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ÖZGÜN MAKALE/ORIGINAL ARTICLE

Assessment of Hematological and Inflammatory Parameters in Patients Receiving Isotretinoin Therapy for Acne Vulgaris

Sistemik İsotretionin Tedavisi Alan Akne Vulgarisli Hastalarda Hematolojik ve İnflamatuar Parametrelerin Değerlendirilmesi

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ABSTRACT

Objectives: Isotretinoin (ISO) is a synthetic analog of vitamin A used at the doses of 0.5–2 mg/kg for four to five months in the treatment of moderate to severe acne vulgaris. In the present study, both hematological and inflammatory parameters were retrospectively assessed in patients receiving ISO therapy for acne vulgaris.

Method: This study included 352 patients who were admitted to the Dermatology Clinic and received oral ISO for the treatment of acne vulgaris were included in the study. Each patient's hematological and inflammatory parameters (hemoglobin, hematocrit, thrombocyte, mean platelet volume, leukocyte, erythrocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil, neutrophil/basophil, thrombocyte/lymphocyte, RDW, PCT and PDW) were evaluated before the treatment and retrospectively evaluated four months after the onset of treatment.

Results: After treatment, a significant decrease was detected in the levels of leukocyte, neutrophil and neutrophil to lymphocyte ratio (NLR) (an indicator of inflammation), and a significant increase was detected in the levels of thrombocyte and procalcitonin (PCT).

Conclusion: In our study, isotretinoin inhibited the anti-inflammatory effect of isotretinoin treatment of acne in patients with NLR decline after treatment with inflammatory markers. Patients with markedly elevated platelet counts or low leukocyte counts should be closely monitored.

Keyword: Isotretinoin, acne vulgaris, inflammatory parameters

ÖZ

Amaç: İsotretinoin sentetik vitamin A analoğudur. Orta ve şiddetli akne vulgariste 0.5-2mg/kg /gün dozunda 4-5 ay süreyle kullanılır. Bu çalışmada oral isotretinoin tedavisi alan akne vulgarisli hastalarda hematolojik ve inflamatuar parametrelerin retrospektif olarak değerlendirilmesi amaçlanmıştır.

Metot: Çalışmaya dermatoloji polikliniğine başvuran ve akne vulgaris tanısıyla oral isotretinoin tedavisi başlanan 352 hasta alındı. Hastaların tedavi öncesi ve tedavi başlangıcından 4 ay son-raki hematolojik ve inflamatuar parametreleri (hemoglobin, hematokrit, trombosit, ortalama trombosit hacmi, lökosit, eritrosit, nötrofil, lenfosit, monosit, eozinofil, bazofil, nötrofil /bazofil, trombosit/lenfosit, RDW, PCT, PDW) retrospektif olarak incelendi.

Bulgular: Tedaviden sonra lökosit, nötrofil ve nötrofil lenfosit oranına (NLO) seviye-lerinde istatistiksel olarak anlamlı bir azalma saptandı. Trombosit ve prokalsitonin (PCT) düzeylerinde istatistiksel olarak anlamlı bir artış saptandı.

Sonuç: Çalışmamızda saptadığımız isotreinoin tedavi sonrası inflamatuar belirteçlerinden NLR düşme akne de isotretinoin tedavisinin antienflamatuar etkisini desteklemektedir. Belirgin olarak trombosit yuksekliği olan veya lökosit düşüklüğü olan hastalarda yakın takip edilmelidir.

Anahtar kelimeler: İsotretinoin, akne vulgaris, inflamatuvar parametreler

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1. INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit mostly present in adolescence. It is clinically characterized by comedones, erythematous papules and pustules, as well as less frequently nodules and pseudocysts (1). Isotretinoin (ISO) is a therapy agent that affects the pathogenesis of acne vulgaris, including abnormal follicular keratinization, bacterial colonization, inflammation and seborrhea (1, 2). The initial dose of ISO is typically 0.5 mg/kg per day, and dose adjustment is required according to patient response or presenting side effects (3). Various organ systems are affected by ISO from its first introduction. ISO may cause problems including mucocutaneous, gastrointestinal and ocular side effects, teratogenicity, hepatotoxicity and dyslipidemia (2, 3). The hematological side effects of ISO are rarely seen in patients, and neutropenia, thrombocytopenia and thrombocytosis have been reported during treatment (4-7).

Recently, it has been shown that neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are indicators of systemic inflammation, and they are associated with the prognosis of various cardiovascular diseases, malignancies and chronic inflammatory diseases (8-11). Mean platelet volume (MPV) is recognized as an indicator of platelet function and activation. Increased MPV levels have been shown to be an independent risk factor for acute myocardial infarction. Moreover, increased MPV levels have been detected in certain systemic inflammatory diseases, and a positive correlation was found between MPV and CRP levels (12, 13).

