Original Article

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# Effect of Biological Therapy on Systemic Inflammatory Markers Among Patients with Chronic Plaque Psoriasis

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**Abstract**

**Aim:** Psoriasis is a chronic systemic inflammatory disease. A generally accepted laboratory marker for monitoring the treatment response of psoriasis is not yet available. The aim of this study was to evaluate the effects of biologic therapy on the novel inflammatory biomarkers neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT) in psoriasis.

**Methods:** Fifty-five patients with psoriasis who received biologic therapy including tumor necrosis factor-alpha, interleukin (IL)-17, IL-12/23, and IL-23 inhibitors for at least three months were retrospectively evaluated. Psoriasis area severity index scores, hemogram data, and C-reactive protein (CRP) levels were analyzed before and after three months of therapy.

**Results:** The CRP, neutrophil count, platelet count, NLR, PLR, and PCT values revealed a significant decrease after three months of therapy, irrespective of the type of biologics used (p=0.008, 0.012, 0.017, 0.001, 0.011, and 0.009, respectively). After treatment, NLR and PLR decreased promptly in parallel with a decrease in CRP, in which NLR has a low-moderate (p=0.025, r=0.303), and PLR has a moderate correlation (p=0.000, r=0.525).

**Conclusion:** Neutrophil-lymphocyte ratio, PCT and particularly PLR parameters derived from hemogram data can be used to assess the effect of biological therapy on systemic inflammation among psoriasis patients.

**Keywords:** Psoriasis, biologic therapy, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

## Introduction

Psoriasis is a chronic inflammatory disease with a frequency of 0.1-3% in various populations. The rates of diabetes mellitus (DM), atrial fibrillation, hypertension, atherosclerosis, stroke, myocardial infarction (MI), cardiovascular mortality, and metabolic syndrome are significantly higher among psoriasis patients. Psoriasis is no longer considered a disease limited only to the skin and joints; yet, it has been a systemic inflammatory disease potentially accompanied by various comorbidities (1). Various markers can be used to access systemic inflammation. Recent studies revealed that neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT) values are potential markers of systemic inflammation, and they are associated with prognosis in several cardiovascular diseases, malignancies, and chronic inflammatory diseases, correlating with C-reactive protein (CRP) values (2-6). Numerous studies in the literature have reported that patients with psoriasis have higher NLR, PLR, MPV, PCT, and CRP values than the control groups (7-13).

Therefore, this study aimed to analyze the changes in the levels of NLR, PLR, MPV, PCT, and CRP, the risk markers for systemic inflammation and cardiovascular diseases, before and after treatment among patients with chronic plaque psoriasis receiving biological therapy.

## Methods

### Compliance with Ethical Standards

The study was conducted according to the Declaration of Helsinki. Ethics approval for the study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Training and Research Hospital with decision number 2022/62. Written informed consent was waived because of the retrospective nature of this study.

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### Study Design

In this single-center cross-sectional study 55 patients with chronic plaque psoriasis who had received biological agents for the first time, at least three months of duration between January 2019 and August 2022 were evaluated.

The exclusion criteria were as follows: a history of malignancy; systemic diseases such as DM, cardiac, renal, or hepatic disease; active infection; inflammatory diseases; dermatological disease other than psoriasis; and previously receiving biological therapy.

Age, gender, duration of disease, family history, scalp and nail involvements, having concomitant psoriatic arthritis, receiving a biological agent, pre- and post-treatment psoriasis area severity index (PASI) values, neutrophil, lymphocyte, and platelet counts, and NLR, PLR, MPV, PCT, and CRP values, were recorded from the patient files. Neutrophil-lymphocyte ratio refers to the counts of neutrophils divided by the number of lymphocytes, and PLR denotes the platelet count divided by the lymphocyte count.

