The effect of biological agent treatment on neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume, and C-reactive protein in psoriasis patients

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Abstract

Introduction: In recent years, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and C reactive protein (CRP) have been shown to be important indicators of systemic inflammation. Studies have shown that NLR, PLR, MPV and CRP are higher in psoriasis patients than in the control group.

Aim: To investigate the NLR, PLR, MPV and serum CRP levels in patients who were treated with biological agents for psoriasis.

Material and methods: In our study, 75 patients who were followed up and had a diagnosis of psoriasis vulgaris and took a biological agent therapy between January 2014 and December 2017 in the Dermatology Clinic of the Dicle University Medical Faculty Hospital were evaluated before treatment, and 3 and 6 months after treatment.

Results: Neutrophil count, lymphocyte count, thrombocyte count, NLR, PLR, MPV and CRP values before the biological agent treatment were statistically higher than the values at 3 and 6 months of treatment. There was no statistically significant difference between pre-treatment neutrophil, lymphocyte, leukocyte, platelet, NLR, PLR, MPV, CRP values and values at 3 and 6 months after treatment when we compared four different biological agents.

Conclusions: It was seen that NLR, PLR, MPV and CRP values decreased independently of the type of the biological agent used in our study. Therefore, we think that these parameters can be used to evaluate the effects of biological agent treatment on systemic inflammation in psoriasis patients and to monitor the course of the disease.

Key words: mean platelet volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio.

Introduction

Psoriasis is a common chronic inflammatory and proliferative skin disease in which genetic and environmental factors play a critical role [1, 2]. The inflammatory nature of the disease is caused by overexpression of tumour necrosis factor tumour necrosis factor α (TNF-α), interferon γ (IFN-γ) and various proinflammatory cytokines [2, 3].

In recent years, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and C reactive protein (CRP) have been shown to be important indicators of systemic inflammation [4–7]. NLR and PLR were found to be associated with interleukin IL-6 and TNF-α, which play an important role in the pathogenesis of psoriasis [8, 9]. Studies have shown that NLR, PLR, MPV and CRP are higher in psoriasis patients than in the control group [8, 10–12].

Aim

In our study, we aimed to investigate the NLR, PLR, MPV and serum CRP levels, which are cheap and easily applicable parameters in evaluating the response to systemic treatment, in patients who were treated with biological agents for psoriasis.
Material and methods

Patients and study design

In our study, 75 patients who were followed up who had a diagnosis of psoriasis vulgaris (PV) and took a biological agent therapy between January 2014 and December 2017 in the Dermatology Clinic of Dicle University Medical Faculty Hospital were evaluated before treatment, and 3 and 6 months after treatment. Patients with moderate-to-severe plaque-type psoriasis vulgaris who did not respond to conventional systemic treatments such as acitretin, methotrexate, and cyclosporine or whose conventional systemic treatment was contra-indicated were included in the study. Age, sex, duration of disease, presence of arthritis, nail involvement, neutrophil, lymphocyte, leukocyte, thrombocyte, NLR, PLR, MPV and CRP values were recorded.

The NLR value was calculated by dividing the number of neutrophils by the number of lymphocytes and the PLR value by dividing the number of platelets by the number of lymphocytes. Complete blood count was performed with Cell-Dyn 3700 (optical scatter laser method, Abbott Diagnostics, Chicago, USA). The CRP level was measured by Beckman Coulter nephelometric method (IMMAGE 800, USA).

Treatments

Infliximab was administered i.v. (5 mg/kg) at weeks 0, 2, 6 and thereafter every 8 weeks. Adalimumab was administered s.c. (80 mg) at week 0 and 1 and thereafter at 40 mg every 2 weeks. Etanercept was administered s.c. (2 × 25 mg or 2 × 50 mg) at week 1 and thereafter every week. Ustekinumab was administered s.c. (45 or 90 mg) at weeks 0, 4, and thereafter every 12 weeks.

Patients who had another skin disease, cardiovascular, gastrointestinal, renal disease, malignancy, diabetes mellitus, infectious and inflammatory disease, and patients not taking the recommended treatment protocol were excluded.

Statistical analysis

Values of the data were taken as pre-treatment-3rd month and 6th month of treatment. In statistical analysis of these data, the variance analysis method was applied in repeated measures. The interaction between time measurements was looked at and compared. A statistically significant result was accepted if \( p < 0.05 \). Statistical analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) package program.

Results

In this study, the results of 75 PV patients before the biological agent treatment and 3 and 6 months after treatment were evaluated.

