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Systemic immune-inflammation index and other inflammatory parameters in patients receiving biological or targeted synthetic DMARDs for inflammatory rheumatic disease

Halise Hande GEZER[1], Ozlem PEHLIVAN[1]

[1] Rheumatology Clinic, Umraniye Training and Research Hospital, Istanbul, Turkey.

Corresponding Author: Halise Hande GEZER
E-mail: hande_snc@hotmail.com

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ABSTRACT

Objective: To investigate the short – and long-term dynamics in inflammation markers [systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/ monocyte ratio (LMR)] before and after biological disease-modifying antirheumatic drugs (bDMARD) or targeted synthetic DMARD (tsDMARD) treatment.

Patients and Methods: Two hundred twenty-six patients (115 women, 47±13.8 years) were included. Age, gender, disease duration, and treatments were recorded retrospectively. Complete blood counts including neutrophil, lymphocyte, platelet, monocyte and acute phase reactants were noted at the visit before the biological treatment, at the 3rd month, 6th month, and the last visit on medication. SII, NLR, PLR and LMR were calculated, and their dynamics over time were compared.

Results: Significant changes were observed over time in all parameters reflecting inflammation (SII, NLR, PLR, LMR, ESR, and CRP) ($p<0.05$). In the correlation analysis of changes at baseline and six months, significant correlations with ΔESR were observed with ΔCRP, ΔPLR, ΔSII and ΔNLR ($p<0.05$), but no correlation with LMR was detected. Also, significant correlations with ΔCRP were noted with ΔNLR, ΔSII, ΔPLR, and ΔLMR ($p<0.05$).

Conclusion: Significant and favourable changes were observed in all inflammatory parameters after treatment, and this variation remained stable as long as the drug was continued.

Keywords: Inflammation, Systemic immune inflammation index, Biological treatment

1. INTRODUCTION

In inflammatory rheumatic diseases, acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) increase with cytokines, including TNF-α and IL-6. ESR and CRP are valuable markers for discriminating inflammatory rheumatic disease from non-inflammatory conditions and also have an essential role in the follow-up of the treatment response and disease activity [1].

In the presence of inflammation, leukocytes, platelets, ferritin and CRP increase, while parameters such as albumin decrease. With the release of cytokines, chemokines, and reactive oxygen derivatives, neutrophils, monocytes, and macrophages migrate to the site of inflammation, and the platelets are displaced from the bone marrow to the periphery, so the proportions of hemogram parameters change [2]. In recent years, new parameters reflecting inflammation apart from ESR and CRP were proposed from the blood cell counts ratio based on the knowledge that blood cell interactions are essential in the pathogenesis of inflammation and immune responses [3]. Of these, the neutrophil-lymphocyte ratio (NLR) is the most commonly used parameter, that was first proposed as an inflammatory marker after recognising that cancer patients sustained neutrophilia with lymphocytopenia, and then several studies showed its association with the poor prognosis in inflammatory rheumatic diseases, cancers, and neurological disease [4-6]. It has been stated that NLR regresses with inflammatory disease treatment and is an independent cardiovascular risk factor in patients with psoriasis [7]. In addition to NLR, platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and mean platelet volume (MPV) are the other parameters reflecting inflammation [8]. Although, these parameters reflect inflammation, different results have been seen in various diseases. In renal disease, PLR was a better marker than NLR in terms of inflammation [9].

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Recently, the composite systemic immune-inflammation index (SII), which was developed to include most of these parameters and is thought to reflect inflammation better, has been created. Geng et al., suggested that SII is a new and simple prognostic predictor for cancer patients and is superior to the other systemic inflammation index, including PLR, NLR, and LMR, reflecting the balance between host inflammatory and immune response status [10].

This study aimed to seek i) the short – and long-term change of NLR, PLR, LMR, and SII with the biological disease-modifying antirheumatic drugs (bDMARD) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARD), ii) the relationship of these parameters with the most commonly used inflammatory parameters including ESR and CRP, and iii) the predictive role of these scores concerning the treatment switch.

