The Effects of COVID-19 on Psoriasis Patients Using Biologic Treatment: Two-Center Retrospective Study

Biyojolik Tedavi Kullanılan Psöriyazis Hastalarına COVID-19’un Etkileri: İki Merkezli Retrospektif Çalışma

ABSTRACT Objective: The aim of our study is to evaluate the status of continuation of treatment of our patients who received biologic treatment during the pandemic and how they were affected by coronavirus disease-2019 (COVID-19). Material and Methods: The clinical processes of patients with moderate-severe plaque psoriasis who were treated with biologics between March 2020 and February 2021 were evaluated. Results: Thirty-three (21.2%) of our 156 psoriasis patients who received biologic therapy stopped treatment at the beginning of the pandemic. Fourteen of the 123 patients who were continuing the treatment were positive for COVID-19. There was no statistical difference between those who continued with biologic treatment and those who did not in the rates of positivity for COVID-19. Conclusion: We have observed that the treatment with biologic agents in psoriasis patients does not increase the COVID-19 transmission risk, does not cause severe disease, and does not increase the hospitalization rate and mortality rate.

Keywords: COVID-19; biological therapy; psoriasis; Psoriasis Area Severity Index


Keywords: COVID-19; biyojolik tedavi; psöriyazis; Psöriyazis Alan Severity Index

The effects of COVID-19 on psoriasis patients using biologic treatment were evaluated in a two-center retrospective study. The aim of our study was to evaluate the status of continuation of treatment of our patients who received biologic treatment during the pandemic and how they were affected by coronavirus disease-2019 (COVID-19). Clinical processes of patients with moderate-severe plaque psoriasis who were treated with biologics between March 2020 and February 2021 were evaluated. Results: Thirty-three (21.2%) of our 156 psoriasis patients who received biologic therapy stopped treatment at the beginning of the pandemic. Fourteen of the 123 patients who were continuing the treatment were positive for COVID-19. There was no statistical difference between those who continued with biologic treatment and those who did not in the rates of positivity for COVID-19. Conclusion: We have observed that the treatment with biologic agents in psoriasis patients does not increase the COVID-19 transmission risk, does not cause severe disease, and does not increase the hospitalization rate and mortality rate.

Keywords: COVID-19; biological therapy; psoriasis; Psoriasis Area Severity Index

The coronavirus disease-2019 (COVID-19) pandemic was declared by the World Health Organization in March 2020, and COVID-19 was the leading cause of death in many countries in 2020.¹ Most COVID-19 patients requiring hospitalization have comorbidities such as hypertension, chronic cardiopulmonary disease, or immunosuppression.² Today, biologic agents are frequently used in many inflammatory skin diseases, especially psoriasis. Bio-logic agents are drugs that affect certain steps of the
immune system. During the pandemic, the use of biologic agents for both dermatologists and patients has led to concerns that it may cause a higher risk of severe COVID-19. On the other hand, COVID-19 causes cytokine storm by triggering the excessive release of many cytokines, especially tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and IL-17, and biologic agents are being tried for the treatment of this cytokine storm.

The purpose of our study is to evaluate the continuation status of treatment of our patients who received biologic treatment during the pandemic and how those who continue and discontinue the treatment are affected by COVID-19.

**MATERIAL AND METHODS**

We certify that we have taken all necessary permissions from our institution and/or department for conducting and publishing the present work. Approval has been obtained from Kahramanmarş Sütçü İmam University Non-invasive Clinical Research Ethics Committee with the decision being dated 22 March 2021 and having no 03 which stated that no obstacles were avoiding the study to be conducted for ethical and scientific aspects. Our study was carried out by the principles of the Declaration of Helsinki. The permit application form for the study, numbered 2021-02-03T09_03_31, was approved by the Ministry of Health of the Republic of Turkey.

Our study is retrospective, descriptive and cross-sectional. In our study, the clinical processes of the patients who were followed up in dermatology clinics of 2 university hospitals between March 2020 and February 2021 and had moderate-severe plaque psoriasis at the first admission and received biologic treatment were evaluated. The data forms were filled in by file scanning or teleconference interview. The data forms were also filled in during the control examinations of patients at the clinic. In the data form, these are questioned: patients’ age, gender, body mass index (BMI), treatment received, date of the beginning of the treatment, the continuation status of treatment, disease severity, smoking, additional disease, additional treatments, pneumococcal and influenza vaccines, history of contact with someone with COVID-19, history of being tested positive for COVID-19, symptoms of COVID-19 if test is positive, treatment method for COVID-19 (without treatment, medication at home, hospitalization, intensive care), and whether there was any sequelae. The data obtained were transferred to the computer.

