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Effect of Isotretinoin Treatment on the Inflammatory Markers in Patients with Acne Vulgaris: A Case-Control Study

İzotretinoin Tedavisinin Akne Vulgarisli Hastalarda İnflamatuar Belirteçler Üzerine Etkisi: Bir Olgu Kontrol Çalışması

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ABSTRACT Objective: Oral isotretinoin can affect inflammation markers in patients with acne vulgaris. This study aims to examine the impact of isotretinoin treatment on inflammatory markers in patients diagnosed with acne vulgaris. **Material and Methods:** Fifty-five patients diagnosed with moderate or severe acne vulgaris according to the Global Acne Grading Scale were included in this study. Patients were evaluated at regular intervals (at 0, 2nd, and 3rd months) during the treatment period. Complete blood count [including mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), plateletcrit, platelet distribution width (PDW), platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW)], Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI), monocyte-high-density lipoprotein (HDL) ratio, monocyte-to-lymphocyte ratio (MLR), MPV/platelet ratio, and serum biochemistry panel were assessed during isotretinoin treatment. Additionally, the Acne Quality of Life Scale was used to assess patients' quality of life. **Results:** A significant increase in PLR and RDW levels was observed during isotretinoin treatment ($p<0.05$). However, SII, SIRI, AISI, monocyte/HDL ratio, NLR, PDW, MPV, sedimentation rate, and C-reactive protein levels did not show a significant change during isotretinoin treatment ($p>0.05$). Furthermore, this study demonstrated that oral isotretinoin treatment reduced the severity of acne and improved patients' quality of life. **Conclusion:** Isotretinoin may have inflammatory effects shown with PLR and RDW. However, other inflammatory markers did not show a significant change during isotretinoin treatment. Further comprehensive studies are needed to better understand the relationship between isotretinoin treatment and inflammatory markers.

Keywords: Isotretinoin; inflammatory markers; acne vulgaris

ÖZET Amaç: Oral izotretinoin, akne vulgarisli hastalarda inflamasyon belirteçlerini etkileyebilir. Bu çalışma, izotretinoin tedavisinin akne vulgarisli hastaların inflamatuar belirteçleri üzerindeki etkilerini incelemeyi amaçlamaktadır. **Gereç ve Yöntemler:** Bu çalışmaya, Global Akne Derecelendirme Ölçeği'ne göre orta veya şiddetli akne vulgarisi tanısı alan 55 hasta dâhil edildi. Hastalar, tedavi başlangıcında ve tedavi süresince düzenli aralıklarla (0, 2 ve 3. aylarda) değerlendirildi. Tam kan sayımı [ortalama trombosit hacmi (mean platelet volume "MPV"), nötrofil-lenfosit oranı (neutrophil-to-lymphocyte ratio "NLR"), plateletkrit, trombosit dağılım genişliği (platelet distribution width "PDW"), trombosit-lenfosit oranı (platelet-to-lymphocyte ratio "PLR"), kırmızı hücre dağılım genişliği (red cell distribution width "RDW")], Sistemik İmmün-İnflamasyon İndeksi (Sİİ), Sistemik İnflamasyon Yanıt İndeksi [Systemic Inflammation Response Index (SIRI)], Toplu Sistemik İnflamasyon İndeksi [Aggregate Index of Systemic Inflammation (AISI)], monosit-yüksek yoğunluklu lipoprotein [high-density lipoprotein (HDL)] oranı, monosit-lenfosit oranı [monocyte-to-lymphocyte ratio (MLR)], MPV/trombosit oranı ve serum biyokimya paneli, izotretinoin tedavisi süresince değerlendirildi. Ayrıca, hastaların yaşam kalitesini değerlendirmek için Akne Yaşam Kalitesi Ölçeği kullanıldı. **Bulgular:** İzotretinoin tedavisi sırasında PLR ve RDW seviyelerinde anlamlı bir artış tespit edildi ($p<0,05$). Ancak, Sİİ, SIRI, AISI, monosit/HDL oranı, NLR, PDW, MPV, sedimantasyon hızı ve C-reaktif protein düzeyleri izotretinoin tedavisi sırasında anlamlı bir değişiklik göstermedi ($p>0,05$). Ayrıca, bu çalışma, oral izotretinoin tedavisinin akne şiddetini azalttığını ve hastaların yaşam kalitesini iyileştirdiğini göstermiştir. **Sonuç:** İzotretinoin, PLR ve RDW ile gösterilebilen inflamatuar etkilere sahip olabilir. Ancak, izotretinoin tedavisi sırasında diğer inflamatuar belirteçlerde belirgin bir değişiklik gözlenmemiştir. İzotretinoin tedavisi ile inflamasyon belirteçleri arasındaki ilişkiyi daha iyi anlamak için daha fazla kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İzotretinoin; inflamatuar belirteçler; akne vulgaris

