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Decrease in inflammation markers with ustekinumab treatment in moderate-severe psoriasis

Orta şiddette ve şiddetli psoriasis hastalarında ustekinumab tedavisi sonrası inflamatuar belirteçlerde azalma

Banu Taşkın, Bachar Memet, Eren Vurgun, Sibel Alper

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Abstract

Purpose: Psoriasis is a chronic, inflammatory, and systemic disease. The disease activity is usually measured by Psoriasis Area and Severity Index (PASI), however, further objective laboratory tools are needed. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and mean platelet volume (MPV) are objectively calculated markers that increase in inflammation. This study aimed to investigate the utility of these markers for follow-up of systemic inflammation and response to treatment.

Material and methods: A total of 25 patients who had moderate or severe psoriasis vulgaris, who received ustekinumab treatment were retrospectively evaluated in the study. In patients, pre-treatment PASI, complete blood count parameters, serum CRP levels and NLR, PLR and MPV values in the follow up when they achieved PASI 75 and/or more improvement were recorded. Patients with an additional inflammatory disease or accompanying infection were excluded from the study.

Results: While a statistically significant decline was recorded in NLR and PLR (p<0.05), no significant change was observed in MPV and CRP after the therapy success where patients achieved an improvement greater than or equal to PASI 75.

Conclusion: We conclude that the correlation with the response to treatment and NLR and PLR levels show that these markers may be beneficial for assessment of disease severity either in combination with current scores or alone. These markers are cost effective predictors that can easily be measured in routine practice.

Key words: Psoriasis, treatment, neutrophil-lymphocyte ratio.

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Öz

Giriş: Psoriasis kronik, inflamatuar ve sistemik bir hastalıktır.Psoriasiste hastalık şiddetini ölçmek için Psoriasis Alan Şiddet İndeksi (PAŞİ) yanı sıra daha objektif laboratuar araçlarına ihtiyaç vardır. Nötrofil lenfosit oranı (NLO), trombosit lenfosit oranı (TLO) ve ortalama trombosit hacmi (OTH) çeşitli inflamatuar hastalıklarda arttığı bilinen belirteçlerdir. Bu çalışmada amacımız orta şiddette ve şiddetli psoriasis vulgarisi olan hastalarda NLO, TLO ve OTH değerlerinin ustekinumab tedavisi ile değişimlerini araştırmaktır.

Gereç ve yöntem: Çalışmada orta şiddette veya şiddetli psoriasis vulgarisi olup, ustekinumab tedavisi verilen kronik plak tipi psoriasis tanılı 25 hasta retrospektif olarak değerlendirilmiştir. Hastaların tedavi öncesi PAŞİ, tam kan sayımı parametreleri, serum CRP seviyeleri ve PAŞİ 75 ve/veya üzeri başarı elde edildikleri kontrollerindeki değerleri kaydedilmiştir. Tam kan sayımı belirteçleri, OTH ve CRP değeri determine edilmiştir. Ek inflamatuar hastalığı ve eşlik eden enfeksiyonu olanlar çalışma dışı bırakılmıştır.

Bulgular: Hastaların PAŞİ 75 başarı ve üzeri elde ettikleri incelemelerde NLO, TLO oranlarında istatistiksel olarak anlamlı düşme (p<0,05) saptanırken OTH ve CRP değerlerinde tedavi başarısı sonrası anlamlı değişiklik izlenmemiştir.

Sonuç: NLO ve TLO değerlerinde tedavi yanıtı alınmasıyla anlamlı düşme olduğu gösterdik. Bu göstergeler rutin pratikte kolay ölçülebilen ve maliyet açısından verimli belirteçlerdir.

Anahtar kelimeler: Psoriasis, tedavi, nötrofil lenfosit oranı.

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Banu Taşkın, MD, Koç University Hospital, Department of Dermatology, Istanbul, Turkey, e-mail: drbanutaskin@gmail.com (https://orcid.org/0000-0002-9651-9258) (Corresponding Author)

Bachar Memet, MD, Koç University Hospital, Department of Dermatology, Istanbul, Turkey, e-mail: dr.bachar@hotmail.com (https://orcid.org/0000-0001-7731-943X)

Eren Vurgun, MD, Sorgun State Hospital, Department of Medical Biochemistry, Yozgat, Turkey, e-mail: eren_vurgun@hotmail.com (https://orcid.org/0000-0002-2288-1123)