**STATISTICAL ANALYSIS**

SPSS version 20.0 statistical package (SPSS Inc., Chicago, IL, USA) program was used in the analysis of the data. In the display of the descriptive statistics of the study; mean±standard deviation, minimum-maximum scores were used for continuous numerical variables, and number (n) and percentage (%) were used for categorical variables. Pearson chi-square and Fisher tests were used for comparison of categorical variables. According to the normality assessment performed with Kolmogorov-Smirnov and Shapiro-Wilk tests, continuous variables were compared with parametric tests (paired sample t-test and t-test in independent groups) where it conformed to normal distribution, and with nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test) where it did not conform to normal distribution. Statistical significance level was accepted as p<0.05.

**RESULTS**

One hundred fifty six psoriasis patients followed and biologic treated in 2 university hospitals in the Eastern Mediterranean region of Türkiye were included in the study. The clinical processes between March 2020 and February 2021 were evaluated. One hundred and three (66%) of our patients continued biologic treatment without interruption from the beginning of the pandemic; 16 (10.3%) of them discontinued the treatment at the beginning of the pandemic and resumed when their concerns subsided; 3 (1.9%) patients discontinued when the polymerase chain reaction (PCR) tests were positive for COVID-19, treatment was started again when they were negative; 1 (0.6%) patient discontinued when COVID-19 was suspected and resumed treatment when was negative test for COVID-19; 33 (21.2%) left the treatment at the beginning of the pandemic and still do not use it.

Those who never interrupted biologic treatment and those who took a short break but were in treat-
ment when were positive for COVID-19 constituted the group that continued the treatment (n=123). Those who stopped the biologic agent and did not receive any treatment during the pandemic constituted the group who did not continue the treatment (n=33). Forty-eight (39%) of the total 123 patients who received biologic treatment during the pandemic were female and 75 (61%) were male. The mean age was 43.37±14.7.

Fourteen of 123 patients on biologic treatment were diagnosed with COVID-19. COVID-19 diagnosis was confirmed by PCR in nasal swab samples. Of 14 patients, 5 (10.4%) were female and 9 (12%) were male. The mean age of those who were diagnosed with COVID-19 was 40.43±11.64. There was no statistical difference between COVID-19 (+) group and COVID-19 (-) group in terms of age and gender (p=0.420 and p=0.787, respectively). There was no statistical difference between the COVID-19 (+) group and the COVID-19 (-) group in terms of mean BMI, smoking, comorbidity, pneumococcal and influenza vaccination rates (Table 1).

One of the 33 psoriasis patients who stopped biologic treatment at the beginning of the pandemic and did not start again was diagnosed with COVID-19 by PCR test. There was no statistical difference in the rates of COVID-19 positivity between those who continue with biologic treatment and those who do not [11.4% (n=14), 3% (n=1), respectively] (p=0.196).

When we analyzed the rates of COVID-19 positivity after contact with a COVID-19 positive person; 13 of the 27 contact patients using biologic treatment and one of the 4 contact patients who discontinued biologic treatment were positive for COVID-19. There was no statistical difference in the rate of being positive for COVID-19 between those who continued biologic treatment and those who did not, after contact with a COVID-19 positive person (48.1%, 25%, respectively) (p=0.607).