The mean age of PV patients was 38.7 ±14.8 years. Thirty-eight (50.6%) of PV patients were male and 37 (49.4%) were female. The mean disease duration of PV patients was 16.0 ±8.7 years.

Forty-eight (64%) of the PV patients had nail involvement and 11 (14.6%) had arthritis. Eighteen (24%) of the PV patients had family history. Thirty-four patients received adalimumab, 20 patients infliximab, 11 patients etanercept, and 10 patients ustekinumab.

Table 1. Pre-treatment, 3rd and 6th month laboratory results of the patients

| Parameter       | Pre-treatment Mean ± SD | After treatment (3rd month) Mean ± SD | After treatment (6th month) Mean ± SD | P-value |
|-----------------|-------------------------|---------------------------------------|--------------------------------------|---------|
| Neutrophil [× 10^3/ml] | 4.59 ±1.31 (1.83–6.74) | 4.64 ±1.27 (2.54–6.72) | 4.63 ±1.27 (2.53–6.64) | < 0.001 |
| Lymphocytes [× 10^3/ml] | 3.27 ±1.72 (1.36–9.60) | 2.84 ±1.52 (1.36–9.60) | 2.86 ±1.53 (1.37–9.62) | < 0.001 |
| Leukocytes [× 10^3/ml]  | 6.80 ±2.50 (1.37–9.54) | 7.89 ±1.24 (5.54–9.55) | 7.88 ±1.23 (5.45–9.58) | 0.077   |
| Platelets [× 10^3/ml]   | 327.34 ±83.08 (162.60–459.12) | 326.78 ±83.82 (160.00–455.87) | 323.62 ±86.17 (157.84–455.00) | < 0.001 |
| NLR               | 1.78 ±1.02 (0.32–4.08) | 2.00 ±1.04 (0.44–4.89) | 1.98 ±1.03 (0.44–4.85) | < 0.001 |
| PLR               | 133.14 ±62.83 (28.56–294.31) | 136.97 ±61.44 (28.03–290.37) | 134.56 ±61.12 (27.80–288.71) | < 0.001 |
| MPV               | 9.72 ±0.79 (7.0–11.7) | 9.60 ±0.75 (6.9–11.4) | 9.45 ±0.77 (6.4–11.3) | < 0.001 |
| CRP [mg/dl]       | 0.84 ±0.37 (0.21–1.74) | 0.55 ±0.21 (0.19–0.95) | 0.38 ±0.16 (0.11–0.84) | < 0.001 |
Neutrophil count, lymphocyte count, thrombocyte count, NLR, PLR, MPV and CRP values before the biological agent treatment were statistically higher than the values at 3 and 6 months of treatment ($p < 0.001$) (Table 1).

The difference between the leukocyte values before the biological agent treatment of the and the values at 3 and 6 months after the treatment was not statistically significant ($p = 0.077$).

There was no statistically significant difference between pre-treatment neutrophil, lymphocyte, thrombocyte, platelet, NLR, PLR, MPV, CRP values and at 3 and 6 months after the treatment when we compared four different biological agents ($p > 0.05$) (Table 2).

**Discussion**

Psoriasis is a chronic inflammatory disease that affects the knees, elbows and extensor side of the extremities, which occurs in about 2–3% of the population [13, 14]. Psoriasis is thought to be a result of complicated relationships between T-lymphocytes, neutrophils, macrophages, mast cells, keratinocytes and dendritic cells [14]. Neutrophils initiate the first step of systemic inflammation and show nonspecific inflammation. Detection of increased neutrophils with neutrophil activation products in psoriatic lesions and peripheral blood and induction of psoriasis with neutrophil-derived IL-1β in psoriatic lesions and peripheral blood and induction of psoriasis with neutrophil-derived IFN-γ, IL-17 and TNF-α supports the opinion that neutrophils play an active role in the pathogenesis of psoriasis [14, 15].