2. PATIENTS and METHODS

Study design and patients

We retrospectively reviewed the medical records of 226 patients with bDMARD or tsDMARD treatment for at least six months from January 2015 to April 2022 at Umraniye Training and Research Hospital, Istanbul. Patients with incomplete data, pregnancy, malignancy and acute and chronic infection during the investigation were excluded from the study.

The study protocol was approved by the Ethical Committee of Umraniye Training and Research Hospital (Number:21/04/2022.146). Informed consent was waived because of the retrospective nature of the study.

Clinical Data and Medications

Patient characteristics were recorded, including age, gender, body mass index (BMI, kg/m2), disease duration, and treatment duration. The inflammatory rheumatic disease was noted and categorised as rheumatoid arthritis (RA), psoriatic arthritis (PsA), other spondyloarthritis (SpA) (axial SpA, peripheral SpA, enteropathic SpA), vasculitis (Behcet's disease, Takayasu's arteritis, Cogan's syndrome), autoinflammatory diseases [familial Mediterrean fever (FMF)], connective tissue diseases [systemic lupus erytematosus (SLE), sjogren, systemic sclerosis)], and adult Still's disease.

Infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab were classified as anti-TNF-α treatments that inhibit the activity of central proinflammatory cytokines TNF-α. Tocilizumab is an inhibitor of the cytokine interleukin-6, and abatacept is a selective modulator of the T-lymphocyte activation pathway. Rituximab was classified as B-cell-targeted therapy, secukinumab as an IL-17 inhibitor, and anakinra and canakinumab as IL-1 inhibitors [11]. Tofacitinib is a targeted, small-molecule inhibitor of JAK1 and JAK3 [12]. TNF-α inhibitors, tocilizumab, abatacept, rituximab, and secukinumab were classified as bDMARD and tofacitinib as tsDMARD. The patients' treatments at the first two visits and, if treatment changed because of unresponsiveness or side effects, at the last visit on medication were noted.

Laboratory Data and Inflammatory Markers

We collected laboratory data, including complete blood counts [white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts], ESR, and CRP before the administration of bDMARD or tsDMARD treatment (baseline), at 3rd month, 6th month, and the last visit on medication.

The NLR and PLR were calculated by dividing the neutrophils and platelets by the lymphocyte count, respectively. The normal NLR range was defined as an NLR score of 1-2, with higher scores indicating low inflammation (2-3), moderate inflammation (3-7), and severe inflammation (>7) [13]. LMR was also calculated according to the lymphocyte count ratio to monocyte count. The SII was calculated from the platelet, neutrophil, and lymphocyte counts using the following formula: SII = platelet×neutrophil/lymphocyte counts [14].

Changes between baseline and six months were analysed for all parameters (ΔSII, ΔNLR, ΔPLR, ΔLMR, ΔESR, ΔCRP). We defined Δ as the difference between inflammatory parameter levels on baseline and six months.

Statistical Analysis

Categorical variables were expressed as percentages, while continuous variables as means (±) or medians [interquartile range (IQR)]. Kolmogorov–Smirnov test was used to verify the normality of the distribution. The chi-squared test (Fischer's exact test when expected numbers were below five) was used for qualitative data. Friedman test was used to compare four consecutive measures of variables, followed by a Tukey posthoc test for pair-wise comparisons. The correlation of the changes between baseline and six months (ΔSII, ΔNLR, ΔPLR, ΔLMR, ΔESR, ΔCRP) with each other was examined by Spearman's test. Receiver operating characteristic (ROC) analysis was performed to evaluate the impact of SII on the treatment switch. The level of significance was set as $p < 0.05$. Data were processed using the Statistical Package for Social Sciences Software (SPSS v22.00. Armonk, IBM Corp).