Sibel Alper, PhD, Koç University Hospital, Department of Dermatology, Istanbul, Turkey, e-mail: sibelalper2010@hotmail.com (https://orcid.org/0000-0001-9086-2250)

Introduction

Psoriasis affects skin with erythematous scaly plaques characterized by immune-mediated chronic inflammation. Recent genome wide association studies have shown that in patients with psoriasis vulgaris there is a strong association IL12/1L23 and IL17 pathway, HLA-Cw0602 and ERAP1 gene [1, 2]. The cellular infiltration consists mainly of CD4 and CD8 T cells and polymorphonuclear leukocytes. Increased proliferation of keratinocytes is observed as parakeratosis in histopathology and subcorneal microabcesses may be detected in skin biopsies. Comorbidity studies have shown association with metabolic syndrome, coronary heart disease in psoriasis. Psoriasis vulgaris is considered as a systemic inflammatory disease in recent years [1].

The severity of the disease must be determined in order to help the patient receive a suitable, efficient and safe therapy. However, there is no method which can thoroughly determine the severity of the disease. The most common scale used to determine the severity of psoriasis is Psoriasis Area Surface Index (PASI). PASI ranks the symptoms of erythema, desquamation [scaling] and induration [infiltration] according to their prevalence on anatomic localization. It is commonly used in the follow-up of the therapy. Another assessment method is Body Surface Area (BSA) which is calculated according to the distribution of the lesions [3]. However, both methods are subjective and in same patient the score may differ depending on the clinician. Moreover, they cannot evaluate the underlying chronic microvascular inflammation [4]. Neutrophils-lymphocytes ratio (NLR), mean platelet volume (MPV) and platelets-lymphocytes ratio (PLR) are simple markers that show systemic inflammatory response and that can be measured with hemogram. NLR is obtained by dividing the number of neutrophils by the number of lymphocytes and PLR by dividing the platelet count by the number of lymphocytes. Recently, NLR and PLR have been accepted as subclinical inflammatory markers and commonly used in several chronic inflammatory conditions such as cardiovascular diseases [5, 6], rheumatoid arthritis [7], inflammatory bowel diseases [8] and malignancies. MPV is a marker of thrombocyte activation. MPV value increases in acute coronary syndrome and is asserted to be a marker for early detection of other cardiovascular risk factors such as atherosclerosis [9], metabolic syndrome, diabetes mellitus [10] and hyperlipidemia [9-11]. It is also asserted that there is relationship between PLR and C reactive protein (CRP) value of NLR and PLR [12].

This study aimed to compare NLR, PLR and MPV values and serum CRP levels in patients with moderate or severe psoriasis before and after ustekinumab therapy to assess their utility in disease management.

Material and methods

A total of 25 patients with moderate or severe chronic plaque psoriasis, who received ustekinumab therapy were retrospectively analysed in this study. Approval was obtained from the scientific research ethics committee. In patients, pre-treatment PASI, complete blood count parameters, serum CRP levels (CRP-Latex, normal range <0.5 mg/dL; <0.1 mg/dL low risk, 0.1-0.3 mg/dL medium risk, >0.3 mg/dL high risk) in the follow ups when they achieved PASI 75 improvement were recorded. Hemoglobin (Hb), neutrophils, lymphocytes, leukocytes, erythrocytes, platelets, MPV were determined in complete blood count. NLR was obtained by dividing the number of neutrophils by the number of lymphocytes and PLR by dividing the platelet count by the number of lymphocytes.

Ustekinumab was administered to the patients every 12 weeks after an induction dose in months 0 and 1. The dose of ustekinumab was 90mg for patients who weighed 100kg or more and 45mg for patients who weighed below 100kg. Patients under the age of 18, pregnant and lactating women, patients who had a disease other than psoriasis, and patients with active infection history were excluded from the study. Patients who had erythrodermic and arthropathic psoriasis were also excluded from the study. All blood tests were analysed in the same laboratory.

Statistical analysis was performed with SPSS 17.0 program. For normally distributed parameters Student-t test was used while Mann-Whitney U test was used for non-normally distributed parameters. Normally distributed parameters were expressed as mean ± standard

deviation values, whereas non-normally distributed parameters were expressed as median values (25th percentile-75th percentile). Shapiro-Wilk test, dependent samples t test for normally distributed parameters and Wilcoxon test for non-normally distributed parameters were used for the differences between pre-treatment and post-treatment parameters. Spearman Rank Correlation was used to find correlations between PASI and CRP values.

