among the patients included in the study, 78.6% (n=147) had used MTX, 25.1% (n=47) CYC and 15.5% (n=29) acitretin as conventional treatment agents (Table 1).

Patients on secukinumab had significantly longer duration of drug use than adalimumab and ustekinumab ($p<0.001$). The change in QFT test results during the follow-up period was not statistically significantly different among patients receiving four different drug groups ($p=0.601$) (Table 2).

The number of patients with a QFT at baseline was in 79 patients, of which 38% (n=30) were women and 62% (n=49) were men (Table 3). The rate of those who became positive during follow-up was 5.3% (n=4) and the rate of those who became negative was 11.8% (n=9). In two patients, the QFT was first positive and then negative again.

When sociodemographic characteristics were analyzed, there was no significant difference in age, gender, disease duration and baseline QFT positivity among patients who used different biologic agents. All patients with a positive QFT received INH prophylaxis and accounted for 46.5% (n=87) of the total patients.

**Table 1. Sociodemographic characteristics**

| **Feature n(%)** | **n(%)** |
|---|---|
| **Age** (mean ± SD) | 42.45±12.48 |
| Gender | |
| Woman | 75 (40.1) |
| Male | 112(59.9) |
| **Duration of illness (years)** (mean ± SD) | 12.66±7.58 |
| **Psoriasis** | |
| Plaque | 166 (88.8) |
| Plaque + nail | 20 (10.7) |
| Palmoplantar | 1 (5.0) |
| **Psoriatic arthritis** | 33 (17.6) |
| **QFT positivity** | |
| Baseline (n=187) | 79 (42.2) |
| 1st year follow-up (n=187) | 82 (43.9) |
| 2nd year follow-up (n=177) | 77 (41.2) |
| 3rd year follow-up (n=122) | 49 (26.2) |
| 4th year follow-up (n=40) | 17 (9.1) |
| 5th year follow-up (n=7) | 2 (1.1) |
| **QFT test variation** | |
| No change | 153 (81.8) |
| Negativized | 22 (11.8) |
| Becoming positive | 10 (5.3) |
| Positive and then negative again | 2 (1.1) |
| **Biological agents** | |
| Adalimumab | 20 (10.7) |
| Ixekizumab | 66 (35.3) |
| Secukinumab | 59 (31.6) |
| Ustekinumab | 42 (22.5) |
| **Duration of use of biological agent (months)** (mean ± SD) | 36.56±11.03 |
| **Medication used** | |
| **INH (n=185)** | 87 (46.5) |
| **MTX** | 147 (78.6) |
| **Cyclosporine** | 47 (25.1) |
| **Acitretin** | 29 (15.5) |

SD: Standard deviation, QFT: Quantiferon test, INH: Isoniazid, MTX: Methotrexate

There was no statistically significant difference in terms of age and gender according to the change in the QFT results of the patients at follow-up (Table 4).

Among patients who had used MTX, 39.5% (n=58) had a positive QFT at baseline and 5.4% (n=8) became positive during follow-up. Among patients who had used CYC, 48.9% (n=23) had a positive test at baseline and 4.3% (n=2) became positive during follow-up. In patients who had used acitretin, 48.3% (n=14) had a positive QFT at baseline and 3.4% (n=1) became positive during follow-up (Table 5).

## Discussion

TB is one of the infectious diseases with the largest reservoir, which is still persisting after many years. The LTBI's 2014 survey put the global burden of TB at 23%, which corresponds to 1.7 billion people. This figure corresponds to almost a quarter of the world's population [8].

In Turkey, the TB death rate (per 100,000 population) and incidence rate (per 100,000 population) in 2017 were 0.53 and 17, respectively. The total number of TB cases was 12,046 in Turkey in 2017 [9]. Due to such a large reservoir worldwide, it is recommended that patients receiving immunosuppressive treatment should be screened as a priority.

The basis of the pathogenesis of autoinflammatory diseases such as psoriasis is a risk factor for latent TB activation [10]. The discovery and increasingly frequent use of biological agents in the treatment of other inflammatory diseases, especially psoriasis, also poses a risk for LTBI. Therefore, LTBI screening before biologic agent treatment and annual routine controls have been included in the treatment protocol in psoriasis patients.