3. RESULTS

Demographic and Clinical Data

A total of 226 patients with bDMARD or tsDMARD were included in the study. The mean age of the patients was 47±13.8 years, and 115 (51.1%) of the patients were female. While the mean disease duration was 120±8.9 months, the mean bDMARD or tsDMARD treatment duration were 49.8±30.3 months. While 43.8% of patients were using corticosteroids at baseline, this rate decreased 28.7% at the last visit. Table I represents the patient's demographic and clinical characteristics.

The mean NLR was 2.66±1.7, indicating normal and increased inflammation in 39.8% and 60.2% of the patients. Of 136 patients

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with increased inflammation, 75 (33.2%) had mild inflammation, 55 (24.3%) moderate, and 6 (2.7%) severe inflammation. Of the six patients with severe inflammation, five were RA, and one was Takayasu arteritis; in terms of treatment, three were on anti-TNF, one was tofacitinib, and one was tocilizumab.

Table I. *Demographic and clinical characteristics of patients with biological treatment (n=226)*

Demographic data	Patients	
Age, years	47 (13.8)	
Female gender	115 (51.1%)	
Disease characteristics		
Disease duration, months	120 (8.9)	
Treatment duration, months	49.8 (30.3)	
Disease		
Rheumatoid arthritis	83 (36.7%)	
Psoriatic arthritis	29 (12.8%)	
Spondyloarthritis excluding PsA	101 (44.7%)	
Vasculitis	5 (2.2%)	
Connective tissue disease	4 (1.7%)	
Hereditary Mediterranean Fever	3 (1.3%)	
Adult onset Still's disease	1 (0.4%)	
bDMARD and tsDMARD received		
	First two visits	**Last visit**
Anti-TNF treatment	168 (74.3%)	167 (73.9%)
Infliximab	6 (2.7%)	9 (4%)
Etanercept	33 (14.6%)	29 (12.8%)
Adalimumab	55 (24.3%)	55 (24.3%)
Golimumab	44 (19.5%)	41 (18.1%)
Certolizumab pegol	30 (13.3%)	33 (14.6%)
Tocilizumab	6 (2.7%)	2 (0.9%)
Rituximab	11 (4.9%)	21 (9.3%)
Abatacept	7 (3.1%)	3 (1.3%)
Tofacitinib	23 (10.2%)	17 (7.5%)
Secukinumab	8 (3.5%)	13 (5.8%)
Anakinra	3 (1.3%)	3 (1.3%)

Data are presented as mean (SD) or n (%)

While there was no difference in NLR, SII, MLR, and CRP values between genders, females had higher ESR (P<0.001) and lower PLR (p=0.01) than males.

When we classified the patients as RA and SpA and compared the basal inflammatory parameters, ESR and NLR were significantly higher in patients with RA than in SpA (p <0.05). Table II represents the basal parameters according to the disease groups.

Table II. *Comparison of basal inflammatory parameters in rheumatoid arthritis and spondyloarthritis patients*

	Rheumatoid arthritis (n=83)	Spondyloarthritis (n=130)	P
SII (x109/L)	755.389 (476.135)	676.677 (492.469)	0.08
NLR	2.36 (1.78)	2.13 (1.1)	0.03
PLR	143 (80.9)	126 (62.8)	0.22
LMR	4.18 (2.75)	4.44 (1.92)	0.52
ESR (mm/h)	40 (36)	31 (35)	0.01
CRP (mg/L)	21 (36.5)	14 (32.5)	0.69

SII: Systemic immune inflammation index, PLR: platelet-neutrophil ratio, LMR: Lymphocyte-monosite ratio, NLR: neutrophil-lymphocyte ratio, ESR: erytrocyte sedimentation rate, CRP: C-reactive protein. Data are presented as median (IQR). Bold indicates statistically significant difference

Time-dependent variation was significantly different in all parameters (p<0.05). A significant change was observed after the treatment compared to the baseline, and no difference was observed in the follow-ups after the treatment (Table III). In Fig. I, the dynamics of inflammatory parameters are shown graphically.

