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Evaluation of the effect of systemic isotretinoin treatment on demodex infestation in acne vulgaris patients

Akne vulgarisli hastalarda sistemik izotretinoinin demodeks enfestasyonu üzerine etkisi

Şeyma Nur Demirtaş*, Gamze Serarslan*, Özlem Makbule Kaya**

*Mustafa Kemal University, Department of Dermatology, Hatay, Türkiye
**Mustafa Kemal University, Department of Parasitology, Hatay, Türkiye

Abstract

Background and Design: *Demodex* mites are common ectoparasites of human hair follicles, and *Demodex folliculorum (D. folliculorum)* and *Demodex brevis* live on human skin. The role of *Demodex* in acne vulgaris remains controversial, and there is limited information regarding the effects of systemic isotretinoin on these mites. This study aimed to determine the presence and type of *Demodex* in acne vulgaris patients and to investigate the impact of oral isotretinoin treatment on *Demodex* infestation.
Materials and Methods: This prospective study included a total of 53 patients with moderate-to-severe acne vulgaris who were scheduled to start oral isotretinoin therapy. Standardized superficial skin biopsies were obtained from lesional areas before treatment and at the third and sixth months of therapy to assess the presence of *Demodex*.
Results: *Demodex* was detected in 31 (58.49%) of the 53 patients (39 female, 14 male). *D. folliculorum* + *Demodex brevis* (n=16), *D. folliculorum* (n=14), and *Demodex brevis* (n=1) were determined. *Demodex* was negative in all patients at 3 and 6 months of treatment. There was no statistically significant difference between *Demodex* positivity and *Demodex* type, disease duration, acne type, or acne localization (p>0.05).
Conclusion: Demodex brevis was frequently observed along with *D. folliculorum*. Oral isotretinoin treatment was effective against *Demodex*. Systemic isotretinoin may be considered a treatment option for patients with demodicosis.
Keywords: Acne vulgaris, *Demodex brevis, Demodex folliculorum,* oral isotretinoin

Öz

Amaç: Demodeks akarları insan saç foliküllerinin yaygın ektoparazitleridir ve *Demodex folliculorum* ve *Demodex brevis* insan derisinde yaşar. Demodeksin akne vulgaristeki rolü tartışmalıdır ve sistemik isotretinoinin bu akarlar üzerindeki etkileri hakkında sınırlı bilgi bulunmaktadır. Bu çalışmada akne vulgarisli hastalarda Demodeksin varlığını ve türünü belirlemek ve oral izotretinoin tedavisinin demodeks infestasyonuna etkisini araştırmak amaçlanmıştır.
Gereç ve Yöntem: Bu prospektif çalışmaya oral izotretinoin tedavisine başlanması planlanan orta veya şiddetli akne vulgarisi olan toplam 53 hasta dahil edildi. Demodeks varlığını değerlendirmek için tedaviden önce ve tedavinin üçüncü ve altıncı aylarında lezyonlu bölgelerden standart yüzeyel deri biyopsisi alındı.
Bulgular: 53 hastanın 31'inde (%58,49) Demodex tespit edildi (39 kadın, 14 erkek). *Demodex folliculorum+Demodex brevis* (n=16), Demodex folliculorum (n=14) ve Demodex brevis (n=1) belirlendi. Demodex, tedavinin 3. ve 6. aylarında tüm hastalarda negatifti. Demodex pozitifliği ile demodex tipi ve hastalık süresi, akne tipi ve akne lokalizasyonu arasında istatistiksel olarak anlamlı bir fark yoktu (p>0,05).
Sonuç: Demodex folliculorum'un yanı sıra Demodex brevis de sıklıkla gözlendi. Oral izotretinoin tedavisi demodeks üzerinde etkiliydi. Sistemik izotretinoin, demodikozisli hastalarda bir tedavi seçeneği olarak düşünülebilir.
Anahtar Kelimeler: Akne vulgaris, *Demodex folliculorum, Demodex brevis,* oral izotretinoin

