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RESEARCH ARTICLE

Investigation of The Anti-İnflammatory Effect of İsotretinoin in Patients with Acne Vulgaris, A New İndicator: Systemic İnflammation Aggregate İndex

Akne Vulgaris Hastalarında İzotretinoinin Antiinflamatuar Etkisinin Araştırılması, Yeni Bir Gösterge: Sistemik İnflamasyon Agregat İndeksi

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ABSTRACT

Objective: Acne vulgaris is a chronic inflammatory skin disease, and isotretinoin. The vitamin A derivative, is widely used in its treatment. The effects of isotretinoin on systemic inflammation remain controversial. Neutrophil-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), systemic immune-inflammatory index (SII), and total index of systemic inflammation (AISI) are inexpensive and easily calculated biomarkers derived from complete blood counts. These markers are used to assess the presence of inflammation in systemic and dermatological inflammatory diseases. This study aimed to evaluate changes in these markers during isotretinoin therapy in acne vulgaris.

Materials and Methods: The study included 183 patients receiving isotretinoin. Complete blood counts were retrospectively recorded at 0, 3, and 6 months, and NLR, SII, SIRI, and AISI values were analyzed.

Results: The absolute neutrophil count decreased at 6 months compared to baseline (p=0.032), and the lymphocyte count increased at 3 and 6 months (p=0.003 and p=0.043, respectively). The platelet count increased at the end of the 3rd month and decreased at the end of the 6th month compared to baseline (p=0.002, p=0.012, respectively). NLR, SIRI, SII, and AISI values have continued to decrease during treatment, and a significant decrease has observed at the end of the 6th month (p=0.001, p=0.006, p=0.016, p=0.029, respectively).

Conclusion: Systemic isotretinoin therapy in patients with acne vulgaris is associated with significant reductions in NLR, SIRI, SII, and AISI. These findings support the presence of a systemic anti-inflammatory effect of isotretinoin and contribute to the ongoing debate regarding its impact on systemic inflammation.

Keywords: Aggregate index of systemic inflammation, isotretinoin, neutrophil-lymphocyte ratio, systemic inflammatory response index, systemic immune-inflammatory index

ÖZET

Amaç: Akne vulgaris, kronik inflamatuar bir hastalıktır. Bir A vitamini türevi olan izotretinoin, akne tedavisinde yaygın olarak kullanılmaktadır. İzotretinoinin sistemik inflamasyon üzerindeki etkileri literatürde çelişkili sonuçlara sahiptir. Nötrofil-lenfosit oranı (NLR), sistemik inflamatuar yanıt indeksi (SIRI), sistemik immün-inflamatuar indeksi (SII) ve sistemik inflamasyonun toplam indeksi (AISI), tam kan sayımından elde edilen, ucuz ve kolay hesaplanabilen biyobelirteçlerdir ve sistemik ve dermatolojik inflamatuar hastalıklarda inflamasyonun varlığını değerlendirmek için kullanılmaktadır. Bu çalışmanın amacı, akne vulgaris hastalarında izotretinoin tedavisi sırasında bu sistemik inflamatuar belirteçlerdeki değişiklikleri değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya, akne vulgaris tedavisi için izotretinoin tedavisi gören 183 hasta dahil edildi. Tam kan sayımları 0, 3 ve 6. aylarda retrospektif olarak kaydedildi ve NLR, SII, SIRI ve AISI değerleri analiz edildi.

Bulgular: Mutlak nötrofil sayısı, başlangıç değerine kıyasla 6. ayda azaldı (p=0,032) ve lenfosit sayısı 3. ve 6. aylarda arttı (sırasıyla p=0,003 ve p=0,043). Trombosit sayısı, 3. ayın sonunda arttı ve 6. ayın sonunda başlangıç değerine kıyasla azaldı (sırasıyla p=0,002 ve p=0,012). NLR, SIRI, SII ve AISI değerleri tedavi sırasında azalmaya devam etmiş ve 6. ayın sonunda önemli bir azalma gözlemlenmiştir (sırasıyla p=0,001, p=0,006, p=0,016, p=0,029).

Sonuç: Akne vulgaris hastalarında sistemik izotretinoin tedavisi, NLR, SIRI, SII ve AISI'da önemli azalmalarla ilişkilidir. Bu bulgular, izotretinoinin sistemik antiinflamatuar etkisinin varlığını desteklemekte ve sistemik inflamasyon üzerindeki etkisine ilişkin süregelen tartışmaya katkıda bulunmaktadır.