There are many studies on screening the QFT at the start and follow-up of biological therapy. When the existing studies are reviewed, there is no clear idea about the value of QFT results during follow-up [11].

In a study by Yuan et al. [12], patients with a positive interferon gamma release assay test were divided into 2 groups, those who received anti-TBC treatment and those who did not, and biologic treatment was initiated. In patients who did not receive prophylaxis, adverse events were higher at 24 week follow-up than at 12 week follow-up. In the group receiving prophylaxis, adverse events did not show a significant difference in the 12th and 24th week follow-ups. At the same time, the risk of consecutive active TB in the prophylaxis and non-prophylaxis groups was 13% and 27%. Relative risk=2.045, 95% confidence interval; p>0.05 was considered significant.

In a single-center 9-year retrospective study conducted by Megna et al. [13], QuantiFERON TB-Gold test conversion rates were 6.5% over a mean period of 3.2 years. Anti TNF-α seroconversion had the highest percentage (35.5% n=7). The lowest seroconversion rate was

**Table 2. Sociodemographic characteristics according to biologic agents used**

| | Biological agents | | | | |
|---|---|---|---|---|---|
| | Adalimumab | Ixekizumab | Secukinumab | Ustekinumab | p-value |
| | n=20 | n=66 | n=59 | n=42 | |
| **Gender** | | | | | |
| Woman | 9 (45) | 23 (34.8) | 23 (39) | 20 (47.6) | 0.577* |
| Male | 11 (55) | 43 (65.2) | 36 (61) | 22 (52.4) | |
| **Age** | 40.4±12.65 | 41.74±12.99 | 41.98±10.18 | 45.21±14.39 | 0.411** |
| **Duration of Illness (years)** (mean ± SD) | 10.5 (6-19) | 10 (6.75-17.25) | 13 (8-20) | 8.5 (6-14.25) | 0.249*** |
| **Duration of use of biological agent (months)** (mean ± SD) | 24 (22.5-42)[a] | 36 (27-45.75)[a,b] | 39 (36-48)[b] | 31 (24-38)[a] | **<0.001*** ** |
| **QFT positivity (Baseline)** | 8 (40) | 29 (43.9) | 25 (42.4) | 17 (40.5) | 0.982* |
| **QFT change in follow-up** | | | | | |
| Negativization | 3 (15) | 6 (9,4) | 6 (10.2) | 7 (16.7) | 0.601**** |
| Positivization | 0 (0) | 2 (3,1) | 5 (8.5) | 3 (7.1) | |
| No change | 17 (85) | 56 (87,5) | 48 (81.4) | 32 (76.2) | |

*Chi-squared test, **One-way ANOVA, ***Kruskal-Wallis test, ****Fisher's Exact Test
Each different letter indicates columns that are statistically significantly different from each other.
The change in QFT test results during the follow-up period was not statistically significantly different among patients receiving four different drug groups (p=0.601). QFT: Quantiferon test, SD: Standard deciation

**Table 3. Gender of patients according to baseline QFT result**

| | QFT positivity (baseline) | | |
|---|---|---|---|
| | Negative | Pozitive | p-value* |
| | n=108 | n=79 | |
| Gender | | | |
| Woman | 45 (41.7) | 30 (38) | 0.611 |
| Male | 63 (58.3) | 49 (62) | |

*Chi-squared test

**Table 4. Age and gender of patients according to QFT change at follow-up**

| | QFT change in follow-up | | | |
|---|---|---|---|---|
| | Negativized | Positivized | No change | Becoming positive and then negative again |
| | n=22 | n=10 | n=153 | n=2 |
| **Age** | 44.18±12.45 | 47.4±11.11 | 41.74±12.53 | 53.5±10.61 |
| **Gender** | | | | |
| Woman | 6 (27.3) | 5 (50) | 63 (41.2) | 1 (50) |
| Male | 16 (72.7) | 5 (50) | 90 (58.8) | 1 (50) |

**Table 5. Prior conventional treatments**

| | MTX treatment | | Cyclosporine treatment | | Acitretin treatment | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| **Baseline QFT test (+)** | 58 (39.5) | 21 (52.5) | 23 (48.9) | 56 (40.0) | 14 (48.3) | 65 (41.1) |
| **Positive in follow-up** | 8 (5.4) | 2 (5.0) | 2 (4.3) | 8 (5.7) | 1 (3.4) | 9 (5.7) |

QFT: Quantiferon test, MTX: Methotrexate

14.7% (n=18) for anti-interleukin (IL)-17. There was no significant difference between the agents included in the biological classes. The study demonstrated the importance of LTBI screening even in Italy, which has a low rate of active TB.