Six (12.8%) of those using secukinumab, 3 (7.9%) of those using ustekinumab, 3 (20%) of those using adalimumab, 1 (7.7%) of those using ixekizumab, and 1 of those using infliximab (50%) were diagnosed with COVID-19 (Table 2). There was no statistical difference in the rate of COVID-19 positivity between patients using TNF-α antagonists (infliximab, adalimumab, etanercept, and certolizumab) and anti-IL agents (secukinumab, ixekizumab, and ustekinumab) (p=0.480). Those who continued biologic treatment and were positive for COVID-19

<table>
<thead>
<tr>
<th>Feature</th>
<th>n=123</th>
<th>COVID-19 (-) n=109</th>
<th>Mean±SD/n (%)</th>
<th>COVID-19 (+) n=14</th>
<th>Mean±SD/n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.37±14.70</td>
<td>43.74±15.06</td>
<td>40.43±11.64</td>
<td>0.420*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Female</td>
<td>48 (39.0)</td>
<td>55 (89.6)</td>
<td>5 (10.4)</td>
<td>0.787**</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
<td>75 (61.0)</td>
<td>92 (88.8)</td>
<td>9 (12.0)</td>
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</tr>
<tr>
<td>BMI (kg/cm2)</td>
<td>25.97±4.90</td>
<td>26.02±4.93</td>
<td>25.57±4.81</td>
<td>0.846***</td>
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<tr>
<td>BMI &lt;25</td>
<td>57 (46.3)</td>
<td>51 (89.5)</td>
<td>6 (10.5)</td>
<td>0.781**</td>
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<tr>
<td>BMI ≥25</td>
<td>66 (53.7)</td>
<td>58 (87.9)</td>
<td>8 (12.1)</td>
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<tr>
<td>Smoking</td>
<td></td>
<td>Yes</td>
<td>46 (37.4)</td>
<td>40 (87.0)</td>
<td>8 (13.0)</td>
<td>0.854**</td>
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<tr>
<td></td>
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<td>No</td>
<td>77 (62.6)</td>
<td>69 (89.6)</td>
<td>8 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Additional disease</td>
<td></td>
<td>Yes</td>
<td>33 (26.8)</td>
<td>28 (84.8)</td>
<td>5 (15.2)</td>
<td>0.522**</td>
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<tr>
<td></td>
<td></td>
<td>No</td>
<td>90 (73.2)</td>
<td>81 (90.0)</td>
<td>9 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination status</td>
<td></td>
<td>Yes</td>
<td>66 (53.7)</td>
<td>56 (84.8)</td>
<td>10 (15.2)</td>
<td>0.157**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>57 (46.3)</td>
<td>53 (93.0)</td>
<td>4 (7.0)</td>
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</tr>
<tr>
<td>Influenza vaccination status</td>
<td></td>
<td>Yes</td>
<td>59 (48.0)</td>
<td>50 (84.7)</td>
<td>9 (15.3)</td>
<td>0.194**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>64 (52.0)</td>
<td>59 (92.2)</td>
<td>5 (7.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Student’s t test; **Chi-square or Fisher test; ***Mann-Whitney U test; SD: Standard deviation; BMI: Body mass index.
were being treated for Type 2 diabetes mellitus (DM), one for chronic hepatitis, one for hypertension, and one for chronic kidney failure.

Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) associated with severe COVID-19 was seen in one of our patients who continued biologic treatment and who was using secukinumab and followed up with a diagnosis of Type 2 DM. Gastrointestinal symptoms were seen in another patient who did not have any additional disease and who used secukinumab. Both patients were male. The first patient was hospitalized without the need for intensive care, and the second patient recovered with medical treatment at home without any sequelae. There was no statistical difference between those who continued biologic treatment and those who did not in terms of the frequency of severe symptoms (p=1.00).

All of the COVID-19 (+) patients who continued biologic treatment recovered without sequelae, 13 had been treated with medical treatment at home, and one required inpatient treatment. A 41-year-old patient who required inpatient treatment was using secukinumab for the treatment of psoriasis, in addition, he was using insulin and oral antidiabetic drugs due to Type 2 DM and was smoking. Symptoms of COVID-19 started after 20 days than the last dose of secukinumab. When COVID-19 improved and treatment was completed, he has continued treatment of secukinumab, and his PASI score didn’t increase during this period. There was no need for hospitalization in the intensive care unit and no deaths related to COVID-19.

In terms of the difference between the mean of PASI score at the beginning of the pandemic and the mean of PASI score at the 12th month of all patients; there was no statistical difference between those who had COVID-19 and those who did not (p=0.782). In terms of the difference between the mean of PASI score at the beginning of the pandemic and the mean of PASI score at the 12th month of patients continuing on biologic therapy; there was no statistical difference between those who had COVID-19 and those who did not (p=0.980) (Table 3).