There are a limited number of clinically controlled studies regarding the effects of ISO on the hematological and inflammatory parameters. In the present study, we aimed to assess the effects of ISO on the hematological and inflammatory parameters in patients receiving ISO therapy for acne vulgaris.

2. METHODS

A total of 352 patients with moderate to severe acne vulgaris who received 0.5 mg–1 mg/kg of ISO therapy, who had a complete patient file, and who were admitted to the Dermatology Outpatient Clinic of Sakarya University, Training and Research Hospital, met the study criteria. These patients were included in the study and were retrospectively evaluated. Their hemoglobin (Hb), hematocrit (Htc), thrombocyte, MPV, leukocyte, erythrocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil, RBC, NLR, PLR, Red Cell Distribution Width (RDW), PCT (Prokalsitonin) and platelet distribution width (PDW) levels were recorded both before the treatment and four months after the onset of treatment.

3.1. Statistical Analysis

Analyses were performed using a statistical software package (IBM SPSS Statistics 20, SPSS Inc. An IBM Corp., Armonk, NY). Analysis of normality of the continuous variables was

performed using the Kolmogorov-Smirnov test. Comparisons between the continuous variables at the baseline evaluation and the fourth month of the treatment were performed using a paired samples t-test. The level of significance was p<0.05.

4. RESULTS

Patients who had a disease or were receiving drug therapy (nonsteroidal anti-inflammatory drugs, anticoagulants, immunosuppressive drugs, oral contraceptives, etc.) that affected their hematological parameters; patients who had anemia, malignancy, an active infection and/or hepatic failure; and patients younger than 15 years of age and older than 45 years of age were excluded from the study. We retrospectively collected data from 352 patients of whom 125 (35.5%) were male and 227 (64.5%) were female. White blood count (WBC), neutrophil, and NLR levels significantly decreased with the use of ISO treatment (p<0.001, p<0,001 and p=0.013, respectively).

There was no significant difference between the pre-treatment and post-treatment values of RBC,Hb, Htc, RDW, MPV, RDW, lymphocyte, monocyte, eosinophil, basophil and PLR. Data were shown in Table 1.

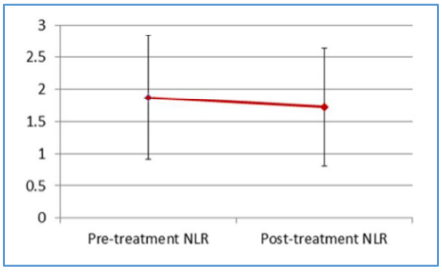

Figure 1: Pre and post treatment results of NLR levels

Table 1: Pre-and post-treatment hematological and inflammatory results of NLR levels

WBC	7.0±1.5	6.3±1.4	<0.001
RBC	4.7±0.5	4.6±0.5	0.216
Hemoglobin	13.4±1.5	13.4±1.4	0.858
Hematocrit	40.3±4.5	40.14.1	0.326
Platelet	271±59	285±61	<0.001
RDW	15.3±2.1	15.4±1.6	0.203
MPV	7.7±1.2	7.8±4.9	0.499
PCT	0.20±0.05	0.21±0.05	0.013
PDW	17.7±1.1	17.7±0.9	0.762
Neutrophil	3.9±1.3	3.7±1.4	0.026
Lymphocyte	2.3±0.7	2.4±0.7	0.072
Monocyte	0.5±0.1	0.5±0.2	0.835
Eosinophil	0.2±0.1	0.2±0.2	0.062
Basophil	0.1±0.1	0.1±0.0	0.797
NLR	1.8±0.9	1.7±0.9	0.005

§ (NLR: Neutrophil to lymphocyte ratio , MPV: Mean platelet volume , PLR: Platelet to lymphocyte ratio, RDW: Red Cell Distribution Width, PDW: Platelet distribution width, PCT: Prokalsitonin, PDW: Platelet distribution width, WBC: White blood count, RBC: Red blood cells)

5. DISCUSSION

In the present study, a decrease in leukocyte, neutrophil and NLR levels and an increase in PCT levels were detected after the treatment. Acne vulgaris has a high incidence in the population, and it can result in severe cosmetic and psychosocial problems due to the potential of it to result in scarring (14). ISO is a synthetic analog of vitamin A that has been used in the treatment of acne vulgaris since the 1980s. It affects all stages of acne vulgaris, and it is the first treatment option for patients who have a high

risk of acne scars (2, 15). The initial dose is adjusted according to the patient's weight, and the recommended dose is between 0.5 and 1.0 mg/kg. The cumulative dose is between 100 and 150 mg/kg. ISO is a highly effective therapy agent; however, it may cause various side effects. Frequent adverse effects of ISO involve mucocutaneous, gastrointestinal and ocular side effects, hyperlipidemia, arthralgia and myalgia; various hematological side effects are seen less frequently (4, 5, 16). It has been reported that ISO has particularly played a role in causing thrombocytopenia, thrombocytosis, agranulocytosis and leukopenia by means of affecting hematological parameters (16, 17). In the present study, orally administered ISO to patients with acne vulgaris resulted in an increase in the hemogram parameters involving thrombocyte and PCT levels and a decrease in leukocyte and neutrophil levels.