Address for Correspondence/Yazışma Adresi: Şeyma Nur Demirtaş, MD, Mustafa Kemal University, Department of Dermatology, Hatay, Türkiye
E-mail: seademirtas@hotmail.com **ORCID:** orcid.org/0009-0009-6166-7048
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Introduction

Acne vulgaris (AV), a chronic inflammatory disease of the pilosebaceous unit, results from the interaction between androgen-induced hyperseborrhea, follicular hyperkeratinization, loss of skin microbial diversity, and inappropriate inflammatory responses[1]. Oral isotretinoin, used in the treatment of AV, induces sebocyte apoptosis to reduce sebum production, inhibits hyperkeratosis, and suppresses cytokine production from keratinocytes[2].

Demodex mites are common ectoparasites of human hair follicles, and only two species live on human skin. *Demodex folliculorum* (DF) is found in hair follicles, and *Demodex brevis* (DB) lives in the sebaceous glands attached to hair follicles. *Demodex* tends to reside in vellus sebaceous follicles, which produce more sebum[3]. The characteristics of the two species are as follows: the opisthosomal end in DF is rounded, while in DB, it is pointed. The length of the opisthosoma in DF was 7/10 of its body length, and in DB, 1/2 or 1/3. The eggs of DF are arrow-shaped, whereas those of DB are smaller[4]. The nose, cheeks, forehead, chin, external auditory canal, scalp, eyelid, and upper chest are predilection areas[5]. *Demodex* can be diagnosed using a non-invasive method called standardized skin surface biopsy (SSSB), which can collect the superficial part of the horny layer and the complete follicle contents[6].

Demodex becomes a pathogenic organism only when there is an abnormal increase in its density. This condition occurs when the balance between *Demodex*, the skin microenvironment, and the human immune system is altered[3]. Studies have reported a high prevalence of *Demodex* in various skin diseases, including rosacea, seborrheic dermatitis, and perioral dermatitis[7]. Different results have been reported in studies on *Demodex* density in AV[8-10].

In this study, it was aimed to determine the *Demodex* density and type with SSSB in patients with AV and to evaluate the effect of oral isotretinoin treatment on *Demodex* density.

Materials and Methods

This prospective study was approved by the local Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee (decision no: 10, date: 01.07.2021) and conducted in accordance with the Declaration of Helsinki. The study was conducted between July 2021 and July 2022 at the dermatology and venereal diseases outpatient clinic of a tertiary hospital. A total of 53 patients over 14 years of age who were diagnosed with moderate-to-severe AV according to the Global Acne Scoring method and planned to start systemic isotretinoin treatment were included in this study[11]. All participants provided written informed consent.

Patients who did not benefit adequately from topical and/or systemic antibiotic treatments, relapsed rapidly after treatment completion, did not receive topical AV therapy for the last three months, and did not receive systemic acne treatment, including systemic isotretinoin, for the last six months were included in the study. Patients who had any systemic disease, psychiatric disorder, or muscle disease; were pregnant or lactating; or had a history of hypervitaminosis A and drug hypersensitivity were excluded from the study.

Age, sex, disease duration, and previous AV treatment were recorded. Acne localization areas were divided into two groups: the face and other regions (shoulder, back, upper extremity, chest, and hip). The patients were grouped according to their acne type as comedonal, papulopustular, or nodulocystic.

Demodex spp. were detected using the non-invasive method, SSSB. Two SSSB samples were collected from the same lesion site before starting systemic isotretinoin treatment and at the third and sixth months of treatment. A 1 cm^2 area was marked on the microscope slide, and a drop of cyanoacrylate was placed in the middle of this area on the other side of the slide. The sample was gently pressed and slowly removed after approximately 30-45 seconds. A few drops of glycerin were added to the samples, and they were covered with a coverslip. It was examined by an expert parasitologist under a light microscope (Leica DM750, Switzerland) at x4, x10, and x40 magnifications. A diagnosis of ≥5 *Demodex* mites per 1 cm^2 was considered positive[6]. Mite species identification was performed in accordance with the relevant literature[12].

