Tuberculosis screening guidelines should be updated and quantiferon test should be a prerequisite prior to the initiation of treatment of psoriasis with biological agents

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Abstract. – OBJECTIVE: With the current study, we aimed at evaluating the quantiferon test results of psoriasis patients treated with biological agents.

PATIENTS AND METHODS: Between April 2019 and June 2021, medical records of patients with psoriasis who were evaluated for latent tuberculosis infection before the initiation of biological agent treatment were reviewed retrospectively.

RESULTS: This study included 132 patients, 50 (37.9%) female and 82 (62.1%) male. The mean disease duration was 16.42±10.99 years (range: 1-49 years). None of the patients had a previous history of tuberculosis. Quantiferon test was negative in 109 (82.6%) patients and positive in 23 (17.4%) patients. Patients with positive quantiferon test results were older than those who had negative quantiferon test results; the mean ages were 50.21±10.79 and 42.98±11.81 years, respectively (p=0.006).

CONCLUSIONS: Within this study, 17.4% of patients with psoriasis had positive quantiferon test results. We suggest that quantiferon test should be performed in all patients with psoriasis especially in the elderly for latent tuberculosis screening before the initiation of biological agent treatment. Moreover, we suggest that psoriasis treatment guidelines with biological agents should include detailed information on the necessity of chest radiograph, choosing tuberculin skin test or interferon gamma release assays such as quantiferon and T-spot test. In addition, controversies on the requirement of screening for latent tuberculosis and prophylactic tuberculosis treatment before the initiation of novel biological agents such as IL-17 and IL-23 inhibitors should be clarified. Furthermore, the duration of latent tuberculosis treatment and the interval between tuberculosis prophylaxis and the initiation of biological agents should be achieved.

Key Words: Biological agents, Latent tuberculosis, Psoriasis, Screening.

Introduction

Psoriasis is a chronic inflammatory immune-mediated cutaneous disorder which affects 2-3% of the population all over the world. Tumor necrosis factor alpha (TNF-α) antagonists, interleukin (IL)-17A inhibitors, IL-12/23 antagonist and IL-23p19 inhibitors are biological agents which are used in the treatment of psoriasis. The treatment of psoriasis aims to suppress inflammation. Biological agents inhibit inflammation by their effect on certain immune pathways which play an important role in the etiopathogenesis of psoriasis.

However, safety concerns have been reported due to both increasing, widespread, long-term use of biological agents and their immunosuppressive effects. For instance, TNF-α inhibitors have been associated with increased risk for infections such as tuberculosis and reactivation of hepatitis B and hepatotoxicity. IL-17 inhibitors have been associated with candidiasis, neutropenia, and inflammatory bowel disease. IL-12/23 antagonist has been associated with cardiovascular side effects and reactivation of latent tuberculosis. However, data on adverse effects of novel biological agents such as IL-17 and IL-23 inhibitors are inadequate.

One of the most important opportunistic infections which may develop in patients under biological agent treatment is latent tuberculosis reactivation. Since TNF-α is a crucial cytokine both in macrophage functions and in granulomatous reaction of tuberculosis, anti-TNF-α treatment may lead to the reactivation of latent tuberculosis. Tuberculosis is included in the most prominent causes of infection related death worldwide. It has been suggested that 25% of the world population might have been affected by latent tuberculosis.
losis. Furthermore, immigrants and refugees may increase the risk of tuberculosis globally and particularly in developed countries. 

Early diagnosis and appropriate treatment of latent tuberculosis infection in patients receiving biological agents decrease the disease incidence. Therefore, all patients with psoriasis should be evaluated carefully for latent tuberculosis infection before the initiation of treatment with biological agents. Nevertheless, signs and symptoms of active tuberculosis infection should be kept in mind in the follow-up of psoriasis patients under any biological agent treatment.

The risk for reactivation of latent tuberculosis infection by IL-12/23 and IL-17 inhibitors has been proposed to be lower compared to TNF-α inhibitors. However, the effect of biological agents except for TNF-α inhibitors on reactivation of latent tuberculosis remains controversial. Data on tuberculosis screening in patients who received anti-IL-17, anti-IL-23 and anti-IL-12/23 are inadequate. Furthermore, it has been suggested that requirement of screening for latent tuberculosis or initiation of prophylactic tuberculosis treatment may be controversial before the treatment with IL-17 and IL-23 inhibitors. On the other hand, poor adherence to latent tuberculosis screening programmes and prophylactic treatment has also been reported in psoriasis patients receiving biological agents.

Within this study, we presented quantiferon test results of psoriasis patients who were screened for tuberculosis before the initiation of treatment with biological agents.