The application of the biological agents was as follows: The first two doses of ustekinumab with four weeks interval, then a dose every 12 weeks as 45 mg for patients <100 kg body weight and 90 mg for those ≥100 kg body weight; the initial adalimumab dose was 80 mg, the second dose was 40 mg one week after the first dose, and then a 40 mg dose every two weeks interval; 400 mg of sertolizumab dose every two weeks interval; 300 mg of secukinumab dose once a week for the initial five weeks, and then once in every four weeks interval; 160 mg of initial ixekizumab dose, then 80 mg dose every two weeks until week 12; 100 mg dose guselkumab with four weeks intervals (first two doses), then application of 100 mg dosages every eight weeks; and the first two doses of risankizumab were 150 mg every four weeks interval, then 150 mg doses every 12 weeks.

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows version 21.0 (SPSS, Chicago, IL, USA). Evaluation of the conformity of the variables to the normal distribution was performed using analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Continuous and discrete variables were presented as mean ± standard deviation and median (minimum-maximum), respectively. The Student's t-test was used to compare the two means of dependent groups. The Kruskal-Wallis test was executed to test the difference in discrete numerical variables in more than two groups. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

## Results

Of the 55 patients included in the study, 28 (50.9%) were female, while 27 (49.1%) were male. The mean age was 49.54±1.95 years. The patients were receiving the following therapies: seven patients (12.72%) tumor necrosis factor alpha (TNF-α) inhibitors (six patients adalimumab, one patient certolizumab); nine patients (16.36%) interleukin (IL)-12/23 inhibitor (ustekinumab); 34 patients (61.82%) IL-17 inhibitors (18 patients secukinumab, 16 patients ixekizumab), and five patients (9.1%) IL-23 inhibitors (four patients guselkumab, one patient risankizumab). Table 1 summarizes the demographic features and clinical attributes of the patients.

**Table 1. Demographic features and clinical attributes of patients**

| | |
|---|---|
| Gender (female/male), n, (%) | 28/27 (50.9/49.1) |
| Age (mean ± SD) | 49.54±1.95 |
| The duration of disease (year) (mean ± SD) | 22.1±1.42 |
| Family history (yes/no), n, (%) | 36/19 (65.45/34.54) |
| The nail involvement (yes/no), n, (%) | 33/22 (60/40) |
| Scalp involvement (yes/no), n, (%) | 39/16 (70.9/29.1) |
| Concomitant arthritis (yes/no), n, (%) | 20/35 (36.36/63.63) |
| Received therapy, n (%) | Adalimumab - 6 (10.9)<br>Sertolizumab - 1 (1.81)<br>Ustekinumab - 9 (16.36)<br>Secukinumab - 18 (32.72)<br>Ixekizumab - 16 (29.1)<br>Guselkumab - 4 (7.27)<br>Risankizumab - 1 (1.81) |
| PASI 0 (mean ± SD) | 18.8±11.38 |
| PASI 3rd month (mean ± SD) | 1.69±2.81 |

SD: Standard deviation, PASI: Psoriasis areata severity index

After three months of biological therapy, there was a statistically significant decrease in the neutrophil count, platelet count, NLR, PLR, PCT, and CRP values of the patients (p=0.008, 0.012, 0.017, 0.001, 0.011, 0.009, respectively). However, there was no statistically significant difference between pre- and post-treatment lymphocyte counts and MPV values (p=0.131, 0.097). Table 2 displays the laboratory measures of the patients before and after three months of biological therapy.

The patients were categorized into four groups based on the type of biological therapy they received. These group classifications were as follows: patients receiving IL-12/23 inhibitors in group 1, TNF-α inhibitors in group 2, IL-17 inhibitors in group 3, and IL-23 inhibitors in group 4. There was no statistically significant difference between these four groups considering the changes in neutrophil count, lymphocyte count, platelet count, NLR, PLR, MPV, PCT, and CRP pre- and post-treatment levels. Table 3 displays the pre- and post-treatment laboratory measures of the groups.