Statistical Analysis

IBM SPSS Statistics 21.0 (IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 were used for statistical analysis. The conformity of continuous variables to a normal distribution was evaluated using the Shapiro-Wilk test. Mean and standard deviation values were used for descriptive statistics. Cross tables were created to compare categorical variables according to the presence of *Demodex* and *Demodex* spp., and test statistics of number (n), percentage (%) and chi-square were provided. The Mann-Whitney U test was used to compare age and disease duration according to the presence of *Demodex* and *Demodex* spp. Statistical significance was set at $p<0.05$.

Results

The study included a total of 53 patients, comprising 39 women (73.6%) and 14 men (26.4%). The mean age of the patients was 21.09±5.42 years (range 14-40 years), and the mean disease duration was 68.06±65.21 months (3-244 months). The patients had previously used the following drugs for AV: systemic isotretinoin (n=10, 18.9%), topical treatments (n=13, 24.5%), and oral antibiotics combined with topical treatments (n=7, 13.3%). In 34% (n=18) of patients, AV was localized only on the face. Seventy-five percent (n=40) of patients had papulopustular AV, 15.1% (n=8) had nodulocystic AV, and 9.4% (n=5) had the comedonal AV. The clinical and demographic characteristics of the patients are presented in Table 1. The total isotretinoin dose was completed at 120 mg/kg/day in all patients, and the duration of treatment ranged from 24 to 32 weeks.

Demodex was positive in 58.5% (n=31) and negative in 41.5% (n=22) of patients before treatment. *Demodex* was negative in all patients at the third and sixth months of treatment.

We determined whether there was a statistical difference between *Demodex*-positive (D+) and *Demodex*-negative (D-) patients in terms of age, disease duration, acne type, and acne localization. The mean age of (D+) patients was 21.42±5.68 years, the mean age of (D-) patients

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was 20.64±5.14 years, and there was no statistically significant difference between them (z=0.697, p=0.486). The mean disease duration in (D-) patients was 74.68 ± 76.58 months, while that in (D+) patients was 63.35 ± 56.67 months, and no statistically significant difference was found between the presence of *Demodex* and disease duration (z=0.073, p=0.972). Of the (D+) patients, 74.2% (n=23) were papulopustular, 16.1% (n=5) nodulocystic, and 9.7% (n=3) comedonal type AV. The AV type of (D-) patients was papulopustular in 77.3% (n=17), nodulocystic in 13.6% (n=3), and comedonal in 9.1% (n=2). There was no statistically significant difference between the presence of *Demodex* and the AV type (p=0.963). 32.3% (n=10) of D+ patients had acne on the face alone, while 67.7% (n=21) had acne on both the face and other regions. In 36.4% (n=8) of (D-) patients, AV was localized only on the face, while 63.6% (n=14) was localized to both the face and other regions. No statistically significant difference was found in the AV region distribution according to the presence of *Demodex* (p=0.756) (Table 2).

Of the (D+) patients, 74.2% (n=23) had papulopustular AV, 16.1% (n=5) had nodulocystic AV, and 9.7% (n=3) had comedonal-type AV. Of the DF+DB positive patients, 75.0% (n=12) had papulopustular and 25.0% (n=4) had nodulocystic type AV. One patient with DB positivity had papulopustular AV.

Table 1. Clinical and demographic characteristics of the patients

Characteristics	n (%)
Sex	
Female	39 (73.6)
Male	14 (26.4)
Age (years), mean ± SD	21.09±5.42
Duration of disease (months), mean ± SD	68.06±65.21
Previous treatments	
None	23 (43.4)
Systemic isotretinoin	10 (18.9)
Topical treatments	13 (24.5)
Oral antibiotics+topical treatments	7 (13.3)
Location of lesions	
Face	18 (34.0)
Face and other Shoulder + back Shoulder + chest Shoulder + chest + back Shoulder + back + hip Shoulder + upper extremity Back + hip Shoulder + chest + upper extremity + back	35 (66.0) 15 6 4 4 3 2 1
Type of acne	
Comedonal	5 (9.4)
Papulopustular	40 (75.5)
Nodulocystic	8 (15.1)