Anahtar Kelimeler: Sistemik inflamasyon agregat indeksi, izotretinoin, nötrofil-lenfosit oranı, sistemik inflamatuar yanıt indeksi, sistemik immün-inflamatuar indeks

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that commonly begins during the second and third decades of life and affects approximately 85% of the population worldwide (1). Clinically, acne is characterized by comedones, papules, and pustules, while severe or untreated cases may result in post-inflammatory hypo- or hyperpigmentation and permanent atrophic or hypertrophic scarring. The etiopathogenesis of acne vulgaris involves four main mechanisms: increased sebum production, follicular hyperkeratinization, Cutibacterium acnes colonization, and inflammation (2). Treatment strategies vary according to disease severity. Topical therapies are generally sufficient for mild acne, whereas systemic treatments are required in moderate to severe cases. Oral isotretinoin is considered the most effective systemic agent, as it targets all major pathogenic mechanisms involved in acne development (3). Despite its well-documented efficacy, isotretinoin is associated with a range of adverse effects involving multiple organs and systems, including xerosis, cheilitis, dry eyes, myalgia, dyslipidemia, photosensitivity, and hepatotoxicity. Additionally, inflammatory conditions such as pancreatitis, inflammatory bowel disease, and arthritis have been reported during isotretinoin therapy (4).

Although acne vulgaris is fundamentally an inflammatory disorder, the impact of isotretinoin on systemic inflammation remains controversial. Previous studies evaluating changes in inflammatory markers during isotretinoin treatment have yielded conflicting results (5,6). Hareedy et al. suggested that isotretinoin may increase systemic inflammatory activity (5), where as Semiz et al. demonstrated a potential anti-inflammatory effect of isotretinoin therapy (6). These inconsistent findings highlight the need for further investigation into the systemic inflammatory effects of isotretinoin.

In recent years, several hematological indices derived from routine complete blood counts have emerged as practical, inexpensive, and reliable markers of systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) have been increasingly used to assess inflammatory burden in various dermatological diseases in which inflammation plays a key role (7–9). The Aggregate Index of Systemic Inflammation (AISI) is a more comprehensive composite marker that incorporates neutrophil, lymphocyte, monocyte, and platelet counts, based on the concept that integrated inflammatory indices provide a more accurate representation of systemic inflammatory status than single parameters alone (7).

To date, there are limited studies evaluating the relationship between isotretinoin therapy and these systemic inflammatory indices. Therefore, the present study aimed to investigate whether systemic inflammation is reduced in patients with acne vulgaris treated with isotretinoin by analyzing changes in inflammatory response markers, with particular emphasis on AISI, alongside NLR, SIRI, and SII.

MATERIALS AND METHODS

The study was designed retrospectively, and included acne vulgaris patients who used isotretinoin between January 2023 and November 2024. Ethics committee approval has been obtained. (2024/5380 ID: 21974). Patients older than 18 years of age who received at least 3 months of isotretinoin 0.5-1 mg/kg/day treatment for acne vulgaris were included in the study. Complete blood count data at the end of the 0th, 3rd and 6th months of treatment were recorded from the patients' files. NLR, SIRI, SII, AISI were calculated using the following formulas.

NLR= neutrophil count /lymphocyte count (×103/μL)

SIRI = neutrophil count x monocyte count/lymphocyte count (×103/μL)

SII = platelet count x neutrophil count/lymphocyte count, (×103/μL)

AISI=neutrophils count x platelets count x monocytes count /lymphocytes count (×103/μL)

Patients with inflammatory, autoimmune or active infectious diseases, malignancy or pregnancy, and those using additional anti-inflammatory drugs or antibiotics in addition to isotretinoin treatment were not included in the study.

The Statistical Package for the Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. Continuous data were expressed as mean ± standard deviation, and the categorical data were expressed as percentages. Kolmogorov– Smirnov test was used to check the distribution of pre-treatment and posttreatment values for normality. Paired sample t-test was used to compare normally distributed values. Statistical significance was described as $p<0.05$.