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Acne vulgaris is a chronic inflammatory disease affecting the pilosebaceous unit stimulated by various pathophysiological mechanisms.[1] The existence of inflammation has been evidenced in all stages of acne lesions. This is supported by immunological, histological, and clinical evidence. Immunological mechanisms underlying the initiation and perpetuation of inflammation in acne may be associated with interactions involving inflammatory mediators such as Cutibacterium acnes, defensins, cytokines, peptidases, neuropeptides, as well as serum lipids and their receptors.[2]

Acne vulgaris is an inflammatory disease, playing a central role in the pathogenesis of inflammation.[3] Elevated activity of interleukin-1 (IL-1), a proinflammatory cytokine, is observed prior to the initiation of follicle hyperproliferation and stimulates the proliferation of keratinocytes.[4] PLT kappa beta regulates various cytokines including IL-10, IL-8, IL-1, and tumor necrosis factor (TNF)-α, and it has been observed that the expression levels of these genes are higher in skin affected by acne compared to adjacent healthy skin. Inflammatory acne lesions exhibit increased levels of several proinflammatory cytokines, such as IL-8, matrix metalloproteinases, granulysin, and β-defensin-4.[5]

Acne is treated with oral isotretinoin (13 cis-retinoic acids) for a very long time. It is the only agent that targets all major etiological factors contributing to the development of acne. It inhibits sebum production, prevents the formation of comedones, and diminishes Cutibacterium acnes colonization on the skin.[6] Moreover, oral isotretinoin exhibits anti-inflammatory effects. Its anti-inflammatory properties are grounded in several mechanisms. It reduces the expression of toll-like receptor 2 in monocytes. It inhibits neutrophil migration and inflammatory Th17 cells while strengthening regulatory T-cell responses. Additionally, it induces the production of IL-10, an anti-inflammatory cytokine.[7]

Complete blood counts (CBC) have been used as a marker of inflammation in recent years. Since 2014, the Systemic Immune-Inflammation Index (SII), particularly in cancer and other diseases, has been employed as a predictive factor. The three primary components of the total blood count are included (neutrophils X platelets/lymphocytes). An increase in this index has been associated with higher inflammatory response and worse prognosis of diseases in previous studies.[8] The Systemic Inflammation Response Index (SIRI) includes three primary components of the total blood count (neutrophils X monocytes/lymphocytes). In some malignancies, It has been utilized to determine prognosis and assess response to treatment.[9,10] Aggregate Index of Systemic Inflammation (AISI) is calculated from four main parameters of the CBC (neutrophils X monocytes X platelets/lymphocytes). It was used to predict prognosis in idiopathic pulmonary fibrosis.[11] The Association of neutrophil/lymphocyte ratio with various chronic diseases has been demonstrated.[12] Neutrophil-to-lymphocyte ratio (NLR) has been demonstrated to correlate with inflammation and disease severity in psoriasis and Behçet's disease.[13,14] In a number of chronic conditions, the mean platelet volume (MPV) value has been utilized as a marker of inflammation.[15] Platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and MPV/platelet levels have all been utilized to determine the severity of the disease and prognosis in sepsis patients.[16] The Monocyte to high- density lipoprotein (Monocyte/HDL) ratio has been investigated in the context of cigarette smoking, and cardiovascular events in patients with chronic renal disease, an autoinflammatory condition. Studies have demonstrated its utility as an inflammation marker.[17,18] Plateletcrit (PCT) and platelet distribution width (PDW) values have been correlated with disease activity and considered as markers of inflammation in rheumatoid arthritis.[19]

Treatment with oral isotretinoin and its impact on inflammatory markers NLR, PLR, monocyte/HDL, SII, and SIRI has been examined in previous studies, but to our knowledge, this is the first research that examines prospectively the change in markers with treatment and the first study to examine the change in AISI. The aim of this study is to investigate the isotretinoin medication affects inflammatory markers in acne vulgaris patients.