**DISCUSSION**

There have been many restrictions during the COVID-19 outbreak. As in many parts of the world, outpatient services were either suspended or continued with serious restrictions in our country.

We observed that there were problems in the treatment of our psoriasis patients who received biologic treatment, as well as the treatment of many other chronic patients, because of restrictions and the concern that the use of biologic agents would increase the risk of infection. In a study conducted in China, 9% of 926 psoriasis patients were receiving biologic treatment, 37.3% of psoriasis patients who used biologic agent during the pandemic did not continue the treatment. In the study in which all psoriasis patients followed up in 2 university hospitals in the Czech Republic were evaluated during the national quarantine (March 16-April 24) due to COVID-19, none of the 117 psoriasis patients using biologic agent did not discontinue the treatment despite safety concerns related to the treatment during the pandemic. In a study on 1,390 patients, 7 (0.5%) patients had temporarily discontinued treatment due to concerns about COVID-19. In a multi-center study conducted in our country, 26.1% of psoriasis patients who did not contact their physician and 20.4% of those who contacted their physician stopped using the treatment (biologic agents and/or other agents) for psoriasis. In another multicenter study conducted in our country, it was noted that 36.1% (73 patients) of 199 patients who received biologic treatment did not comply with the treatment. According to the results of these studies, the rate of non-adherence to treatment varies between 0% and 37.3%. In our study, the rate of discontin-
using biologic treatment during the pandemic was 21% due to the fact that the lesions almost completely regressed at the beginning of the pandemic, the concern that the use of biologic agents would increase the risk of infection, and the access to health services was limited.

TNF and IL-17 are elevated in patients with psoriasis, which may induce inflammation in patients with psoriasis and predispose them to infections. Therefore, those with psoriasis are at a higher risk of developing pneumonia, which is associated with a higher mortality rate from COVID-19 infection. At the same time, biologic agents used in the treatment of severe psoriasis can cause a decreased immune response and increased susceptibility to life-threatening infections and severe manifestations of coronavirus infection. On the other hand, biologic agents used in the treatment of psoriasis suppress the excessive release of cytokines that cause severe disease in COVID-19.5,12,13

The real question here was whether to continue or discontinue biologic treatment. Therefore, it should be evaluated how patients who continue and stop biologic treatment are affected by COVID-19. Although there are many studies about the course of COVID-19 and using biologic agents in psoriasis patients, in studies evaluating the course of COVID-19 in patients using biologic agents, there was no control group, or incompatible in terms of disease severity, or large differences in sample size between patients and the general population. However, we think that our results are more meaningful because, as far as we know, our study is the first study comparing the course of COVID-19 in patients with moderate-severe psoriasis who continue and discontinue biologic therapy. However, the limitation of our study was that our sample size was small.

Brazzelli et al. detected at least one symptom suggestive of COVID-19 infection in 16 of 100 psoriasis patients receiving biologic treatment and 17 of 80 psoriasis patients receiving topical therapy, which they evaluated for 5 months at the beginning of the pandemic, they did not notice a difference between the 2 groups with psoriasis in terms of the risk of getting COVID-19 and the risk of more severe disease. However, COVID-19 was not confirmed by PCR testing and in these 2 groups the severity of psoriasis was not specified.14 According to the results of our study, there was no difference in the rate of getting COVID-19 after contact with someone diagnosed with COVID-19 between moderate-severe plaque psoriasis patients who continued and did not continue biologic treatment.

In the 4-month follow-up of 965 psoriasis patients using biologic agent without a control group, 2 patients were diagnosed with

<table>
<thead>
<tr>
<th>TABLE 3: Mean of PASI scores at the beginning of the pandemic and mean of PASI scores at the 12th month of the pandemic.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patients who continuing biologic treatment (n=123)</td>
</tr>
<tr>
<td>The patients who discontinued treatment (n=33)</td>
</tr>
<tr>
<td>All patients (n=156)</td>
</tr>
<tr>
<td>COVID (+)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>The mean of PASI score at the beginning of the pandemic</td>
</tr>
<tr>
<td>The mean of PASI score at the 12th month of the pandemic</td>
</tr>
<tr>
<td>The mean of change in PASI at 12th month of the pandemic</td>
</tr>
</tbody>
</table>