Table 2. Comparison of acne type and location according to the presence of demodex before treatment

		Demodex (+) n (%)	Demodex (-) n (%)	p
Acne type				
	Comedonal	3 (9.7)	2 (9.1)	0.963*
	Papulopustular	23 (74.2)	17 (77.3)	
	Nodulocystic	5 (16.1)	3 (13.6)	
	Total	31	22	
Acne location				
	Face	10 (32.3)	8 (36.4)	0.756**
	Face and other regions	21 (67.7)	14 (63.6)	
	Total	31	22	

*Likelihood ratio value, ****Pearson chi-square value,

Discussion

In our study, *Demodex* spp. were detected in 58.5% of the patients before oral isotretinoin treatment. Different results have been obtained in various studies investigating *Demodex* positivity in AV. For example, Erdal and Albayrak[8] reported a rate of 10%, Aktaş Karabay and Aksu Çerbay[8] reported 27.9%, and Akçınar et al.[10] reported 42.6%. While Okyay et al.[13] reported that *Demodex* was not related to acne, Akçınar et al.[10] reported a significant relationship. A meta-analysis reported an association between AV and *Demodex* infestation[5].

There are very few studies reporting *Demodex* spp. Badawi Yousif et al.[14] reported that DF was detected in 12 of 60 AV patients, whereas DB was not detected in AV patients. Maldonado-Gomez et al.[15] reported that *Demodex* infestation was present in 29.7% of 138 patients with AV and all cases were DF. In contrast to the above studies, we detected DB at a very high rate.

Demodex infestation can cause multiple skin disorders, grouped under the terms demodicosis or demodicidosis. A high density of *Demodex* is thought to play a pathogenic role in demodicosis. Topical medicines such as metronidazole and permethrin, or systemic medicines such as ivermectin and metronidazole, can be used in the treatment of demodicosis[3].

In our study, while 58.5% of the patients were *Demodex*-positive before isotretinoin treatment, *Demodex* was negative in all of the patients included in the study at the third and sixth months of the treatment. *Demodex* resides in areas with high sebum production and is thought to use the cholesterol ester in sebum as food[16]. Oral isotretinoin alters vitamin A metabolism, suppresses sebum production, and restricts sebaceous gland growth[17]. Isotretinoin also alters skin barrier function and changes cutaneous lipid composition and skin microflora[18]. Thus, isotretinoin may have reduced the habitat and food sources of *Demodex* mites through one or more of the above-mentioned effects, which may have led to a decrease in *Demodex* density. There are few reports on the use of systemic isotretinoin in the treatment of *Demodex*. One of these is an experimental study performed by *ex vivo* culture of human *Demodex* mites, and it has been reported that isotretinoin reduces

mite density[19]. Another case report described a patient diagnosed with demodicosis who was successfully treated with oral isotretinoin and topical permethrin cream[20]. A recent study showed that isotretinoin reduced *Demodex* density in patients with AV and rosacea[21].

Study Limitations

This study has several limitations, including a relatively small sample size, a single-center design, and the absence of a control group.

Conclusion

In our study, DB frequently accompanied DF in patients with AV, and systemic isotretinoin treatment was effective against *Demodex*. Systemic isotretinoin may be a treatment option for patients with demodicosis or those with *Demodex*-related symptoms.

Ethics

Ethics Committee Approval: This prospective study was approved by the local Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee (decision no:10, date: 01.07.2021) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: All participants the patient's legal guardians provided written informed consent.

Footnotes

Authorship Contributions

Concept: Ş.N.D., G.S., Ö.M.K., Design: Ş.N.D., G.S., Ö.M.K., Data Collection or Processing: Ş.N.D., Analysis or Interpretation: Ş.N.D., G.S., Literature Search: Ş.N.D., Writing: Ş.N.D.

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

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