**Patients and Methods**

Between April 2019 and June 2021, medical records of the patients with psoriasis who were evaluated for latent tuberculosis infection before the initiation of biological agent treatment were reviewed retrospectively. Gazi University Ethics Committee approval was obtained for this study (approval number: 2021-670). Quantiferon test, chest radiograph, respiratory symptoms such as cough, sputum, dyspnea, chest pain, B symptoms such as fever, night sweats and weight loss, respiratory rate, oxygen saturation, previous history of tuberculosis infection, exposure to individuals with tuberculosis infection and previous prophylactic tuberculosis treatment were evaluated.

**Statistical Analysis**

Statistical analysis was performed using SPSS 22.0 statistical package programme (IBM Corp., Armonk, NY, USA). Continuous variables were defined as the mean±standard deviation and categorical variables were defined as percentages. The differences between two groups were evaluated by Mann-Whitney U test. The *p*-value <0.05 was considered significant.

**Results**

The study included 132 patients, 50 (37.9%) female and 82 (62.1%) male. The mean age of the patients was 44.24±11.92 years (range: 18-65 years). 119 (90.2%) patients had psoriasis vulgaris, 7 (5.3%) patients had generalized pustular psoriasis, 4 (3.3%) patients had palmoplantar psoriasis and 2 (1.5%) patients had palmoplantar pustular psoriasis (Table I). The mean disease duration was 16.42±10.99 years (range: 1-49 years). 54 (40.9%) patients were treated with ustekinumab, 30 (22.7%) with adalimumab, 27 (20.5%) with ixekizumab, 9 (6.8%) with infliximab, 9 (6.8%) with secukinumab, 2 (1.5%) with etanercept and 1 (0.8%) patient received certolizumab pegol. 86 (65.2%) patients were biologic naive whereas, 46 (34.8%) patients were treated with biological agents previously. 127 (96.2%) patients had unremarkable past medical history for pulmonary diseases. However, 3 (2.3%) patients had chronic obstructive pulmonary disease and 2 (1.5%) patients had asthma. 7 (5.3%) patients had been diagnosed with Coronavirus disease 2019 (COVID-19) previously. None of the patients had a previous history of tuberculosis. Only 2 (1.5%) patients stated that they had been exposed to individuals with tuberculosis infection.

Quantiferon test was negative in 109 (82.6%) patients and positive in 23 (17.4%) patients (Table II). Quantiferon test was negative in both patients who have been exposed to individuals with tuberculosis infection. The mean age of the patients with positive and negative quantiferon test were 50.21±10.79 and 42.98±11.81 years, respectively (*p*=0.006). No significant difference was observed between quantiferon test results and disease duration (*p*=0.243). Among the evaluation of respiratory symptoms, cough was observed in 1 (12.5%) patient with positive and 7 (87.5%) patients with negative quantiferon test results (*p*=0.706). Expectoration was observed in 3 (42.9%) patients with positive and in 4 (57.1%)
patients with negative quantiferon test results ($p=0.069$). Chest pain was observed only in one patient who had a negative quantiferon test result. All eight patients with dyspnea had negative quantiferon test results. B symptoms such as fever, night sweats and weight loss were not observed in any patients with negative quantiferon test results. However, one patient with a positive quantiferon test result had a complaint of night sweats. Respiratory rate and oxygen saturation were within normal limits in all patients.

81 (61.4%) patients with negative quantiferon test results and 15 (11.4%) patients with positive quantiferon test results had normal chest radiograph. Hilar fullness was detected in 14 (10.6%) patients with negative quantiferon test results and in 4 (3%) patients with positive quantiferon test results. Pulmonary nodule was detected in 8 (6.1%) patients with negative quantiferon test results and in 1 (0.8%) patient with positive quantiferon test result. Chest radiograph showed increased reticular density in 3 (2.3%) patients with positive and in 1 (0.8%) patient with negative quantiferon test result. 2 (1.5%) patients with homogeneous density on chest radiograph, 1 (0.8%) patient with paratracheal heterogeneity, 1 (0.8%) patient with increased cardiothoracic ratio and 1 (0.8%) patient with left costophrenic

Table I. Characteristics of patients with psoriasis.