*Unpaired t-test: PASI: Psoriasis Area Severity Index; SD: Standard deviation.
COVID-19 and recovered the infection at home without the need for hospitalization, they suspended the biologic treatment while they had COVID-19 and continued thereafter. In the first months of the pandemic, during the 1-month follow-up of 168 psoriasis patients who used biologic treatment without a control group, mild symptoms thought to be due to COVID-19 were observed in 3 patients, but this was not confirmed by PCR testing. Mahil et al. evaluated 374 patients with COVID-19 and psoriasis from 25 countries, 267 of the patients were receiving biologic treatment, 44 of the patients with COVID-19 who received biologic treatment required hospitalization and 4 of the patients resulted in death. In the 12-month follow-up of 156 patients, we identified 14 patients who were positive for COVID-19 while using biologic agent, 3 of whom interrupted biologic treatment during the disease. Only one patient who continued biologic treatment required hospitalization due to COVID-19. Our patients who were hospitalized had risk factors for the poor prognosis of COVID-19 (male gender, smoking, and Type 2 DM).

Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) have been associated with severe COVID-19. According to the results of our study, the use of biologic treatment in psoriasis patients does not increase the frequency of severe symptoms.

According to the meta-analysis results of Emrahimi et al., which included a total of 10,509 cases, similar to the results of our study, the rate of hospitalization of psoriasis patients using biologic agents with COVID-19 was 0.1%, and deaths due to COVID-19 were not reported. At the same time, these meta-analysis results showed that similar to our study, psoriasis patients using biologic agents are not more susceptible to getting COVID-19 and the severe clinical course of the disease.

In the study of Kara Polat et al., in which there was no control group, exacerbation of skin lesions was observed in 55% of psoriasis patients with COVID-19. However, our study shows that there is no statistical difference between those who were diagnosed with COVID-19 and those who were not in terms of the difference between the mean of PASI scores at the beginning of the pandemic and the mean of PASI scores at the 12th month (p=0.782). In Mroz et al.’s study, 6 of 8 psoriasis patients using biologic agents during COVID-19 had exacerbation of skin lesions, but there was no difference between psoriasis patients using other systemic agents and disease flare. In terms of the difference between the mean of PASI scores at the beginning of the pandemic and the mean of PASI scores at the 12th month of patients continuing on biologic treatment; there was no statistical difference between those who were diagnosed with COVID-19 and those who were not (p=0.980). The limitation of our study in evaluating the effect of COVID-19 on the severity of psoriasis was that PASI scores could not be evaluated immediately after COVID-19. We evaluated PASI scores at the beginning and the 12th month of the pandemic.

CONCLUSION

Our study has shown that the use of biologic agents in psoriasis patients does not increase the susceptibility to getting COVID-19, does not cause severe disease progression, and does not increase hospitalization rate and mortality rate. According to our results, together with the literature, we think that discontinuing biologic treatment is not the right decision as it will lead to a higher disease burden and costs and lead to higher pro-inflammatory states that may worsen the cytokine storm associated with COVID-19.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mine Müjde Kuş, Perihan Öztürk; Design: Mine Müjde Kuş, Perihan Öztürk; Control/Supervision: Mine Müjde Kuş,
Perihan Öztürk, Asena Çiğdem Doğramacı; Data Collection and/or Processing: Asena Çiğdem Doğramacı, Mehmet Enes Güner, Yemliha Bozkurt, Hülya Nazik, Mehmet Kamil Mülayim; Analysis and/or Interpretation: Mine Müjdde Kuş, Mehmet Kamil Mülayim; Literature Review: Mine Müjdde Kuş, Asena Çiğdem Doğramacı, Mehmet Enes Güner, Yemliha Bozkurt, Hülya Nazik, Mehmet Kamil Mülayim; Writing the Article: Mine Müjdde Kuş; Critical Review: Perihan Öztürk, Asena Çiğdem Doğramacı; References and Fundings: Perihan Öztürk, Asena Çiğdem Doğramacı, Hülya Nazik, Mehmet Kamil Mülayim; Materials: Mine Müjdde Kuş, Perihan Öztürk, Asena Çiğdem Doğramacı, Hülya Nazik, Mehmet Kamil Mülayim.

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