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Evaluation of COVID-19 risk in patients on systemic retinoid therapy

Sistemik retinoid tedavisi alan hastalarda COVID-19 riskinin değerlendirilmesi

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Abstract

Background and Design: Systemic retinoids are commonly used medications in dermatology and indicated in various skin disorders such as acne vulgaris and psoriasis. Data about the risk of Coronavirus disease-2019 (COVID-19) in patients using systemic retinoids are limited. Thus, this study aimed to investigate the risk of COVID-19 in patients undergoing systemic retinoid therapy.
Materials and Methods: A total of 186 patients who have undergone systemic isotretinoin and acitretin therapy were recruited. Patients who presented to the dermatology clinic for various skin diseases, such as eczema, vitiligo, tinea, etc., who were not on systemic retinoid therapy, and who received topical medications comprised the control group. The development of COVID-19 in the retinoid therapy group and the control group was retrospectively reviewed using hospital database.
Results: The mean age of the patients in the retinoid therapy group was 25.72±0.67 and that in the control group was 25.4±0.62. Moreover,165 patients received isotretinoin, and 21 patients received acitretin treatment. The isotretinoin dosage ranged from 0.5 to 0.8 mg/kg wheras the acitretin dosage ranged between 10 and 25 mg/day. Two patients (1.07%) in the retinoid therapy group and 8 (4.3%) patients in the control group were diagnosed with COVID-19. None of the patients receiving acitretin was diagnosed with COVID-19. COVID-19 diagnosis was established in the 2nd and 3rd months of isotretinoin treatment, and lung involvement was not observed. No significant difference regarding the number of COVID-19 cases and disease severity was found between the two groups (p=0.105; p=0.258, respectively).
Conclusion: Isotretinoin and acitretin use was not associated with increased COVID-19 risk or disease severity. Systemic retinoids appear to be a safe treatment modality in the COVID-19 era.
Keywords: Systemic retinoid, isotretinoin, acitretin, COVID-19, risk

Öz

Amaç: Sistemik retinoidler dermatolojide akne vulgaris ve psoriazis gibi çeşitli hastalıklarda endike olan yaygın kullanılan tedavilerdir. Sistemik retinoid kullanan hastalarda Koronavirüs hastalığı-2019 (COVID-19) gelişimi riski ile ilgili çalışmalar kısıtlı sayıdadır. Çalışmanın amacı sistemik retinoid tedavisi alan hastalarda COVID -19 gelişimi riskini araştırmaktır.
Gereç ve Yöntem: Sistemik izotretinoin ve asitretin tedavisi almakta olan 186 hasta çalışmaya alındı. Çeşitli dermatolojik hastalıkları (ekzema, vitiligo, tinea vs.) nedeniyle dermatoloji kliniğine başvurmuş topikal medikasyonlarla tedavi edilen ve sistemik retinoid tedavisi almayan 186 hasta kontrol grubu olarak alındı. Hastane verileri incelenerek sistemik retinoid tedavi grubunda ve kontrol grubunda COVID-19 gelişimi retrospektif olarak değerlendirildi.
Bulgular: Retinoid tedavi grubundaki hastaların yaş ortalaması 25,72±0,67, kontrol grubundaki hastaların ise 25,4±0,62 olarak saptandı (p=0,27). Yüz altmış beş hasta isotretinoin, 21 hasta asitretin tedavisi almıştı. İzotretinoin dozu 0,5-0,8 mg/kg arasında, asitretin dozu ise 10-25 mg/kg arasında değişmekteydi. İzotretinoin almakta olan 2 hastada, kontrol grubundaki 8 hastada COVID-19 gelişimi izlendi. Asitretin kullanan

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hastaların hiçbirinde COVID-19 gelişimi görülmedi. COVID-19 tanısı izotretinoin tedavisinin 2. ve 3. ayında konuldu ve akciğer tutulumu saptanmadı. İki grup arasında COVID-19 gelişen olgu sayısı ve hastalık şiddetleri arasında istatistiksel olarak anlamlı fark bulunmadı (p=0,105; p=0,258).
Sonuç: İzotretinoin ve asitretin kullanımı COVID-19 gelişimi riski ve hastalık şiddeti açısından risk artışı oluşturmamaktadır. COVID-19 sürecinde sistemik retinoid tedavileri güvenli tedavi modaliteleri olarak gözükmektedir.
Anahtar Kelimeler: Sistemik retinoid, izotretinoin, asitretin, COVID-19, risk

Introduction

Since December 2019, patients with unexplained pneumonia have been found in Wuhan, China. A new pathogen, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was defined as the cause, which thereafter led to a pandemic[1,2]. The use of some medications for various disorders has been speculated to be a risk factor for Coronavirus disease-2019 (COVID-19).