<table>
<thead>
<tr>
<th>Patients (n = 132)</th>
<th>Female 50 (37.9%)</th>
<th>Male 82 (62.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>44.24 ± 11.92</td>
<td>16.42 ± 10.99</td>
</tr>
<tr>
<td>Psoriasis type (n/%)</td>
<td>Psoriasis vulgaris 119 (90.2%)</td>
<td>Generalized pustular 7 (5.3%)</td>
</tr>
<tr>
<td>Treatment (n/%)</td>
<td>Anti-TNF-α 42 (31.8%)</td>
<td>Anti-IL-12/23 54 (40.9%)</td>
</tr>
<tr>
<td>Medical history (n/%)</td>
<td>Chronic obstructive pulmonary disease 3 (2.3%)</td>
<td>Asthma 2 (1.5%)</td>
</tr>
<tr>
<td>Previous treatment (n/%)</td>
<td>Biologic naive 86 (65.2%)</td>
<td>Previous biologic 46 (34.8%)</td>
</tr>
<tr>
<td>Quantiferon (n/%)</td>
<td>Negative 109 (82.6%)</td>
<td>Positive 23 (17.4%)</td>
</tr>
<tr>
<td>Previous history of tuberculosis (n)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exposure to patients with tuberculosis (n/%)</td>
<td>2 (1.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

17.4% patients had positive quantiferon test results, however, none of the patients were diagnosed with active tuberculosis.

Table II. Patients with positive and negative quantiferon test results.

<table>
<thead>
<tr>
<th>Positive quantiferon 23 (17.4%)</th>
<th>Negative quantiferon 109 (82.6%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>50.21 ± 10.79</td>
<td>42.98 ± 11.81</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>14.69 ± 12.10</td>
<td>16.78 ± 10.77</td>
</tr>
<tr>
<td>Cough (n/%)</td>
<td>1 (12.5%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Expectoration (n/%)</td>
<td>3 (42.9%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Chest pain (n/%)</td>
<td>-</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Dyspnea (n/%)</td>
<td>-</td>
<td>8 (6.1%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>Night sweats 1 (0.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Exposure to patients with tuberculosis (n/%)</td>
<td>-</td>
<td>2 (1.5%)</td>
</tr>
</tbody>
</table>

Patients with positive quantiferon test results were older than those who had negative quantiferon test results ($p = 0.006$).
angle blunting had negative quantiferon test results.

Among the patients with positive quantiferon test results, 14 (60.9%) of them had not received prophylactic tuberculosis treatment previously. Therefore, these patients were recommended to use 300 mg/day isoniazid for 9 months. None of the patients had an active tuberculosis infection.

**Discussion**

Latent tuberculosis is a common, asymptomatic tuberculosis infection that occurs following exposure to tuberculosis bacilli. Therefore, diagnosis of latent tuberculosis is not always easy to make and immunosuppressive drugs such as biological agents may lead to active tuberculosis infection\(^5\). It has been suggested that the risk for the progress of latent tuberculosis to active disease that is transmissible and symptomatic was 10%\(^{19}\). Since patients with latent tuberculosis infection are substantial reservoir for active tuberculosis, early diagnosis, and appropriate treatment of latent tuberculosis infection in high-risk populations such as immunocompromised individuals or individuals contacted with active tuberculosis patients are mandatory to control this public health problem worldwide\(^{20,21}\).

Tuberculin skin test and interferon gamma release assays such as quantiferon and T-spot tests can be used to detect latent tuberculosis. Higher sensitivity and specificity for the diagnosis of latent tuberculosis have been reported in interferon gamma release assays compared to tuberculin skin test\(^{19,21,22}\). False positive tuberculin skin test results can be obtained in Bacillus Calmette-Guerin (BCG) vaccinated individuals\(^{23}\). Therefore, interferon gamma release assays are convenient particularly in BCG vaccinated individuals\(^{22,24}\).

Joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines of care for the management and treatment of psoriasis with biologics recommends performing purified protein derivative (PPD), T-spot or quantiferon test before treatment with TNF-α inhibitors and IL-12/23 antagonist in order to exclude latent tuberculosis. PPD or quantiferon test have also been recommended before treatment of psoriasis with IL-17 inhibitors. Furthermore, chest radiograph is recommended in patients with positive tuberculosis test results\(^1\). EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris published by European Dermatology Forum recommends performing interferon gamma release assays before the treatment of psoriasis with TNF-α inhibitors, IL-12/23 antagonist, IL-17 inhibitors and IL-23p19 inhibitors\(^{25}\). British Association of Dermatologists recommends interferon gamma release assay or interferon gamma release assay accompanied by tuberculin skin test for latent tuberculosis screening before biological agent treatment. Chest radiograph might be performed if local policies required\(^3\). Swiss S1 guidelines on the systemic treatment of psoriasis vulgaris stated that before etanercept, infliximab, adalimumab, ustekinumab, secukinumab, patients should be screened for tuberculosis including chest radiograph\(^{26}\). Japanese guidance for biologic use in psoriasis recommends performing tuberculin skin test, quantiferon or T-spot test and chest radiograph to exclude latent tuberculosis in psoriasis patients before biological agent treatment\(^{27}\).