Results

Mean age of the patients included in the study was 42.52 (±12.6). Ten patients (%40) were female and 15 patients (%60) were male. Mean duration of the disease was 11.48 years [±7.09] and mean PASI score was 17.02.

Pre-treatment and post-treatment blood count parameters are given in Table 1. Pre-treatment NLR was 2.34 (median 1.71-2.73) and NLR after PASI 75 was achieved was 1.93 [median 1.59-2.75]. The difference was statistically significant (p=0.023) (Figure 1). A significant difference was recorded between pre-treatment PLR value (125.8; med 87.5-143.5) and post-treatment PLR value (107.5; med 83.2-137.9). MPV value was 9.77 μm^3 (±0.89) before the therapy and 9.83 μm^3 (±1.28) after the therapy. The difference was not significant (p=0.76).

Pre-treatment CRP level was 0.28ng/dL (med 0.09-0.69) and post-treatment CRP level was 0.22ng/dL (med 0.06-0.57). The difference was not statistically significant (p=0.25). No significant relationship was found between pre-treatment and post-treatment PASI and CRP values.

When female and male genders were compared pre-treatment PASI value was found statistically significantly higher in male patients (p=0.043). No difference was recorded between female and male genders in terms of NLR, PLR and MPV values (Table 2).

Table 1. Pre-treatment and post-treatment parameters

Parameters	n	Pre-treatment	Post-treatment	*p*
Hb (g/dL)	25	14.88±1.25	14.80±1.35	0.55
WBC (10^3 /mm^3)	25	8.61±2.74	8.50±1.78	0.84
Nc (10^3 /mm^3)	25	4.95 (4.18-6.77)	4.86 (4.32-5.82)	0.08
Lc (10^3 /mm^3)	25	2.40±0.68	2.52±0.83	0.25
N/L ratio	25	2.34 (1.71-2.73)	1.93 (1.59-2.75)	**0.023**
Pc (10^3 /mm^3)	25	262 (219-312)	247 (220-288)	**0.04**
MPV (μm^3)	25	9.77±0.89	9.83±1.28	0.76
P/L ratio	25	125.8 (87.5-143.5)	107.5 (83.2-137.9)	**0.04**
CRP	25	0.28 (0.09-0.69)	0.22 (0.06-0.57)	0.25

Hb, hemoglobin; WBC, white blood cell count; Nc, neutrophil count; Lc, lymphocyte count; N/L ratio, neutrophil to lymphocyte ratio; P/L ratio, platelet to lymphocyte ratio; Pc, platelets count; MPV, mean platelet volume; CRP, C-reactive protein
Hb, WBC, Lc, and MPV were expressed as mean±SD. CRP, PLR, Nc, N/L and Pc were expressed as median (25th percentile-75th percentile)

Table 2. Comparative clinical and biochemical characteristics of patients according to gender

	Male (n=15)	Female (n=10)	*p*
Age	42.5±10.1	42.6±16.9	0.98
Duration of psoriasis (months)	9.3±6.8	14.7±7.0	0.07
PASI	16.6 (13.5-19.8)	12.6 (11.0-15.0)	**0.043**
Hb (g/dL)	15.2±1.1	14.3±1.2	0.053
WBC ($10^3/mm^3$)	8.65±3.15	8.56±2.16	0.94
Nc ($10^3/mm^3$)	5.14 (4.31-6.62)	4.90 (3.85-7.25)	0.82
Lc ($10^3/mm^3$)	2.47±0.70	2.32±0.68	0.60
N/L ratio	2.32 (1.67-2.85)	2.40 (1.87-2.97)	0.70
Pc ($10^3/mm^3$)	264 (241-308)	227 (205-316)	0.21
MPV (μm^3)	9.78±1.0	9.76±0.75	0.96

Hb, hemoglobin; WBC, white blood cell count; Nc, neutrophil count; Lc, lymphocyte count; N/L ratio, neutrophil to lymphocyte ratio; Pc, platelets count; MPV, mean platelet volume; Hb, WBC, Lc, and MPV were expressed as mean±SD, PLR, Nc, N/L ratio and Pc were expressed as median (25^{th} percentile-75^{th} percentile).