The relationship between the changes in NLR, PLR, MPV, PCT, and CRP pre- and post-treatment values and the PASI scores was insignificant. However, there was a statistically significant, albeit low-moderate correlation, between the CRP and NLR pre- and post-treatment value changes (p=0.025, r=0.303), whereas the difference in PLR was statistically significant with a moderate correlation (p=0.000, r=0.525). Table 4 depicts the relationship between pre- and post-treatment changes among NLR, PLR, MPV, PCT, and CRP values.

## Discussion

Psoriasis is a chronic inflammatory disease in which T lymphocytes, neutrophils, macrophages, mast cells,

**Table 2. Laboratory measures of patients before and after three months of biological therapy**

| | Pre-treatment (mean ± SD) | Post-treatment (3rd month) (mean ± SD) | p-value |
|---|---|---|---|
| Neutrophil count (x10$^3$/mL) | 4.47±1.54 | 3.91±1.13 | 0.012 |
| Lymphocyte count (x10$^3$/mL) | 2.11±0.56 | 2.25±0.59 | 0.131 |
| Platelet count (x10$^3$/mL) | 270.27±65.76 | 257.69±57.2 | 0.017 |
| NLR | 2.22±0.89 | 1.8±0.66 | 0.001 |
| PLR | 134.42±40.66 | 120.16±32.92 | 0.011 |
| MPV | 9.51±1.18 | 9.34±1.23 | 0.097 |
| PCT | 0.25±0.05 | 0.24±0.05 | 0.009 |
| CRP (mg/L) | 4.06±4.7 | 2.47±2.04 | 0.008 |

Student's t-test was used for analysis. SD: Standard deviation, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

**Table 3. Pre- and post-treatment laboratory measures of the groups**

| | The therapy group | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | Pre- and post-treatment difference Median (min-max) | p-value |
|---|---|---|---|---|---|
| Neutrophil count (x10$^3$/mL) | 1 | 4.09±1.36 | 3.7±1.12 | -0.24 (-0.42-2.79) | 0.784 |
| | 2 | 4.7±0.80 | 4.3±0.92 | 0.26 (-1.10-1.69) | |
| | 3 | 4.6±1.76 | 3.9±1.20 | 0.39 (-3.13-8.31) | |
| | 4 | 3.9±0.83 | 3.2±0.78 | 0.70 (-0.31-1.62) | |
| Lymphocyte count (x10$^3$/mL) | 1 | 2.10±0.49 | 2.30±0.52 | -0.01 (-1.25-0.63) | 0.262 |
| | 2 | 2.12±0.71 | 2.40±0.64 | -0.21 (-1.24-0.74) | |
| | 3 | 2.16±0.56 | 2.16±0.55 | -0.04 (-1.27-1.63) | |
| | 4 | 1.67±0.40 | 2.46±0.93 | -1.10 (-2.84)-(-0.10) | |
| Platelet count (x10$^3$/mL) | 1 | 275.44±64.20 | 259.66±41.50 | 15.0 (-24-74) | 0.672 |
| | 2 | 305.71±74.84 | 284.14±65.26 | 15.0 (-8-63) | |
| | 3 | 258.52±64.21 | 246.73±58.50 | 8.5 (-50-177) | |
| | 4 | 291.20±61.14 | 291.60±49.18 | -4.0 (-53-44) | |
| NLR | 1 | 1.91±0.66 | 1.65±0.46 | 0.25 (-0.19-0.95) | 0.31 |
| | 2 | 2.55±1.29 | 1.89±0.68 | 0.43 (0.15-2.08) | |
| | 3 | 2.21±0.89 | 1.87±0.72 | 0.28 (-1.14-4.34) | |
| | 4 | 2.38±0.50 | 1.43±0.47 | 0.92 (-0.07-2.43) | |