Rocha-Pereira et al. reported an increased number of neutrophils in psoriasis patients and found that the number of neutrophils was significantly higher in patients with active psoriasis than in inactive patients [16]. Yamanaka et al. showed that biological agent treatments did not significantly alter IFN-γ, IL-17 and TNF-α production from lymphocytes in patients with severe psoriasis, but blocked neutrophil activation in patients. In addition, there was no difference between infliximab and

| Parameter | Biological agent | Pre-treatment Mean ± SD | After treatment (3rd month) Mean ± SD | After treatment (6th month) Mean ± SD | P-value |
|-----------|------------------|--------------------------|---------------------------------------|---------------------------------------|---------|
| Neutrophil [× 10^3/ml] | Etanercept | 4.70 ± 1.25 | 4.88 ± 0.68 | 4.86 ± 0.69 | 0.725 |
| | Adalimumab | 4.65 ± 1.35 | 4.62 ± 1.45 | 4.61 ± 1.45 |
| | Infliximab | 4.40 ± 0.45 | 4.59 ± 1.35 | 4.59 ± 1.34 |
| | Ustekinumab | 4.60 ± 1.11 | 4.53 ± 1.05 | 4.52 ± 1.05 |
| Lymphocyte [× 10^3/ml] | Etanercept | 3.23 ± 1.25 | 2.64 ± 0.81 | 2.66 ± 0.79 |
| | Adalimumab | 3.01 ± 1.47 | 2.61 ± 1.17 | 2.62 ± 1.17 |
| | Infliximab | 3.58 ± 2.05 | 3.16 ± 1.91 | 3.19 ± 1.91 |
| | Ustekinumab | 3.55 ± 2.28 | 3.20 ± 2.30 | 3.22 ± 2.30 |
| Leukocyte [× 10^3/ml] | Etanercept | 6.32 ± 2.77 | 8.15 ± 0.99 | 8.15 ± 0.97 |
| | Adalimumab | 6.69 ± 2.62 | 7.82 ± 1.32 | 7.82 ± 1.31 |
| | Infliximab | 7.30 ± 2.25 | 7.98 ± 1.31 | 7.98 ± 1.31 |
| | Ustekinumab | 6.68 ± 2.50 | 7.64 ± 1.19 | 7.61 ± 1.16 |
| Platelet [× 10^3/ml] | Etanercept | 312.89 ± 97.39 | 313.35 ± 96.28 | 317.78 ± 95.38 |
| | Adalimumab | 337.94 ± 84.23 | 337.36 ± 85.30 | 331.97 ± 90.98 |
| | Infliximab | 320.81 ± 65.88 | 319.92 ± 67.47 | 318.47 ± 67.57 |
| | Ustekinumab | 320.29 ± 101.04 | 319.26 ± 101.81 | 318.59 ± 102.15 |
| NLR | Etanercept | 1.82 ± 1.17 | 2.09 ± 0.97 | 2.05 ± 0.96 |
| | Adalimumab | 1.93 ± 1.10 | 2.13 ± 1.15 | 2.12 ± 1.15 |
| | Infliximab | 1.61 ± 0.96 | 1.86 ± 1.03 | 1.84 ± 1.01 |
| | Ustekinumab | 1.58 ± 0.70 | 1.73 ± 0.71 | 1.72 ± 0.71 |
| PLR | Etanercept | 108.68 ± 46.98 | 129.06 ± 52.94 | 126.93 ± 52.49 |
| | Adalimumab | 136.57 ± 68.22 | 149.63 ± 63.96 | 146.38 ± 64.34 |
| | Infliximab | 110.50 ± 49.93 | 123.25 ± 52.74 | 121.32 ± 51.53 |
| | Ustekinumab | 118.66 ± 79.77 | 130.09 ± 76.77 | 129.25 ± 76.49 |
| MPV | Etanercept | 9.88 ± 0.85 | 9.69 ± 0.76 | 9.51 ± 0.74 |
| | Adalimumab | 9.65 ± 0.94 | 9.55 ± 0.92 | 9.36 ± 0.98 |
| | Infliximab | 9.71 ± 0.63 | 9.63 ± 0.56 | 9.54 ± 0.53 |
| | Ustekinumab | 9.80 ± 0.45 | 9.66 ± 0.39 | 9.49 ± 0.24 |
| CRP [mg/dl] | Etanercept | 0.98 ± 0.37 | 0.6 ± 0.20 | 0.35 ± 0.10 |
| | Adalimumab | 0.80 ± 0.36 | 0.56 ± 0.23 | 0.39 ± 0.20 |
| | Infliximab | 0.87 ± 0.33 | 0.55 ± 0.19 | 0.37 ± 0.14 |
| | Ustekinumab | 0.79 ± 0.50 | 0.49 ± 0.20 | 0.37 ± 0.14 |
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Ustekinumab in terms of decreased neutrophil activity after treatment with a biological agent [17]. Similarly, in our study, it was observed that the number of neutrophils decreased independently of the type of the biological agent.