MATERIAL AND METHODS

The approval of our study was obtained from the Cumhuriyet University Medical Faculty's Ethics Committee (date: July 26, 2022, no: 2022-07/6). The study was conducted in compliance with the Declaration of Helsinki, the Patient Rights Act, and ethical norms. Written informed consent was obtained from all patients.

Fifty five patients with severe to moderate acne vulgaris who were treated with 0.5-1 mg/kg of isotretinoin were evaluated. This was a prospective study conducted. Inflammatory parameters including C-reactive protein (CRP), MPV, PCT, PDW, red cell volume distribution width (RDW), NLR, PLR, Monocyte/HDL, MLR, MPV/Platelet, SII, AISI, and SIRI of receiving isotretinoin treatment acne patients were recorded (Table 1). In addition, other laboratory parameters were assessed, including low-density lipoprotein (LDL) cholesterol, total cholesterol, and HDL cholesterol, as well as mean corpuscular volume (MCV), white blood cells (WBC), hemoglobin (Hb), platelets, hematocrit (HCT), neutrophil, lymphocyte, monocyte, eosinophil, and basophil. The inflammatory and other laboratory parameters of the patients were evaluated at regular intervals (at 0, 2nd, and 3rd months) during the treatment period. Patients with any liver disease, diabetes mellitus, inflammatory disease, active infection, or hematological disease were not included in the study. The Acne Quality of Life Scale (AQOL) was used to evaluate the quality of life and Global Acne Grading System (GAGS) was used to assess acne severity.

STATISTICAL ANALYSIS

The software package IBM® SPSS (Ver: 23.0) based in the USA, was used to analyze the study's data. The Shapiro-Wilk test was applied to assess the normality of variables. Mean±standard deviation was provided for normally distributed variables and median (minimum-maximum) was provided for variables that were not normally distributed. Friedman and Wilcoxon's tests were used for paired group data that were not normally distributed. The paired Student's t-test and Repeated-Measures analysis of variance were used to assess the normally distributed data for the paired groups. A p value of <0.05 was regarded as significant.

RESULTS

In this study, 16 (29.1%) males and 39 (70.9%) females were included in the receiving isotretinoin treatment of acne patients. The patients' mean age was 20.0±3.2 years, and their mean body mass index was 20.6±2.83 kg/m^2.

The mean AQOL and GAGS scores significantly decreased during isotretinoin treatment ($p<0.05$).

The findings of the biochemical and CBC parameters showed that during isotretinoin treatment, the levels of the serum enzymes aspartate aminotransaminase (AST), gamma glutamyl transferase (GGT), total cholesterol, triglycerides, and LDL increased statistically significantly *($p<0.05$)*. However, WBC, Hb, platelets, HCT, MCV, neutrophil, lymphocyte, monocyte, eosinophil, basophil, HDL, and alanine aminotransferase (ALT) levels were no sta-

TABLE 1: Inflammatory indexes and formulas related to inflammatory parameters.

Inflammatory indexes	
Monocyte-to-high-density lipoprotein ratio	Monocyte count/High-density cholesterol count
Monocyte-to-lymphocyte ratio	Monocyte count/Lymphocyte count
Mean platelet volume-to-platelet ratio	Mean platelet volume count/Platelet count
Neutrophil-to-lymphocyte ratio	Neutrophil count/Lymphocyte count
Platelet-to-lymphocyte ratio	Platelet count/Lymphocyte count
Systemic Immune-Inflammation Index	(Neutrophil count X Platelet count)/Lymphocyte count
Aggregate Index of Systemic Inflammation	(Neutrophil count X Monocyte count X Platelet count)/Lymphocyte count
Systemic Inflammation Response Index	(Neutrophil count X Monocyte count)/Lymphocyte count

TABLE 2: Changes of laboratory parameters with isotretinoin treatment.