**Table 3. Continued**

| | The therapy group | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | Pre- and post-treatment difference Median (min-max) | p-value |
|---|---|---|---|---|---|
| PLR | 1 | 128.71±30.36 | 117.47±29.32 | -1.01 (-19.85-45.27) | 0.171 |
| | 2 | 156.26±49.33 | 122.37±39.90 | 18.48 (-27.79-127.66) | |
| | 3 | 124.44±33.24 | 119.25±32.54 | 8.08 (-76.54-72.29) | |
| | 4 | 182.04±55.84 | 128.05±40.8 | 20.77 (3.77-177.59) | |
| MPV | 1 | 9.60±0.97 | 9.32±0.90 | 0 (-1.1-0.9) | 0.719 |
| | 2 | 9.37±0.60 | 9.38±0.93 | -0.3 (-0.7-1.7) | |
| | 3 | 9.64±1.34 | 9.41±1.43 | 0.25 (-0.8-2.33) | |
| | 4 | 9.10±1.03 | 8.92±0.73 | 0.2 (-0.3-0.6) | |
| PCT | 1 | 0.25±0.05 | 0.24±0.03 | 0.010 (-0.03-0.07) | 0.896 |
| | 2 | 0.28±0.06 | 0.26±0.07 | 0.006 (-0.02-0.07) | |
| | 3 | 0.24±0.05 | 0.23±0.05 | 0.014 (-0.06-0.16) | |
| | 4 | 0.26±0.04 | 0.25±0.04 | 0.003 (-0.03-0.04) | |
| CRP | 1 | 5.43±9.48 | 3.17±2.89 | -0.06 (-2.64-25.45) | 0.123 |
| | 2 | 5.69±3.73 | 2.16±1.31 | 2.13 (-0.3-9.0) | |
| | 3 | 3.47±2.75 | 2.59±1.95 | 0.52 (-3.34-6.2) | |
| | 4 | 3.37±4.79 | 0.85±0.91 | 0.10 (-0.91-10.11) | |

Group 1: IL-12/23 inhibitory (ustekinumab for nine patients)
Group 2: TNF alpha inhibitory (adalimumab for six patients, sertolizumab for one patient)
Group 3: IL-17 inhibitory (secukinumab for 18 patients, ixekizumab for 16 patients)
Group 4: IL-23 inhibitory (guselkumab for four patients, risankizumab for one patient)
Kruskal-Wallis test used for analysis.
SD: Standard deviation, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

**Table 4. The correlative change between neutrophil lymphocyte ratio, platelet lymphocyte ratio, mean platelet volume, platelet crit, and C-reactive protein values before and after therapy**

| | | Change in CRP | p-value |
|---|---|---|---|
| Spearman's rho | Change in NLR | 0.303 | **0.025** |
| | Change in PLR | 0.525 | **0.000** |
| | Change in MPV | -0.181 | 0.186 |
| | Change in PCT | 0.063 | 0.648 |

Spearman correlation test was used for analysis. NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

dendritic cells, keratinocytes, and various cytokines released from these cells play a role in its pathogenesis (14). Numerous studies have focused on markers that could be used to assess disease activity and therapy response among patients with psoriasis. The literature revealed that various cytokines, including IL-6, TNF-α, IL-17A, IL-23, and adhesion molecules such as E-selectin and intracellular adhesion molecule-1, are at a more elevated level among patients with psoriasis; consequently, they pose potential for use as disease activity markers (1,15). However, these markers are inconvenient tools for clinical practice because of their high cost and labor-intensive study requirements. Therefore, there is a demand for low-cost and straightforward approaches that have the capacity to assess psoriasis disease activity and therapy response.

The complete blood cell count is a laboratory test routinely performed in daily clinical practice and estimates the number of leukocytes, erythrocytes, and platelets in the bloodstream and the indices related to these cells (16). Recent studies have demonstrated that NLR, PLR, MPV, and PCT values acquired from complete blood cell counts are proportionate to the severity of systemic inflammation in cardiovascular diseases, malignancies, and chronic inflammatory diseases (2-6). Various studies have indicated that the mentioned values are higher in patients with psoriasis than in controls (7-13).