Studies conducted in different countries and even different studies conducted in the same country reported different rate of positive quantiferon test results in patients with psoriasis before biological agent treatment. Positive quantiferon test results have been reported in 8.2% of patients with psoriasis vulgaris who were candidates for biological agent treatment in Italy\(^9\). However, Bua et al\(^{28}\) reported that 39% of Italian patients with psoriasis had positive quantiferon test results before biological agent treatment. It has been reported that 13.4% of psoriasis patients who were evaluated for latent tuberculosis before treatment with ustekinumab had positive quantiferon test results in Taiwan\(^{22}\). Positive quantiferon test results have also been reported in 18% of psoriasis patients treated with IL-17 inhibitors in Taiwan\(^{29}\). In China, Shu et al\(^{30}\) reported positive quantiferon test results in 45.2% of psoriasis patients before receiving secukinumab. In a study from Portugal, Ramos et al\(^{31}\) reported positive tuberculosis screening results with tuberculin skin test and quantiferon in 45.2% of the patients with diseases such as psoriasis, Crohn’s disease, multiple sclerosis, ankylosing spondylitis before treatment with biologic agents. Georgieva et al\(^{32}\) detected latent tuberculosis in 10.1% patients with Crohn’s disease before anti-TNF-α treatment in Bulgaria. Medina-Gil et al\(^{33}\) evaluated latent tuberculosis prevalence in patients with psoriasis before biological agent treatment in Miami, Florida.
and they reported positive tuberculin skin test in 4.5% of the patients. Neema et al. detected latent tuberculosis infection in 29.5% of the patients and active tuberculosis in 1.9% of the patients with psoriasis prior to systemic treatment by tuberculin skin test and chest radiograph in India. In Spain, prevalence of latent tuberculosis has been found 20.5% in psoriasis patients by tuberculin skin test and chest radiograph performed for biological agent treatment.

In many countries such as Sweden, Spain, Denmark, Germany, Austria, France, United Kingdom and in the United States, BCG vaccine is not routinely administered. Furthermore, immigrants from countries with high tuberculosis rate lead to increased incidence of tuberculosis infection in European countries. Since 80% of the cases with active tuberculosis occur as a result of progression of latent tuberculosis, treatment should focus on untreated individuals with latent tuberculosis.

Moreover, there are discrepancies between psoriasis treatment guidelines about the duration of latent tuberculosis treatment and time to start biological agent following tuberculosis treatment. British Association of Dermatologists recommends combination of isoniazid and rifampicin for 3 months or isoniazid alone for 6 months in the treatment of latent tuberculosis. These drugs should be initiated 2 months before the administration of biological agents. Swiss S1 guidelines on the systemic treatment of psoriasis vulgaris recommends using isoniazid for 9 months for the treatment of latent tuberculosis and to start biological agents 1 month after the initiation of isoniazid. According to Japanese guidance for biologic use in psoriasis, latent tuberculosis should be treated with isoniazid for 6 months and biological agents should be received 3 weeks after the initiation of isoniazid treatment. However, no information about treatment of latent tuberculosis has been included in Joint AAD-NPF guidelines of care for the management and treatment of psoriasis and EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris.

**Conclusions**

Within this study, 17.4% patients with psoriasis had positive quantiferon test result performed for screening biological agent treatment. We suggest that quantiferon test should be performed in all patients with psoriasis especially in elderly for latent tuberculosis screening before the initiation of biological agent treatment. Immigrants from countries with high tuberculosis rate may lead to increased incidence of tuberculosis infection especially in countries where BCG vaccine is not administered routinely such as in Europe and in the United States. Psoriasis treatment guidelines with biological agents should include detailed information on the requirement of chest radiograph, choosing tuberculin skin test or interferon gamma release assays such as quantiferon and T-spot test and latent tuberculosis screening intervals during the treatment with biologic agents. Controversies on the requirement of screening for latent tuberculosis and prophylactic tuberculosis treatment before novel biological agents such as IL-17 and IL-23 inhibitors should also be clarified. Consensus on duration of latent tuberculosis treatment and the most convenient interval between tuberculosis prophylaxis and initiation of the biological agents should be reached.

**Conflict of Interest**
The Authors declare that they have no conflict of interests.

**Funding**
None.

**Ethics Approval**
The research meets the ethical guidelines and Gazi University Ethics Committee. The approval was obtained prior to this study (approval number: 2021-670).

**Informed Consent**
Informed consent was obtained from all participants included in the study.

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