Variables	Pre-treatment Median (minimum-maximum)	2nd month Median (minimum-maximum)	3rd month Median (minimum-maximum)	References	p value
WBC (x10³/µl)	6.9 (3.7-14.8)	6.5 (3.7-12.1)	6.5 (3.6-13.0)	4-10.5	0.748
Platelet (x10³/µl)	273.0 (2.6-456.0)	283.0 (165.0-456.0)	276.0 (29.7-463.0)	150-450	0.154
Hb (g/dl)	14.0 (9.7-137.0)	13.9 (1.6-17.0)	13.7 (10.1-168.0)	12.5-16	0.900
HCT (%)	41.4 (33.3-52.3)	41.6 (31.1-49.2)	41.3 (32.2-51.8)	37-47	0.754
MCV (fL)	84.3 (23.2-93.5)	84.7 (22.6-94.3)	83.3 (26.0-96.0)	78-100	0.281
Neutrophil (x10³/µl)	3.6 (1.3-11.9)	3.7 (1.6-8.2)	3.4 (1.1-9.11)	2-7.15	0.608
Lymphocyte (x10³/µl)	2.3 (0.5-3.7)	2.2 (1.0-4.8)	2.1 (1.3-4.3)	1.16-3.18	0.152
Monocyte (x10³/µl)	0.5 (0.3-1.0)	0.5 (0.2-1.0)	0.5 (0.3-1.0)	0.29-0.71	0.103
Eosinophil (x10³/µl)	0.1 (0.01-0.8)	0.08 (0.02-3.6)	0.08 (0.01-0.5)	0.03-0.27	0.472
Basophil (x10³/µl)	0.04 (0.01-0.3)	0.04 (0.01-0.3)	0.03 (0.01-0.3)	0.01-0.05	0.451
ALT (U/L)	12.0 (7.0-33.0)	12.0 (3.0-36.0)	14.0 (5.0-78.0)	0-33	0.267
AST (U/L)	16.0 (10.0-49.0)	20.0 (13.0-39.0)	19.0 (14.0-61.0)	0-32	***<0.001*****
GGT (U/L)	10.0 (0.0-24.0)	15.0 (4.0-26.0)	13.0 (7.0-27.0)	6-42	***<0.001*****
Total cholesterol* (mg/dl)	148.9±26.1	166.6±30.6	163.6±26.3	100-200	***<0.001*****
LDL (mg/dl)	81.0 (32.0-154.0)	94.0 (41.0-171.0)	91.5 (0.16-198.0)	40-100	***<0.001*****
HDL (mg/dl)	55.0 (34.0-112.0)	54.0 (33.0-110.0)	52.0 (28.0-97.0)	50-85	0.077
Triglyceride (mg/dl)	65.0 (23.0-232.0)	78.0 (34.0-326.0)	83.5 (35.0-381.0)	40-150	***<0.001*****

*Normally distributed variables are shown as mean±standard deviation;**p<0.05; WBC: White blood cells; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; ALT: Alanine aminotransferase; AST: Aspartate aminotransaminase; GGT: Gamma glutamyl transferase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

tistically significant difference during isotretinoin treatment *(p>0.05)* (Table 2).

Inflammatory markers that CRP, sedimentation, MPV, PCT, PDW, SII, NLR, Monocyte/HDL, MLR, MPV/PLT, SIRI, and AISI levels were no statistically significant difference during isotretinoin treatment *(p>0.05)*. However, PLR and RDW levels were statistically significant increases during isotretinoin treatment *(p<0.05)* (Figure 1) (Table 3).

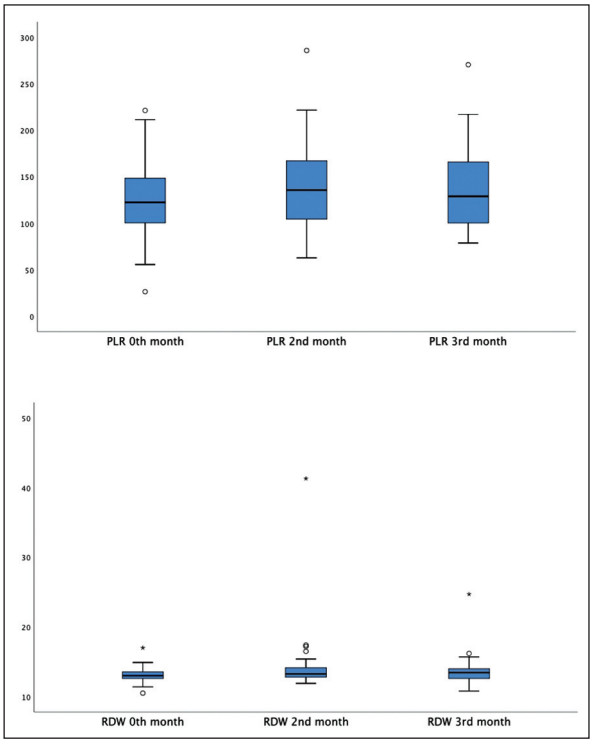

FIGURE 1: Changes of PLR and RDW inflammatory parameters with isotretinoin treatment.
PLR: Platelet to lymphocyte ratio; RDW: Red cell volume distribution width.