Due to its short half-life, CRP, an acute-phase protein, is extremely sensitive to inflammation and is typically employed in the disease follow-up process. Numerous studies have revealed it is higher among patients with psoriasis than in healthy controls, corresponds to the disease severity, and declines with systemic cures (17). The findings of the two separate studies in which patients with psoriasis were analyzed initially and 12 weeks after

etanercept therapy revealed that the CRP levels drastically declined by therapy (18,19). A study focusing on 142 psoriasis patients who received adalimumab therapy because they failed to respond satisfactorily to etanercept, narrowband UVB, and methotrexate therapies reported a substantial decrease in CRP levels at the 16th week of the therapy, concurrently correlated with a drop in PASI score (20). The current study also found a significant decline in CRP levels after 12 weeks of therapy, regardless of the type of biological agent used, establishing a positive correlation between diminished NLR, PLR, and CRP values.

Studies have reported that patients with psoriasis retain higher neutrophil counts and neutrophil activation products in their lesions and peripheral blood (21). Focusing on psoriasis, Yamanaka et al. (22) discovered that neutrophil activity products were lower in the peripheral blood of psoriasis patients who received biological therapy (ustekinumab and infliximab) than those who did not. In addition to promoting hemostasis, platelets contribute significantly to inflammation by releasing proinflammatory cytokines. They seem to have played a critical role in the pathogenesis of psoriasis by escalating the release of inflammatory cytokines by promoting leukocyte migration of activated platelets to the skin (23). Studies have indicated that platelet activation markers are higher in the plasma of psoriasis patients than in the general population, and there is also a correlation between plasma levels of these markers and PASI score (24). As compatible with the findings of this study, the literature review also revealed that several studies investigating psoriasis patients before and after biological therapy revealed a significant decline in neutrophil and platelet counts after therapy (25,26).

Various studies have reported that NLR may pose a potent marker for identifying systemic inflammation (27). Studies have also indicated that NLR is significantly higher among patients with psoriasis and corresponds to disease severity (11,17,28). A study comparing 39 psoriasis patients and 49 healthy controls discovered that the NLR level was more elevated in psoriasis patients than in the control group; however, there was no significant change in NLR values after three months of narrowband ultraviolet B therapy. The authors attributed this outcome to the ineffective reduction of inflammation by phototherapy (29).

As initially depicted in the literature in 2008, studies have reported that PLR is proportional to the degree of systemic inflammation due to thrombocytosis and lymphopenia. The subsequent studies in the forthcoming years further revealed that PLR had the potential to be a critical marker for systemic inflammation in various chronic inflammatory and cardiovascular diseases (30). However, several studies reported that it was more prevalent among patients with psoriasis than in the control groups, correlating it with the PASI score (11,28). Najar Nobari et al. (31) analyzed 80 patients with psoriasis vulgaris who received TNF-α inhibitor therapy for 12 months, indicating that NLR and PLR values significantly reduced with therapy consistent with the decrease in PASI scores.

As compatible with the findings of the current study, the literature review identified the study of Çevirgen Cemil and Ataş (25), who focused on 42 psoriasis patients and analyzed them before and after the third month of therapy with biological agents, reporting a substantial decline in NLR, PLR, and CRP post-treatment values. In another study, regardless of the type of biological used, a significant reduction in NLR, PLR, and CRP post-treatment values was observed in 186 patients with psoriasis vulgaris and 50 patients with psoriatic arthritis who were evaluated before starting therapy and once during the first 12 months of therapy (either 2-4 months, 5-7 months, or 11-12 months) (32).