Systemic retinoids have been increasingly used in dermatology for the treatment of psoriasis, keratotic genodermatoses, and severe acne and as therapy and/or chemoprevention of skin cancer[3]. Retinoids are the derivatives of vitamin A or all-trans retinol or synthetic compounds that are structurally and/or functionally similar to vitamin A[4]. Systemic retinoids include tretinoin, isotretinoin (13-cis-retinoic acid), etretinate, acitretin, bexarotene, and alitretinoin[5]. Side effects of systemic retinoids include skin and mucosal dryness (xerosis, cheilitis, and conjunctivitis), retinoid dermatitis, skin fragility, palmoplantar desquamation, pruritus, and hair loss, which are cutaneous side effects[3].

In the literature, contradictory opinions exist about the safety of using systemic retinoids during the pandemic. The use of systemic retinoids raises a concern of increased COVID-19 risk because xerosis of the oral and nasal mucosa is a very common side effect of retinoids. On the contrary, some authors argue that isotretinoin may have a protective role in COVID-19 development by immunomodulation and downregulation of androgen and angiotensin-converting enzyme-2 (ACE2) receptors[6-8].

Moreover, only a few limited studies have investigated the frequency of COVID-19 development during systemic retinoid treatment. Thus, in this study, we aimed to compare the frequency of COVID-19 in patients on isotretinoin and acitretin treatment with controls who did not receive this treatment.

Materials and Methods

This retrospective cross-sectional controlled study was approved by the Kırşehir Ahi Evran University Faculty of Medicine Local Ethics Committee (approval number: 2021-06/66, date: 23.03.2021). Informed consent was obtained from the patients. Demographic and clinic data including age, diagnosis, presence of comorbid diseases, immunosuppressive diseases, or immunosuppressive drug use of patients who received isotretinoin or acitretin between March 2020 and December 2020 were obtained from the hospital database. Patients who came to the dermatology clinic for various skin complaints and prescribed topical treatments were included in the control group. The patients in the retinoid treatment group were classified according to treatment duration as follows: patients with treatment duration of 1 month, 2 months, and ≥3 months. Admission to the COVID-19 outpatient clinic was evaluated for both groups, and COVID-19 cases diagnosed with either computed tomography (CT) findings or polymerase chain reaction results were obtained from the hospital database.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Data were presented as mean ± standard deviation or as number with percentage (%). Statistical difference between the groups was analyzed using Student's t-test for mean values. Chi-square test was used to compare the number of cases diagnosed with COVID-19 in both groups.

Results

A total of 186 patients (female, n=134; male, n=52) were included in the study. The mean ages of the patients were 24.39±0.67 in the retinoid therapy and 25.4±0.62 in the control group (p=0.27) (Table 1). In total, 165 patients were taking isotretinoin treatment and 21 patients were taking acitretin. Moreover, 22 patients in the isotretinoin group had treatment duration of 1 month, 31 patients had 2 months, 112 patients had ≥3 months. All patients in the acitretin group had treatment duration of ≥3 months. Two patients (1.07%) taking isotretinoin were diagnosed with COVID-19 after treatment initiation. One of these patients was in the second month of treatment and the other was in the third month of isotretinoin treatment. The dose of isotretinoin was between 0.5 and 0.8 mg/kg. None of the patients taking acitretin was diagnosed with COVID-19 during the follow-up. In the control group, 8 (4.3%) patients were diagnosed with COVID-19. No significant difference was found in the number of patients diagnosed with COVID-19 over time between the groups (p=0.105). Lung involvement was not observed in any of the COVID-19 cases in the retinoid treatment group, whereas two mild, one moderate, and two severe pneumonia cases were detected in the CT images of patients with COVID-19 in the control group, and three cases had no lung involvement. No significant difference was found between groups regarding COVID-19 severity (p=0.258) (Table 2).