DISCUSSION

In this present study, we evaluated the impact of the isotretinoin therapy on inflammatory markers and other laboratory parameters in acne vulgaris patients.

Oral isotretinoin treatment may cause an increase in serum lipids and hepatic enzymes. In previous studies, systemic isotretinoin treatment was associated with an increase in triglycerides, total cholesterol, LDL, and ALT levels.[20,21] Similar to the literature, in this study, a significant increase in LDL, triglyceride, and total cholesterol levels were observed with treatment. AST and GGT levels increased statistically significantly at 3rd months of isotretinoin treatment compared to baseline. The increase in ALT levels during isotretinoin treatment was not statistically significant.

TABLE 3: Changes of inflammatory parameters with isotretinoin treatment.

Variables	Pre-treatment Median (minimum-maximum)	2nd month Median (minimum-maximum)	3rd month Median (minimum-maximum)	p value
CRP	0.6 (0.02-4.1)	0.7 (0.06-118.0)	0.7 (0.1-6.1)	0.187
Sedimentation	5.0 (2.0-27.0)	5.0 (2.0-25.0)	5.0 (2.0-28.0)	0.387
MPV*	10.1±0.8	10.1±0.8	10.1±0.7	0.696
PCT	0.2 (0.09-0.4)	0.2 (0.2-0.4)	0.2 (0.2-0.4)	0.292
PDW	11.3 (8.3-15.9)	11.5 (1.4-16.0)	11.4 (8.3-15.9)	0.989
RDW (%)	13.0 (10.5-17.0)	13.3 (11.9-41.3)	13.5 (10.8-24.7)	***<0.001*****
NLR	1.5 (0.5-7.5)	1.6 (0.5-4.6)	1.5 (0.5-5.96)	0.681
PLR	122.8 (26.3-472.9)	137.0 (62.7-285.9)	129.0 (78.7-270.6)	***0.008*****
Monocyte/HDL	0.01 (0.00-0.61)	0.009 (0.004-0.02)	0.01 (0.0-0.03)	0.792
MLR	0.2 (0.1-0.6)	0.2 (0.1-0.5)	0.2 (0.01-0.4)	0.616
MPV/Platelet	0.03 (0.02-0.6)	0.03 (0.02-0.06)	0.03 (0.0-0.2)	0.35
SII	401.6 (161.5-2337.0)	475.0 (150.0-1463.3)	416.0 (198.2-2308.4)	0.602
SIRI	0.8 (0.2-10.1)	0.9 (0.2-4.3)	0.8 (0.1-3.7)	0.602
AISI	208.3 (1.6-3688.3)	256.1 (66.2-1375.5)	193.8 (26.7-1246.5)	0.492

*Normally distributed variables are shown as mean±standard deviation; **p<0.05; CRP: C-reaktive protein; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; RDW: Red cell volume distribution width; NLR: Neutrophil-to-lymphocyte ratio ; PLR: Platelet lymphocyte ratio; Monocyte/HDL: Monocyte to high-density lipoprotein ratio; MLR: Monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; AISI: Aggregate Index of Systemic Inflammation.

In recent years, research studies have focused on investigating the impact of oral isotretinoin therapy on the CBC. In the study conducted by Özuğuz et al. a significant increase in monocyte levels was shown with oral isotretinoin treatment.[22] Seçkin et al. observed a significant increase in platelet levels with 3-month oral isotretinoin therapy, whereas Ataseven and Ugur Bilgin observed a significant decrease in platelet levels.[23,24] Önder and Ozturk showed a significant decrease in the neutrophil count after 3 months of oral isotretinoin therapy compared to the baseline.[25] However, Hansen et al. reported that oral isotretinoin treatment did not cause any change in CBC parameters.[21] In this study, there was no significant change in neutrophil, platelet, lymphocyte, monocyte, eosinophil, and basophil levels with treatment.