Table III. *Inflammatory parameter dynamics in patients treated with bDMARD or tsDMARD*

Parameters	Pre-treatment 1	After treatment (3rd month) 2	After treatment (6th month) 3	Last visit 4	P	Pairwise comparisons* P
SII (x10⁹/L)	705.719 (876.458)	497.453 (323.540)	483.199 (362.803)	543.420 (381.318)	**<0.001**	1 vs 2: <0.001 1 vs 3: <0.001 1 vs 4: <0.001
NLR	2.25±1.39	1.84 (0.86)	1.9 (1.12)	1.95 (1.2)	**<0.001**	1 vs 2: <0.001 1 vs 3: <0.001 1 vs 4: 0.001
PLR	127 (69)	121 (50.3)	116 (50.2)	114 (52.9)	**<0.001**	1 vs 2: <0.001 1 vs 3: <0.001 1 vs 4: <0.001
LMR	4.36 (2.18)	4.34 (2)	4.35 (2.38)		**0.004**	1 vs 2: 0.004 1 vs 3: <0.001
ESR (mm/h)	35 (36)	20 (17)	20 (18)	23 (18.8)	**<0.001**	1 vs 2: p<0.001 1 vs 3: p<0.001 1 vs 4: p<0.001 2 vs 4: <0.001
CRP (mg/L)	16.5 (34)	6 (9.92)	5 (8.3)	9.7 (1.4)	**<0.001**	1 vs 2: p<0.001 1 vs 3: p<0.001 1 vs 4: p<0.001

SII: Systemic immune inflammation index, PLR: platelet-neutrophil ratio, LMR: Lymphocyte-monosite ratio, NLR: neutrophil-lymphocyte ratio, ESR: erytrocyte sedimentation rate, CRP: C-reactive protein.
Data are presented as median (IQR). Bold indicates statistically significant difference.
** Friedman Test with Tukey Multiple Pairwise Comparisons*

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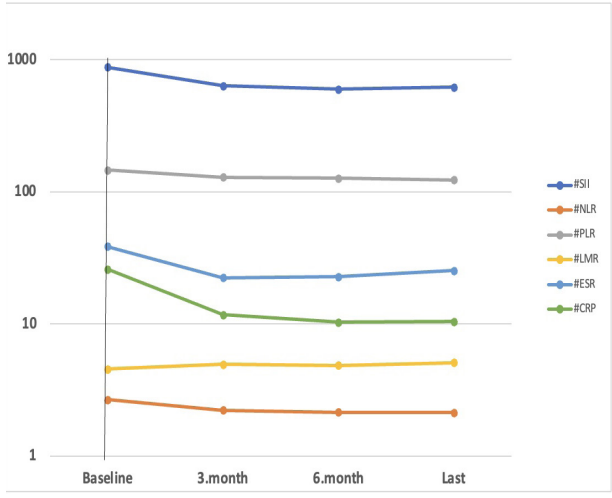

Figure 1. *SII, NLR, PLR, LMR, ESR, and CRP dynamics in patients receiving biological and targeted synthetic DMARDs*

Table IV shows the correlation of changes in inflammatory parameters in the first six months. ΔESR showed a positive correlation with ΔCRP, ΔSII, ΔPLR, and ΔNLR ($p<0.05$). There was no correlation between ΔESR and ΔLMR ($p>0.05$). Also, ΔCRP showed a positive correlation with ΔESR, ΔSII, ΔNLR, Δand PLR and a negative correlation with ΔLMR ($p<0.05$).