In the literature, ISO has been shown to have various and contradictory effects on platelet count and volume. For example, Karadag et al. reported only a moderate increase in the platelet levels of 70 patients in their study. Any variation in the other hematological parameters (Hb, Hct, MPV and WBC) in accordance with ISO therapy (18). On the other hand, Bruno et al. performed a study on 94 patients, and they did not detect any variation at all in the laboratory findings of patients using ISO therapy (19). Meanwhile, Schmutz et al. reported an increase in platelet levels caused by low doses of ISO (20).

In the literature, there are case reports identifying patients with thrombocytopenia in accordance with using ISO. The projected causes of thrombocytopenia were organized under three categories: (a) an immune-mediated response, (b) a non-immune mediated response and (c) bone marrow suppression (5, 21, 22). However, the studies that have been conducted regarding the mechanisms of ISO therapy on platelets are not adequate or satisfactory.

In a phase-1 study performed on patients with myelodysplastic syndromes, elevated levels of platelets were observed in 5 of 15 patients (23). Retinoic acid promotes the synthesis of hematopoietic progenitors, which is the progenitor of the hematovascular system, and it is derived from human embryonic stem cells (24). All-trans retinoic acid (ATRA), an analog of vitamin A, has been used in the treatment of acute promyelocytic leukemia for years. ATRA induces megakaryopoiesis of progenitor cell line MEG-0126. In the present study, significantly increased levels of platelets and PCT after the fourth month of the treatment were detect-ed. This significant increase was correlated with the Notion that ISO may induce megakaryopoiesis via a similar mechanism and cause increased levels of platelets.

Michaëlsson et al. reported significantly decreased levels of leukocyte and neutrophil in patients using ISO for acne (4). Similarly, Friedman et al. reported a case in which leukopenia and neutropenia were associated with ISO therapy (6). In another case report, ISO-induced

agranulocytosis was reported (27). In a community-based study involving 13,772 patients, leukocyte and hemoglobin levels were measured before and during treatment; low leukocyte and high hemoglobin counts were detected in the measurements obtained during treatment, whereas no significant difference was observed with regard to the platelet levels of the patients (26). In the present study, a statistically significant decrease of leukocyte and hemoglobin counts was observed. The mechanisms of ISO on hemogram parameters are not clear yet. In patients with decreased cell count levels, immune-mediated mechanisms, nonimmunological mechanisms and bone marrow suppression were held responsible (27).

Inflammation is an important factor in acne development. Anti-inflammatory and immune modulatory effects of ISO have been well-documented. Karadag et al. reported statistically significant levels of proinflammatory cytokines, such as TNF-alpha, IL-4, IL-17 and IFN-gamma, in patients with acne in comparison to a control group, and a statistically significant decrease was found in these markers after ISO treatment in patients with acne. They demonstrated the immune regulatory effect of ISO in acne treatment (28).

NLR, PLR and RWD are inflammatory markers easily measured from peripheral blood samples. They are also used as inflammatory markers in various diseases (8-11, 29-32). Moreover, it has been reported that the values of NLR, PLR and RWD were correlated with other inflammatory markers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (8-11, 29-32). Seckin et al. conducted a study on 112 patients receiv-ing ISO therapy for acne and found that, while no significant variation was detected with re-gard to NLR or PLR values, statistically significant decreased levels of RDW were detected (33). As far as we know, this was the first study reporting decreased levels of NLR following treatment, although the presence of studies examining NLR levels performed on patients re-ceiving ISO for acne is scarce.

6. CONCLUSION

In conclusion, the detected decreased levels of NLR, an indicator of inflammatory response, following treatment supported the prior research regarding the anti-inflammatory effect of ISO therapy in the treatment of acne vulgaris. The elevated levels of thrombocytes after treatment might be related to the effect of retinoids on the bone marrow. However, the contradictory results obtained from the literature as well as the studies that have not found any variation display the fact that the mechanisms of ISO on the hematological parameters are complex. Studies at the molecular levels should be conducted to clearly re-veal this interaction. A better understanding of the side effects of ISO and of the blood parameters associated with ISO will provide convenience in patient follow-up. Patients who have significantly elevated levels of thrombocyte or decreased levels of leukocyte may re-

quire closely monitored follow-up. It is necessary to perform prospective studies involving a large number of patients.

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