Cosansu et al. retrospectively investigated the anti-inflammatory effect of oral isotretinoin in 156 patient groups receiving oral isotretinoin treatment and 100 healthy control groups.[26] After 3 months of oral isotretinoin treatment, SII and SIRI showed a statistically significant decrease. In another study, in 190 patients receiving oral isotretinoin treatment and 66 healthy controls, the treatment's effects on SII and other inflammatory markers were retrospectively analyzed. Before treatment, SII was found to be significantly higher in the patient group than in the control group. In the third month of treatment, SII was similar to the control group. SII decreased significantly in the group of patients receiving oral isotretinoin treatment.[27] In our study, no statistically significant changes in SII, SIRI, and AISI levels were observed during oral isotretinoin treatment.

Most studies have shown that neutrophil/lymphocyte and platelet/lymphocyte ratios do not change with systemic isotretinoin treatment.[21,23,25] In the study by Tamer et al. it was observed that the platelet/lymphocyte ratio increased significantly with isotretinoin treatment.[28] In another study, it was observed that neutrophil/lymphocyte and platelet/lymphocyte ratios decreased significantly and monocyte/HDL ratio increased significantly after systemic isotretinoin treatment.[29] During systemic isotretinoin treatment of acne vulgaris, there are conflicting results regarding the changes in these inflammatory parameters. A statistically significant increase in platelet/lymphocyte ratio was observed with isotretinoin treatment in present study. However, there was no statistically significant change in neu-

trophil/lymphocyte, monocyte/lymphocyte, monocyte/HDL, and MPV/PLT ratios.

In a study evaluating MPV as an inflammatory marker during isotretinoin treatment, it was shown to decrease significantly with treatment.[28] A study conducted by Ataseven and Ugur Bilgin showed that MPV decreased significantly with treatment.[24] In another study on the effect of oral isotretinoin treatment on hematologic parameters, there was no significant change in MPV value, while RDW increased significantly after the first month of treatment.[30] In another study, an increase was found in RDW, MCV, PLT, MPV, and PCT values, while a decrease was found in neutrophil values with oral isotretinoin treatment.[31] In the current study, a significant increase RDW and PLR values were observed with oral isotretinoin treatment. However, the MPV values did not show a statistically significant change. It is known that isotretinoin reduces IL-4, IL-17, TNF, and interferon gamma levels and is an immunoregulatory and anti-inflammatory drug.[32] In the current study, the effect of isotretinoin on inflammation was evaluated by examining inflammatory parameters. However, there were not found anti-inflammatory effect of isotretinoin during treatment.

In inflammatory diseases, CRP value is used in the follow-up of inflammatory diseases. In a study, patients using oral isotretinoin showed a significant decrease with treatment.[33] In another study, there was no statistical difference in CRP values after 4 months of oral isotretinoin treatment.[34] However, there was a study showing a significant increase in CRP levels with 6 months of oral isotretinoin treatment.[35] In present study, no significant change was observed in CRP levels with treatment. One study showed that sedimentation values increased significantly after 6 months of oral isotretinoin therapy.[35] In present study, no significant change was observed in sedimentation values.

Our study has a number of limitations, such as its single-center design and limited sample size.

CONCLUSION

In conclusion, we prospectively evaluated patients with acne vulgaris using oral isotretinoin showed that oral isotretinoin treatment significantly increased RDW and PLR. Oral isotretinoin treatment did not cause statistically significant changes in neutrophil/lymphocyte, monocyte/HDL, SII, SIRI, and AISI values. There were not found anti-inflammatory effect of isotretinoin during treatment in this study. Treatment with oral isotretinoin and its impact on inflammatory markers NLR, PLR, monocyte/ HDL, SII, and SIRI has been examined in previous studies, but this study is the first to prospectively examine the change in markers with treatment and the first study to examine the change in AISI. To clarify the relationship between systemic isotretinoin treatment and markers of inflammation, further studies are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melih Akyol, Mustafa Tosun, Mahir Dığış;* ***Design:*** *Mahir Dığış, Mustafa Tosun, Rukiye Yasak Güner;* ***Control/Supervision:*** *Rukiye Yasak Güner, Melih Akyol;* ***Data Collection and/or Processing:*** *Mustafa Tosun, Mahir Dığış;* ***Analysis and/or Interpretation:*** *Mustafa Tosun, Melih Akyol, Mahir Dığış;* ***Literature Review:*** *Mahir Dığış, Rukiye Yasak Güner;* ***Writing the Article:*** *Mustafa Tosun, Mahir Dığış;* ***Critical Review:*** *Melih Akyol, Mahir Dığış;* ***References and Fundings:*** *Mahir Dığış;* ***Materials:*** *Mustafa Tosun, Mahir Dığış.*

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