Table IV. *Correlations of change in inflammatory parameters at six months*

		ΔSII	ΔNLR	ΔPLR	ΔLMR	ΔESR	ΔCRP
ΔSII	Spearman' rho p-value	-					
ΔNLR	Spearman' rho p-value	**0.906** <0.001	-				
ΔPLR	Spearman' rho p-value	**0.703** <0.001	**0.607** <0.001	-			
ΔLMR	Spearman' rho p-value	**-0.487** <0.001	**-0.539** <0.001	**-0.498** <0.001	-		
ΔESR	Spearman' rho p-value	**0.316** <0.001	**0.249** <0.001	**0.337** <0.001	**-0.121** 0.06	-	
ΔCRP	Spearman' rho p-value	**0.467** <0.001	**0.385** <0.001	**0.292** <0.001	**-0.221** 0.001	**0.504** <0.001	-

SII: Systemic immune inflammation index, PLR: platelet-neutrophil ratio, LMR: Lymphocyte-monosite ratio, NLR: neutrophil-lymphocyte ratio, ESR: erytrocyte sedimentation rate, CRP: C-reactive protein

At least two bDMARD or tsDMARD were used in 79 patients, 147 continued with the first biologic therapy, and the median treatment switch number was 1 (range:1-4). The ROC curve evaluated the predictive value of the SII, NLR, PLR, and LMR for treatment switch by comparing the AUC area. While, no significant results were found in the whole patient group, the analysis was repeated only with RA and PsA patients since there may not be an acute phase elevation in disease activity in axial spondyloarthritis. The AUC of the SII, NLR, PLR, and LMR for treatment switch in RA and PsA were 0.531, 0.506, 0.512, and 0.480, respectively (Fig. II), indicating that SII is superior to other inflammatory parameters. The optimal cut-off value of baseline SII to predict treatment switch was>$648x10^9$, with 65% sensitivity and 52% specificity (95% confidence interval 1.013–1.986, p =0.04).

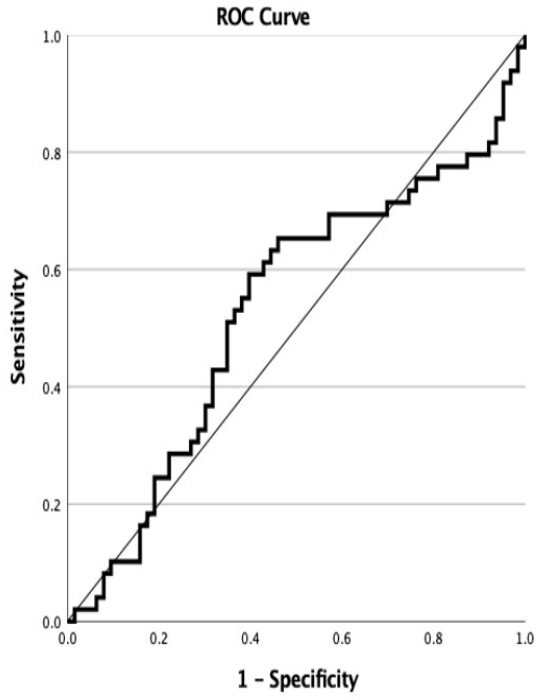

Figure 2. *Receiver operator characteristic (ROC) curve of systemic immune inflammation index (SII) for predicting treatment switch in patients with rheumatoid arthritis and psoriatic arthritis.*

4. DISCUSSION

Although, several clinical studies have investigated inflammatory parameters in rheumatic patients, information on the change of these parameters, especially SII, is lacking after the new treatments bDMARD and tsDMARD. Therefore, we performed a clinical retrospective study to evaluate the dynamics of these parameters in a population of different patient groups and found that NLR, SII, and PLR decreased within three months of initiation of treatment and remained stable at reduced levels for at 6^{th} months and as long as the drug was continued; similarly, LMR increased dramatically at three months and remained stable. These results demonstrate a rapid and significant reduction in inflammation parameters under bDMARD or tsDMARD treatment.