Similarly, another study focusing on 75 psoriasis patients and analyzing them before receiving therapy and at the 3$^{rd}$ and 6$^{th}$ months of therapy reported a statistically significant decrease, regardless of the type of biological therapy used, in NLR, PLR, and CRP post-treatment levels, posing concurrent findings with the current study (26). This study found a significant relationship, albeit a low-moderate correlation, between the decrease in CRP and NLR levels; however, a significantly moderate positive correlation was found between the PLR levels. There was no significant relationship between PASI and these parameters for the level decrease. Accordingly, it is conceivable to state that NLR, PLR, and CRP are inadequate parameters for monitoring the clinical severity of the disease in psoriasis patients, whereas NLR and especially PLR are effective parameters in the follow-up of systemic inflammation.

The main platelet volume is a potential indicator of platelet function and activation. High MPV values are considered an independent risk factor for acute MI, renal artery stenosis, DM, hypertension, and hyperlipidemia. These values are also high in various systemic inflammatory diseases and are positively related to CRP (18). According to the literature, its level correlates with the PASI score in patients with psoriasis and is higher in patients with arthritis (13,18,33). In a study conducted with 59 patients with psoriasis, Capo et al. (33) scrutinized the pre-treatment and six-month effects of TNF-α inhibitors, identifying a significant decline in post-treatment MPV values and an adverse correlation between the decrease in MPV value and the PASI score. Therefore, they concluded that MPV was an ineffective marker for identifying disease activity (33). Asahina et al. (32) also revealed that MPV was not

an effective marker for systemic inflammation since it was lower among patients with psoriatic arthritis than in patients with psoriasis vulgaris, displayed a negative correlation with CRP, and was elevated after biological therapy. The current study correspondingly identified no substantial difference between pre- and post-treatment MPV values and no correlation between CRP and MPV decline. Therefore, it is viable to claim that MPV is not a reliable marker to demarcate the severity of inflammation.

Plateletcrit refers to the number of platelets in a unit of blood. The MPV X platelet count equation yields PCT. It serves as a marker for platelet aggregation and cardiovascular disease (34). Studies have established that it is associated with the severity of inflammation in Behçet's disease, inflammatory bowel diseases, and malignancies (13). Plateletcrit was typically higher in patients with psoriasis compared to the control group, and its level indicated the severity of the disease (35). Çevirgen Cemil and Ataş (25) assessed the PCT value of psoriasis patients, reporting a significant decline in PCT value after three months of biological therapy. Notwithstanding the therapy agent type, the current study similarly identified a substantial decrease in PCT value after 3-month therapy, albeit establishing no correlation between CRP and PCT decline. Therefore, PCT may also be a potential marker in the follow-up of systemic inflammation among patients with psoriasis; however, further and broad-prospective studies are required to prove it.

### Study Limitations

The limitations of this study are that it is retrospective in nature, comprises a limited number of patients, and has a short patient follow-up period. However, assessment of dependent groups, evaluation of patients who have not received biological therapy before, and exclusion of patients with inflammatory and infectious diseases are the main strengths of this study.

## Conclusion

Irrespective of the biological therapy category, this study demonstrated that the values of NLR, PLR, PCT, and CRP, the markers for systemic inflammation and cardiovascular morbidity, substantially lowered after therapy, that there was a low-moderate correlation between the CRP and NLR decline, and that there was a moderately positive correlation between the decrease in PLR level. In addition, it established that NLR, PLR, and PCT values obtained from hemogram data, particularly PLR values, can be low-cost and easily accessible parameters to potentially use in analyzing biological therapy effects on systemic inflammation in psoriasis patients. The study findings provided supportive evidence that biological agent therapy lowers the risk of systemic inflammation and cardiovascular morbidity in patients with psoriasis.

### Ethics

**Ethics Committee Approval:** Ethics approval for the study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Training and Research Hospital with decision number 2022/62.

**Informed Consent:** Written informed consent was waived because of the retrospective nature of this study.

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

### Authorship Contributions

Surgical and Medical Practices: S.K., I.D.O., Concept: S.K., Design: S.K., Data Collection or Processing: S.K., I.D.O., Analysis or Interpretation: S.K., I.D.O., Literature Search: S.K., Writing: S.K.

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

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