Discussion

With the emergence of the COVID-19 pandemic, the safety of the use of some medications has raised some suspicions due to the possibility of increased susceptibility to COVID-19. Systemic retinoids are one of these drug groups because mucosal epithelial cells, which are considered an integral part of the innate immune system, are affected during treatment[9]. Mucosal epithelial cells play a significant role in the defense against infections by providing physical barrier including the mucociliary clearance of antigens and producing antimicrobial agents[9]. Retinoid treatment causes deterioration in nasal mucociliary clearance, mild inflammation, and significant reactive changes in the respiratory epithelium. The breakdown of nasal mucosa may cause a predisposition to coronavirus invasion by exposing ACE2 receptor localized in the basal layer of the non-keratinizing squamous epithelium, which acts as

Table 1. The demographic features of the patient and control group and the number of cases diagnoses with COVID-19

	Retinoid treatment group		Control group	p
	Isotretinoin group	Acitretin group		
Number of cases	165	21	186	1.00
Age	23.4±0.69	42.35±3.80	25.4±0.62	0.27
Gender				
Male	39	13	52	1.00
Female	126	8	134	
Number of cases diagnosed with COVID-19	2	0	8	0.105
COVID-19 severity				
No lung involvement	2	-	3	0.258
Mild pneumonia	-	-	2	
Moderate pneumonia	-	-	1	
Severe pneumonia	-	-	2	

COVID-19: Coronavirus disease-2019

Table 2. Characteristics of the patients diagnosed with COVID-19

COVID-19 patients			Symptoms	Chest CT findings
Retinoid treatment group				
	Age	**Gender**		
Patient 1	26	Female	Score throat	-
Patient 2	21	Male	Cough	-
Control group				
	Age	**Gender**		
Patient 1	26	Female	Headache	-
Patient 2	25	Female	Fever	Moderate pneumonia
Patient 3	27	Male	Cough	-
Patient 4	23	Female	Diarhea, cough, dispnea	-
Patient 5	28	Female	Cough	Mild pneumonia
Patient 6	27	Male	Arthralgia	Mild pneumonia
Patient 7	29	Male	Cough	Severe pneumonia
Patient 8	34	Female	Cough	Severe pneumonia

COVID-19: Coronavirus disease-2019, CT: Computed tomography

the receptor-binding domain for the SAR-CoV2 virus spike complex[10,11]. In our study, no significant difference was found between the retinoid treatment group and the control group as regards the number of cases and severity of COVID-19. Most of our patients (133 of 186 patients) had treatment duration of >3 months. This is a valuable observation because longer treatment duration of systemic retinoid causes more mucosal side effects that are thought to be related with infection risk. Our results suggest that isotretinoin and acitretin use does not increase the risk and severity of COVID-19. In the literature, some authors presented contrasting opinions that isotretinoin may have a protective role against COVID-19 with several mechanisms. Isotretinoin has been found as the strongest downregulator of ACE2 receptor, which is required for the entry of COVID-19[6] and a potential inhibitor of PLpro, which is an enzyme with a significant role in coronavirus replication and host infection[12]. Isotretinoin was suggested to suppress cytokine release syndrome (cytokine storm) by suppressing T-cell-mediated immunity at non-toxic concentrations[13]. Additionally, TMPRSS2, which is a part of the priming process of SARS-CoV-2's spike protein, is sensitive to dihydrotestosterone (DHT) and isotretinoin inhibits DHT. All-trans retinoic acid has also been shown to have promising effects on emphysema[14]. In our study, although the number of COVID-19 patients was higher in the control group, no significant difference was found, suggesting that isotretinoin treatment acts as a protective factor against COVID-19. This result may be also related to the small sample size of the study.

Study Limitations

The study is limited by the retrospective design and small sample size.

Conclusion

The results of this study reveal that there was not an increase in COVID-19 risk with systemic retinoid use; therefore, systemic retinoids can be regarded as "safe" during the COVID-19 era. Further studies with larger series of patients are necessary to investigate the protective role of isotretinoin against COVID-19.

Ethics

Ethics Committee Approval: This retrospective cross-sectional controlled study was approved by the Kırşehir Ahi Evran University Faculty of Medicine Local Ethics Committee (approval number: 2021-06/66, date: 23.03.2021).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.M.A., K.Ö., Concept: K.Ö., Design: K.Ö., Data Collection or Processing: E.M.A., Analysis or Interpretation: E.M.A., K.Ö., R.A., Literature Search: E.M.A., K.Ö., Writing: E.M.A., K.Ö.

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