Rheumatic diseases are associated with systemic inflammation and elevated acute phase reactants. In clinical practice, ESR and CRP have frequently used parameters reflecting inflammation

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and response to therapy [15]. Usually, high ESR, leukocytosis, left shift, anaemia, and thrombocytosis have diagnostic value in predicting inflammatory or infectious diseases. Apart from these tests, new markers have been developed recently from hemogram parameters. NLR was the first identified marker reflecting inflammation and was defined by the rapidly increasing neutrophils and the oppositely decreased lymphocytes in sepsis. The opposite changes in neutrophil and lymphocyte counts are a multifactorial and complex dynamic process depending on the regulation of various immunologic, neuroendocrine, humoral and biologic processes such as margination/emargination, mobilisation/redistribution, accelerated/delayed apoptosis, the influence of stress hormones and sympathetic/parasympathetic imbalance of the vegetative nervous system [13]. It has started to be used in many fields after its importance in the diagnosis and treatment follow-up in sepsis. High NLR values are associated with severe inflammation, cancer, injury, trauma or major surgery and mark the worsening prognosis regarding morbidity or mortality. Ahn et al., showed that NLR reflects vasculitis activity and suggest that physicians should pay more attention to patients with NRL at diagnosis ≥5.9 in terms of relapse [16]. In a study in RA, Uslu et al., showed that the mean NLR was 2.1, which was higher than healthy controls, and NLR was correlated with disease activity [17]. In our study, NLR was found to be 2.6 higher than these values since, our patient population was high disease activity requiring biological treatment. Although, no study was conducted on patients receiving biological therapy for the active rheumatic disease similar to our patient group, the mean NLR was 2.9 in psoriasis patients receiving biological treatment for severe disease [7].

As NLR is a parameter indicating inflammation, it is a risk factor in cardiovascular diseases. It has been shown that all-cause mortality and coronary heart disease increase above the cut-off point of ≥ 2.15 [18]. Although, we did not evaluate the cardiovascular morbidity and mortality of the patients, our baseline NLR ratio was 2.6. It decreased to 2.2 in the 3rd month and 2.1 in the 6th month, which means these patients are at risk for cardiovascular diseases. There is a significant decrease in NLR with biological therapy, which may benefit cardiovascular diseases.

Biological therapies provide both symptomatic relief and functional improvement by reducing inflammation. Change in ESR and CRP with biological treatment is known and expected, but NLR reflecting inflammation has recently been used frequently to evaluate the treatment effect. In a study showing the change of NLR after a biological therapy in psoriasis, a rapid and significant decrease was observed in the first three months, and significantly lower levels were sustained throughout the following treatment years, which is in agreement with our results [7].

In addition to neutrophils and lymphocytes, monocytes play an essential role in inflammation. They accumulate in the vessel wall, transform into macrophages, and contribute to the release of proinflammatory cytokines. Decreased lymphocytes and increased monocytes in inflammation cause a decline in the LMR ratio. With the reduction of inflammation with treatment, the LMR ratio is expected to increase, as in our study [2].