In a single-center retrospective study conducted in Taiwan, which has a high TB case rate, the seroconversion rate was low (7.3%) in patients using IL-12/23 inhibitors during a 6-year follow-up [14].

In the 2021 World Tuberculosis Report, in a single-center retrospective study conducted in China, where 8.5% of all TB cases in the world and 50% of resistant strains were found, QFT conversion rates were 5.43% and 5.26% consecutively in patients receiving adalimumab and secukinumab as monotherapy at 17.13 months follow-up [15].

The rate of patients with positive QFT results at baseline was 42.2% (n=79), while the rate of patients who became negative during follow-up was 11.8% (n=22). Of the 79 patients with positive QFT results, 27.85% (n=22) had negative QFT results over time. In the first serial follow-up of QFT test results conducted by Akdogan et al. [11]. in Turkey, 34 (39.5%) of 86 patients with positive QFT results before the start of biology treatment showed seroreversion over time. But there was no mention of whether QFT seroreversion rates differed between groups. In the same study, there was no statistically significant difference between biologics in terms of the risk of QFT seroconversion (p=0.09). During follow-up, patients with negative initial QFT results became negative in the follow-up 2 years later and then seroconverted again. The rate of patients with a positive QFT test during follow-up was 5.3% (n=10). There was no statistically significant difference between both seroreversion and seroconversion rates in QFT test results during the follow-up period

in the biological agent groups included in our study (p=0.601). In a retrospective cohort study, it was shown that inflammatory diseases may be a factor in negative results in QFT test [16]. In our study, it was noteworthy that 39.5% (n=58) of patients using MTX were seropositive before the use of biological agents and seroconverted with a rate of 5.4% (n=8) during follow-up; among patients using CYC, 48.9% (n=23) had a positive test at baseline and 4.3% (n=2) became positive during follow-up. In patients using acitretin, 48.3% (n=14) had a positive QFT at baseline and 3.4% (n=1) became positive during follow-up. It could not be clarified whether the positive results during follow-up were due to false negativity in the initial negative QFT due to previous immunosuppressive conventional treatment or to the biological agent used. There were no active cases of TB.

The change in baseline and follow-up QFT results of the patients included in the study did not show a significant difference in terms of age and gender. The duration of drug survival was highest in patients on secukinumab. Although there was no significant difference between the agents, the rate of QFT test positivity was higher in the adalimumab group compared to the others. All patients with QFT results completed 9 months of INH treatment regardless of the biologic agent they used. Although there was no specific protocol, biologic agent treatment was given 1 month after INH initiation.

### Study Limitation

Considering the geographical location of our country and the migration rate of immigrants, it is an inevitable result that we are among the endemic countries. Therefore, regardless of the LTBI activation rate of the biological agents used, screening for LTBI in every patient should be performed in a complex manner with detailed anamnesis, physical examination and chest radiography, not with QFT alone. Likewise, questioning of the patients, chest radiography and QFT test results should be performed without omission in the annual follow-up of the patient.

## Conclusion

Positive QFT test observed during follow-up should be investigated in detail with the pulmonology department. In addition, it should be kept in mind that there may be false negativity at the beginning due to immunosuppressive conventional treatments used by the patients before the biologic agent. It should also be taken into account that seroreversion may be due to false QFT positivity and negativity during follow-up may be due to both this reason and decreased QFT sensitivity in patients receiving INH treatment.

### Ethics

**Ethics Committee Approval:** This study protocol was reviewed and approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Research Ethics Committee (decision number: 749867, date: 15.11.2022).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: B.E., T.M., Design: B.E., T.M., Ş.B., Data Collection or Processing: T.M., Analysis or Interpretation: B.K.E., Literature Search: T.M., Writing: B.E., T.M.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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