RESULTS

A total of 183 patients were included in the study, comprising 148 females (80.9%) and 35 males (19.1%). The mean age of the cohort was 26.15 ± 6.61 years (range: 18–45 years). No statistically significant changes were observed in total white blood cell (WBC) counts during isotretinoin treatment. However, the absolute neutrophil count showed a significant decrease at the 6-month follow-up compared with baseline ($p = 0.032$). In contrast, lymphocyte counts significantly increased at both the 3rd and 6th months of treatment ($p = 0.003$ and $p = 0.043$, respectively). Monocyte counts did not demonstrate significant changes throughout the treatment period. Platelet counts exhibited a biphasic pattern, with a significant increase at the 3rd month of treatment followed by a significant decrease at the 6th month compared with baseline ($p = 0.002$ and $p = 0.012$, respectively). Inflammatory indices derived from complete blood count parameters, including the NLR, SIRI, SII, and AISI, demonstrated a progressive decline throughout isotretinoin therapy. Statistically significant reductions in all indices were observed at the end of the 6-month treatment period ($p = 0.001$, $p = 0.006$, $p = 0.016$, and $p = 0.029$, respectively). Detailed laboratory and inflammatory marker

Table 1. Changes in complete blood count and inflammation parameters according to measurement time during the treatment process.

	0. Month	3. Month	6. Month	P1	P2
WBC ($\times10^3/\mu L$)	6.90±1.47	6.99±1.45	6.65±1.36	0.414	0.303
Neutrophils count ($\times10^3/\mu L$)	3.87±1.19	3.84±1.08	3.58±1.01	0.756	0.032
Lymphocyte count ($\times10^3/\mu L$)	2.31±0.55	2.42±0.56	2.35±0.56	0.003	0.043
Monocyte count ($\times10^3/\mu L$)	0.53±0.16	0.53±0.16	0.52±0.14	0.423	0.851
Platelets count ($\times10^3/\mu L$)	283.89±55.75	291.81±53.41	280.70±52.58	0.002	0.012*
NLR	1.76±0.66	1.64±0.51	1.57±0.49	0.022	0.001
SIRI	0.93±0.48	0.88±0.38	0.83±0.35	0.126	0.006
SII	500.05±213.05	478.88±175.79	440.92±151.93	0.157	0.016
AISI	269.71±152.80	258.15±124.23	235.42±109.01	0.310	0.029

WBC: White blood cell NLR: Neutrophil lymphocyte ratio, SIRI: systemic inflammation response index, SII: systemic immune-inflammation index, AISI: Aggregate index of systemic inflammation.
The data are presented with the mean ± standard deviation.
P1: value for the difference between 0th month and 3rd month group
P2: value for the difference between 0th month and 6th month group
*: platelet level decreased at month 6 of treatment compared to month 0.

values are presented in Table 1.

DISCUSSION

In the present study, we demonstrated a significant reduction in inflammatory markers derived from complete blood count parameters during isotretinoin treatment in patients with acne vulgaris. Although isotretinoin is widely and effectively used in the treatment of acne vulgaris, its impact on systemic inflammation remains controversial, with both pro-inflammatory and anti-inflammatory effects reported in the literature (5,6,10,11). Several experimental and clinical studies have supported the immunomodulatory and anti-inflammatory properties of isotretinoin. Dispenza et al. reported that isotretinoin inhibits Toll-like receptor 2 and 4 expression, reduces T helper cell activity, and exerts immunomodulatory effects (11). Similarly, Karadağ et al. demonstrated that isotretinoin decreases the release of pro-inflammatory cytokines such as TNF-α, IL-4, IL-17, and IFN-γ from T lymphocytes, suggesting a regulatory effect on adaptive immune responses (10). In contrast, Hareedy et al. reported increases in erythrocyte sedimentation rate, C-reactive protein, and ferritin levels, acute phase reactants, indicating a potential pro-inflammatory effect of isotretinoin (5). These conflicting findings underline the complexity of isotretinoin's systemic effects and the need for further investigation using accessible inflammatory markers.