NLR is an inexpensive, easy-to-use inflammatory marker that is obtained by dividing the total number of neutrophils by the number of lymphocytes. NLR has been shown to increase in many diseases such as metabolic syndrome, ankylosing spondylitis, rheumatoid arthritis, vitiligo and lichen planus [1, 4, 5, 18–20]. Increased levels of several cytokines such as TNF-α, IL-6, IL-12 and IL-17 in psoriasis have been shown to cause elevation in NLR [8].

Kim et al. showed that NLR was increased in psoriatic patients compared to the control group and there was a positive correlation between PASI score and NLR [20]. Erik Toprak et al. reported that NLR levels were not affected after 3 months of phototherapy in patients with psoriasis, and this was probably due to the presence of residual inflammation [21]. Asahina et al. have shown that NLR had decreased in patients with psoriasis after 12 months of treatment with biological agents and there is no difference between treatments used. It has also been reported that NLR may be used to assess systemic inflammation and monitor disease course after treatment [22].

In our study, after 6 months of treatment with a biological agent, NLR was found to be reduced independently of the type of the biological agent used.

Platelets play a role in many processes such as inflammation and immunity [23, 24]. PLR is obtained by dividing the platelet count by the lymphocyte count. In recent years it has been reported that PLR value may be a marker of systemic inflammation [8, 18, 22]. Unal et al. found that PLR values were significantly higher in patients with psoriasis than in the control group. In this study, it was also stated that PLR may be a better inflammatory parameter than NLR [8].

Boyraz et al. have detected significantly lower levels of PLR in patients with ankylosing spondylitis treated with anti-TNF-α than in the control group and have also indicated that PLR can be used as an appropriate marker to monitor disease progression [18]. Asahina et al. reported that the PLR value was significantly decreased after treatment with any of the infliximab, adalimumab and ustekinumab in psoriatic patients, but the mean reduction rate was found to be numerically lower in ustekinumab treatment than infliximab and adalimumab treatments [22]. In our study, it was observed that the PLR values decreased independently of the type of the biological agent used.

MPV is considered an in vivo marker of platelet reactivity. Many studies have suggested that MPV plays an important role as a marker of inflammation and shows disease activity and anti-inflammatory treatment efficacy in chronic inflammatory diseases [6, 12, 25]. Canpolat et al. showed MPV has a positive correlation with PASI score in patients with psoriasis and that MPV was higher in patients with psoriatic arthritis than in those without arthritis [26].

In a study, anti-TNF-α therapy was started for 21 patients with rheumatoid arthritis who did not have cardiovascular disease, and the values of MPV were measured before treatment and at the 2nd and 12th weeks of treatment. Anti-TNF-α treatment has been shown to cause a significant increase in MPV over the course of treatment [19].

Asahina et al. reported that MPV values did not change significantly after treatment in patients with psoriasis who received biological agents but a significant increase was observed at some time points after treatment with infliximab or adalimumab in psoriatic arthritis patients [22].

In our study, we observed that, unlike the data in the literature show, there was a decrease in MPV values independently of the type of the biological agent used. Like NLR and PLR, we think that MPV can also be used to evaluate the effects of biological agent treatment on systemic inflammation.

CRP is an acute phase protein that is produced predominantly by hepatocytes by the action of cytokines such as IL-6 and TNF-α [27]. It has been shown that serum CRP levels increase in psoriasis patients and that there is a positive correlation between CRP levels and disease severity [10].

Strober et al. reported that after treatment with etanercept a significant reduction in CRP levels was shown at third month of treatment and this reduction may be due to IL-6 inhibition [7]. In a study, CRP levels were significantly reduced when adalimumab was administered to patients with psoriasis with suboptimal response to etanercept, methotrexate, and db UVB treatment [28].

Asahina et al. have shown in psoriasis patients that TNF-α antagonists (infliximab and adalimumab) inhibit CRP more than IL-12/23 p40 antagonist (ustekinumab) [29]. Since TNF-α is required for CRP synthesis, inhibition of CRP by TNF-α antagonists is mainly due to the direct effects of TNF-α on CRP [22].

In our study, the CRP values before biological agent treatment were statistically significantly higher than the values at 3 and 6 months of treatment. When etanercept, adalimumab, infliximab, and ustekinumab treatments were compared, there was no statistically significant difference between CRP values before treatment and values at 3 and 6 months of treatment.

Conclusions

It was seen that NLR, PLR, MPV and CRP values decreased independently of the type of the biological agent used in our study. Therefore, we think that these parameters can be used to evaluate the effects of biological agent.
treatment on systemic inflammation in psoriasis patients and to monitor the course of the disease.

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Conflicts of interest
The authors declare no conflict of interest.

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