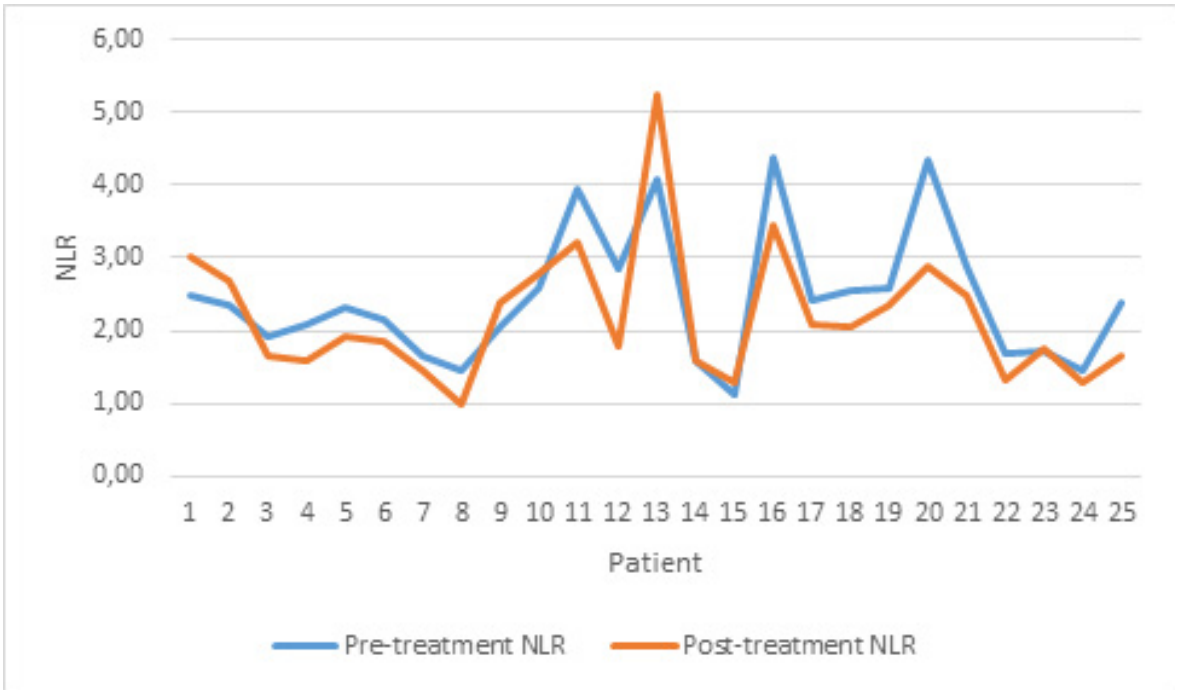

Figure 1. Comparison of pre-treatment and post-treatment NLR

Discussion

Although there are not clinically significant biomarkers for psoriasis, the fact that inflammatory markers in peripheral circulation are high, suggests that the disease is deeply associated with various systemic diseases [12]. It was revealed in various studies on this context that thrombocyte activation increased in patients with psoriasis [13, 14]. MPV value is the simplest parameter to analyzed to predict thrombocyte activation among the wide variety of methods measuring thrombocyte activation [15]. However, contradictory results related to MPV value were observed in patients with psoriasis in the studies. Karabudak et al. [16] found that MPV level was higher in patients with mild/moderate psoriasis compared to the control group. Canpolat et al. [17] and Kim et al. [18] found that MPV was higher in patients with psoriasis and revealed a positive correlation with the severity of the disease. On the other hand, Saleh et al. [19] and Işık et al. [20] did not find a significant difference between

patients with psoriasis and the control group in terms of MPV. Işık et al. [20] found a weak relationship between PASI and MPV. They reported that MPV was effected by lifestyle, diet, and diseases such as hyperlipidemia, DM, etc. and suggested that these findings were present in increased rates among patients with psoriasis compared to the normal population, causing the higher MVP value. Beyan et al. [21] reported that MPV was not sufficient to evaluate thrombocyte activation. Since there was no control group in our study, the relationship between MVP and systemic inflammation could not be demonstrated. Furthermore, no significant difference was recorded between pre-treatment and post-treatment MVP values. The relationship between MVP elevation and severity of Psoriasis is controversial in the literature further studies with wide range of case series are needed in order to clarify the role of thrombocytes in inflammation. Asehina et al. [12] also commented that these differences in MVP were also seen in Rheumatoid artritis studies, but the exact cause of this discrepancy between clinical studies is unkown.