Changes in complete blood count parameters and derived inflammatory indices during isotretinoin therapy have been widely studied; however, results remain inconsistent. Ataseven et al. reported a decrease in platelet counts after at least three months of isotretinoin treatment (12), whereas Kutlu et al. observed no significant changes in platelet or neutrophil counts but reported increased lymphocyte counts and decreased NLR values (13). Tamer et al. found an increase in platelet counts, no change in neutrophil or monocyte counts, and a decrease in lymphocyte counts (14). Similarly, Seçkin et al. reported increased platelet counts without significant changes in NLR after at least five months of treatment (15). Önder et al. found a decrease in neutrophil counts but no significant changes in lymphocyte counts, monocyte counts, or NLR (16). In contrast, Hareedy et al. observed decreases in both platelet counts and NLR values (5), while Demirci et al. reported increased platelet counts accompanied by decreased neutrophil counts and NLR after six months of treatment (17). Esen et al. demonstrated no significant changes in lymphocyte, monocyte, or platelet counts but observed a decrease in NLR due to reduced neutrophil counts after at least three months of isotretinoin therapy (18). In our study, platelet counts showed a transient increase at the third month of treatment, followed by a decreasing trend at the sixth month. Concurrently, lymphocyte counts increased, neutrophil counts decreased, and NLR values significantly declined throughout the treatment period. These findings support the hypothesis that isotretinoin exerts a time-dependent modulatory effect on hematological inflammatory parameters.

Recently, multicomponent inflammatory indices derived from routine blood counts have gained increasing attention as prognostic and monitoring tools in various inflammatory diseases (9,19). Turan et al. reported no changes in neutrophil, monocyte, or platelet counts during isotretinoin treatment but observed increased lymphocyte counts and decreased SII values, and also demonstrated that patients with acne vulgaris had higher baseline neutrophil, monocyte, platelet, and SII values compared with healthy controls (20). Çoşansu et al. found increased platelet and lymphocyte counts along with decreased NLR, SII, and SIRI levels after at least three months of isotretinoin treatment. In the same study, platelet counts were higher in patients with acne vulgaris than in healthy controls prior to treatment, while no differences were observed in neutrophil or lymphocyte counts or inflammatory indices between the two groups (21).

AISI, which integrates neutrophil, monocyte, platelet, and lymphocyte counts, has recently emerged as a comprehensive marker of systemic inflammation (22,23). Zorlu et al. demonstrated decreases in neutrophil and monocyte counts after six months of isotretinoin treatment, along with an increase in lymphocyte percentage despite a decrease

in absolute lymphocyte counts. Platelet counts increased, particularly during the early phase of treatment, while SII, SIRI, and AISI values significantly decreased over the treatment course (24). In line with these findings, our study showed a continuous decrease in neutrophil counts during isotretinoin therapy, an early increase followed by a later decline in platelet counts, stable monocyte counts, and increased lymphocyte counts, ultimately resulting in significant reductions in NLR, SIRI, SII, and AISI.

Taken together, our findings suggest that isotretinoin therapy is associated with a systemic anti-inflammatory effect as reflected by multiple hematological inflammatory indices. The observed reductions in composite markers such as AISI, SII, and SIRI may provide a more comprehensive understanding of isotretinoin's immunomodulatory role in acne vulgaris.

Limitation

This study has several limitations that should be acknowledged. First, its retrospective design may limit the ability to establish causal relationships. Second, acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate were not simultaneously evaluated, which may have restricted a more comprehensive assessment of systemic inflammation. In addition, the potential effects of different isotretinoin dosing regimens could not be analyzed. Finally, the absence of a healthy control group precluded direct comparisons between patients with acne vulgaris and the general population. Despite these limitations, we believe that the findings of the present study contribute valuable data regarding the systemic inflammatory effects of isotretinoin therapy. Further well-designed prospective studies incorporating acute-phase reactants, dose–response analyses, and appropriate control groups are warranted to clarify the relationship between isotretinoin treatment, systemic inflammation, and hematological parameters.

CONCLUSION

The findings of the present study indicate that systemic isotretinoin therapy is associated with a significant reduction in blood-count-derived inflammatory markers, including NLR, SII, SIRI, and particularly the Aggregate Index of Systemic Inflammation (AISI), in patients with acne vulgaris. These results support the anti-inflammatory effect of isotretinoin at the systemic level and suggest that composite inflammatory indices may better reflect treatment-related changes than single hematological parameters. Given their low cost, wide availability, and ease of calculation, these indices, especially AISI, may serve as practical tools for monitoring inflammatory response and treatment efficacy in patients receiving isotretinoin therapy. Future prospective studies are warranted to further validate their clinical utility.

DECLARATIONS

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