Platelet-lymphocyte ratio is another parameter revealing shifts in platelet lymphocyte counts in several conditions, including inflammatory disease, thrombotic states and malignancy. Undulations in platelet counts in rheumatic diseases imply nonspecific inflammatory thrombopoiesis, with the release of reactive cells from the bone marrow to the bloodstream, migration to and excessive consumption at inflammatory websites, and their destruction via binding to anti-platelet antibodies [3]. One of the areas where thrombocytosis and PLR are most useful for diagnosis is large-vessel vasculitis, especially temporal arteritis. In a study involving 537 patients, thrombocytosis rate was observed in patients diagnosed with temporal arteritis with positive temporal artery biopsy. It was stated that thrombocytosis is an essential clue in diagnosing temporal arteritis [19, 20]. The shift in this parameter generally correlates with other inflammatory markers reflecting systemic inflammation. When PLR and NLR were evaluated together, it showed an increase in platelets and neutrophils and a decrease in lymphocytes in the active RA [21]. In our study, PLR correlated with all other inflammatory parameters and had a high correlation with NLR, the most frequently investigated and used parameter for inflammation. Although, many studies have evaluated these parameters in inflammatory diseases, there are few researches on their fluctuations after anti-inflammatory treatment. There are only four small studies evaluating PLR. In one of these, a significant decrease in PLR and DAS28 was observed after rituximab treatment [22], and in the other research, a substantial reduction in both PLR, NLR and CRP was observed after bDMARD treatment in PsA [23]. In another study in ankylosing spondylitis, platelet count was correlated with disease activity, and anti-TNF treatment decreased the platelet count. In regression analysis, a high platelet count may predict a poorer response to anti-TNF-α therapy [24]. Similar to our results, in the last study conducted in 2020, NLR, PLR, MPV and CRP decreased after the biological treatment, including infliximab, etanercept, adalimumab and ustekinumab, and this result was independent of drug [8]. Our baseline PLR ratio was 146, which decreased significantly over time to 129 in the 3rd month and 127 in the 6th month. Platelet-lymphocyte ratio also reflects atherosclerosis by showing inflammation like NLR. Active platelets and interactions of platelets with other cells could initiate inflammation in the arterial wall, thus partially explaining atherosclerosis associated with chronic inflammation [25].

The systemic immune inflamation index is a novel biomarker including neutrophils, platelets, and lymphocyte count. Although, there are a few studies on rheumatic diseases, it is essential, especially in determining the prognosis in malignancies, including renal, lung, prostate and oesophagus cancer. SII is vital in prognosis because of neutrophils' role in regulating angiogenesis, chemokine and cytokine release, and the production of chemokines and cytokines from platelets in metastases of malignancies [26]. SII has been evaluated in rheumatic diseases, including RA, PsA, Still's disease, and

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vasculitis, but post-treatment results were not analysed in these studies [14, 27-30]. To the best of our knowledge, this is the first study to evaluate SII in response to immunosuppressive therapy in rheumatic diseases. Similar to other parameters, SII decreased significantly at three months and remained stable at reduced follow-up levels. The change at six months was also significantly correlated with other parameters. The ROC analysis for its role in predicting switches in biological therapy was superior to other parameters. Although, low sensitivity and specificity, SII≥ $648x10^9$ at baseline can predict the treatment switch in RA and PsA. In Behçet disease, SII was significantly higher in the active patients and determined a cut-off value of 552.12 for SII with relatively high sensitivity and specificity. CRP is a commonly used test to evaluate disease activity in clinical practice. The marker most associated with a change in CRP at six months was ESR and then SII, followed by NLR. [30].

There may be some possible limitations in this study. The first was that it was a single-center, retrospective study. The other was that the confounding effect of additional rheumatic drugs could not be evaluated because patients in the SpA group generally received only bDMARD treatment, while other patients such as RA, PsA and SLE often received additional csDMARD or steroid treatment.

In conclusion, significant changes were observed in all inflammatory parameters after treatment, and this change remained stable as long as treatment continued. SII, NLR, LMR and PLR are simple and cheap markers. They may be seen as valuable markers for demonstrating systemic inflammation in rheumatic disease and may also indicate treatment response.

Compliance with Ethical Standards

Ethical Approval: The study protocol was approved by the Ethical Committee of Umraniye Training and ResearcHospital (Number:21/04/2022.146). Informed consent was waived because of the retrospective nature of the study.

Financial Support: No special funding was obtained.

Conflict of Interest Statement: There is no conflict of interest.

Authors' Contributions: HHG, OP: Idea/ Concept, HHG: Design, OP: Control/Supervision. HHG, OP: Data Collection and processin, . HHG, OP: Analysis, HHG, OP: Literature review. HHG, OP: Critical review. Both authors approved the final version of the article.

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