Neutrophils initiate the first line of defense in inflammation and lymphocytes function as regulators and protectors of inflammation. An infiltrate that is rich in T lymphocytes and neutrophils is found in psoriatic lesion while leukocyte and neutrophil values are high in peripheral blood with the effect of chemotactic factors [22]. Leukocytes, monocytes and neutrophils were significantly high and lymphocytes were low in the blood of patients with psoriasis compared to the control group [23]. Kim et al. [24], Sen et al. [25], Unal et al. [26] and Polat et al. [4] found NLR higher in patients with psoriasis compared to the control group and revealed that there was a positive correlation between NLR and PASI. On the other hand, Ataseven et al. [27] could not find any correlation with PASI although they found NLR levels higher in patients with psoriasis compared to the control group. Even though there is a strong relationship between psoriasis disease activity and NLR in most of the studies, there are few studies showing the relationship between this value and treatment. Zhang et al. investigated the level of NLR in the use of therapeutic antibodies, 18 patients on brodilumab and 12 patients on ustekinumab, and showed significant reduction in NLR of anti-body treated patients compared to control group [28]. Similarly, in our study, we detected a statistically significant decrease in psoriasis patients under ustekinumab treatment and concluded that NLR could be an indicator of disease activity.

Another indicator, PLR was found high in patients with coronary artery in the presence of atherosclerosis and in inflammatory diseases [29]. It was asserted that PLR had better relationships with inflammatory cytokines such as IL-6 and TNF-alpha compared to NLR and that it was thereby a better inflammation marker than NLR [30]. PLR assessment in patients with psoriasis is relatively low. PLR value was found higher in patients with psoriasis compared to the control groups in all studies [4, 24, 31, 32]. Pekdas et al. [31] revealed that the correlation of PLR value with PASI was more than that with NLR. In our study, we compared NLR and PLR values of the patients with moderate and severe psoriasis and without an additional disease, before and after biological therapy; and recorded a significant decline in these values. The fact that NLR and PLR values, which are considered to be inflammation markers in the body, decreased with treatment suggested that they can be used as an inflammation markers for psoriasis as well.

Sen et al. [25] revealed that the high-sensitive (hs)-CRP level was higher as well as the NLR level in patients with psoriasis compared to the control group and that it was in correlation with PASI and NLR. Beygi et al. [33] reported that high CRP level was associated with moderate and severe disease but not with mild disease. Moreover, they asserted that CRP-like PASI-was a value that could show the severity of the disease in non-treatable psoriatic patients without arthritis. Our study consisted of patients with moderate and severe psoriasis who did not have arthropathy; and the change in CRP after achieving PASI 75 was not significant. This can be explained by low number of patients. Moreover, hs- CRP test can give more significant results in these cases.

Asahina et al. [12] evaluated NLR, PLR, MPV and CRP values before and after various biological therapies and found higher rates in patients with psoriatic arthritis. It was concluded in the study that NLR and PLR could be used to follow up the course of the disease in order to

evaluate the inhibition of systemic inflammation especially after the therapy.

Gender-based difference of psoriasis in hematologic parameters was previously analyzed by Raghavan et al. [34] and PASI and MPV were found higher in male gender. However, the number of female patients in that study was low compared to the general distribution. In our study, we found PASI level statistically significantly higher in male gender, which is consistent with literature [35]. However, we found no difference in hematologic parameters, NLR, MPV and PLR values between the genders.

Limitations of our study are as follows; the number of the patients was relatively low and we did not perform any comparison with other systemic therapies. Multicenter and prospective studies with higher number of patients are needed in the future.

As conclusion, we revealed in our study that there was no significant change in MPV and CRP values before and after ustekinumab in patients with moderate and severe psoriasis vulgaris, however, that a significant decline was recorded in NLR and PLR values after the patients responded to the therapy. Although there are many studies that correlate these indicators with disease activity, there are few studies on post-treatment values. These markers are cost effective predictors that can easily be measured in routine practice. NLR and PLR can also be used while following up the course of the disease to evaluate the inhibition of systemic inflammation especially after the therapy. Further studies are needed for the use of these new biomarkers in proper management of psoriatic patients.

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

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Contributions of the authors to the article

B.T. is the lead scientist who initiated the study. B.T. and B.M. developed the theory and edited the material method section. E.V. evaluated the data in the results section, and S.A. acted as the theoretical consultant. In addition, all authors discussed the entire study and confirmed its final version.