

How are Acne Vulgaris Patients Using Oral Isotretinoin Affected by Covid-19?

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ABSTRACT Introduction: It has been reported that the use of oral isotretinoin may have positive and negative effects on the course of COVID-19 and the risk of transmission.

Objectives: The purpose of our study is to evaluate how our patients that took oral isotretinoin during the pandemic were affected by COVID-19.

Methods: The clinical processes of moderate-to-severe acne vulgaris patients between March 2020 and February 2021 were evaluated.

Results: Of 102 moderate-to-severe acne patients, 67 were using oral isotretinoin and 35 were using a topical treatment. Of 27 patients who tested positive for COVID-19, 16 (59.3%) were using oral isotretinoin and 11 (40.7%) were using topical treatment, there was no statistical difference in the rates of COVID-19 positivity between the two groups ($P = 0.412$). The rates of positive tests for COVID-19 were similar between contacted patients of two groups ($P = 0.391$). Loss of smell/taste was lower in patients using oral isotretinoin compared to patients receiving topical treatment (46.7% and 72.7%, respectively.). Headache symptoms were less common in patients using oral isotretinoin ($P = 0.047$).

Conclusions: The use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission. The patients using oral isotretinoin had a lower incidence of taste/smell loss and headache.

Introduction

The coronavirus disease 19 (COVID-19) pandemic was declared by the World Health Organization in March 2020, and COVID-19 was the leading cause of death in many countries in 2020 [1]. No specific treatment has yet been found for COVID-19. In addition, as in other branches of medicine, the positive and/or negative effects of the drugs we frequently use in dermatology on the course of COVID-19 remain unclear.

Oral isotretinoin (13-cis-retinoic acid), a synthetic analog of vitamin A, is a first-generation retinoid used for the treatment of acne vulgaris [2]. Nasal mucosal dryness is observed in two-thirds of patients during oral isotretinoin treatment [3].

The COVID-19 agent SARS-CoV-2 enters the human body through Angiotensin-Converting Enzyme-2 (ACE2) receptors. ACE-2 receptor expression was found in the basal layer of nonkeratinized squamous epithelium in the nasal mucosa. Isotretinoin has the effect of revealing ACE-2 receptors by causing nasal mucosa dryness and down-regulating ACE-2 receptors at the same time [4-6]. Biological processes showing the pharmacological functions of vitamin A for the treatment of COVID-19 have been defined and its therapeutic mechanisms have been proven by signaling pathways and it is thought that it can be used in the treatment of COVID-19 [7]. However, some authors suggested that COVID-19 is a hypervitaminosis of vitamin A and that all drugs metabolized in the liver should be discontinued [8].

Objectives

According to these data in the literature, the effects of oral isotretinoin, a vitamin A derivative, on the transmission and course of COVID-19 are not clear. The aim of our study is to evaluate whether the use of oral isotretinoin affects the findings and symptoms of COVID-19 and the risk of transmission.

Methods

Our study was a retrospective, descriptive and cross-sectional study. The clinical processes of moderate-to-severe acne vulgaris patients aged 16 years and older who were followed up in our clinic between March 2020 and February 2021 and using oral isotretinoin at a dose of 0.5-1mg/kg or topical treatment (patients who do not accept systemic treatment), were evaluated.

The data form was filled via file scanning, during control examination, or by teleconference interview method. In the data, form followings were questioned: patients age, gender, body mass index, treatment received, disease severity,

smoking, additional disease, additional treatments, pneumococcal and influenza vaccines, history of contact with someone with COVID-19, whether patients had COVID-19, if they had, symptoms, treatment of choice (without treatment, with medication at home, inpatient, in intensive care), whether there were any sequelae.

The obtained data were transferred to the computer. SPSS version 20.0 statistical package program was used in the analysis of the data. In the representation of the descriptive statistics of the study, mean \pm standard deviation (SD), minimum-maximum values for continuous numerical variables, number (N), and percentage (%) were used for categorical variables. Pearson chi-square and Fisher tests were used to compare categorical variables. According to the normality evaluation made by Kolmogorov-Smirnov and Shapiro-Wilk tests; Parametric tests (paired sample t-test and t-test in independent groups) were used where continuous variables fit the normal distribution, and nonparametric tests (Mann-Whitney U test, Kruskal Wallis test) were used where they did not fit the normal distribution. Statistical significance level was accepted as $P < 0.05$.

Results

The study included 102 moderate-to-severe acne patients aged 16 years and older who were followed up and treated in our clinic, using oral isotretinoin at a dose of 0.5-1mg/kg or topical treatment (topical retinoid or topical benzoylperoxide plus clindamycin) for at least two months. The clinical processes between March 2020 and February 2021 were evaluated.

Of the 67 patients who took oral isotretinoin during the pandemic, 52 (77.6%) were female and 15 (61%) were male, mean age was 22.64 ± 6.62 . Of 35 patients who used topical treatment, 19 (54.3%) were female and 16 (61%) were male, the mean age was 25.74 ± 8.16 .

Twenty (74.1%) of the women and 7 (25.9%) of the men had a history of 27 COVID-19 positivity confirmed by polymerase chain reaction (PCR) in the nasal swab sample. The mean age of those who were positive for COVID-19 was 24.88 ± 8.65 , and there was no statistical difference in age and gender between those who were positive for COVID-19 and those who were negative for COVID-19 ($P = 0.773$ and $P = 0.556$, respectively). There was no statistical difference between COVID-19 positive and COVID-19 negatives in terms of body mass index (BMI) average, smoking, additional disease status, acne severity, pneumococcal and influenza vaccination status (Table 1).

Of the 27 patients who were positive for COVID-19, 16 (59.3%) were using oral isotretinoin and 11 (40.7%) were using a topical treatment. There was no statistical difference in COVID-19 positivity rates between patients using oral isotretinoin and patients using topical treatment ($P = 0.412$).

Table 1. Sociodemographic and clinical characteristics of the acne vulgaris patients (comparison between COVID-19-positive and negativepatients)

	COVID (+) mean ± SD / N (%)	COVID (-) mean ± SD / N (%)	P
Age	24.88 ± 8.65	23.28 ± 6.76	0.773 ^a
BMI	23.25 ± 2.88	22,64 ± 3.01	0.201 ^a
Gender			
Male	7 (25.9)	24 (32.0)	0.556 ^b
Female	20 (74.1)	51 (68.0)	
Smoking			
Yes	4 (14.8)	15 (20.0)	0.553 ^b
No	23 (85.2)	60 (80.0)	
Additional disease			
Yes	1 (3.7)	7 (9.3)	0.678 ^b
No	26 (96.3)	68 (90.7)	
Pneumococcal vaccine			
Yes	0 (0.0)	4 (5.3)	0.571 ^b
No	27 (100)	71 (94.7)	
Influenza Vaccine			
Yes	1 (3.7)	2 (2.7)	0.607 ^b
No	26 (96.3)	73 (97.3)	

BMI = body mass index; SD = standard deviation.

^aMann-Whitney u test; ^bChi-squared or Fisher test for the comparison between the groups.

Considering the rates of COVID-19 transmission after contact with a COVID-19 positive person, COVID-19 positivity in 14 of 29 patients, who were using oral isotretinoin and came into contact with someone that tested positive for COVID-19 was confirmed by PCR test; COVID-19 positivity in 11 of 18 patients who were using the topical treatment and came into contact with someone that tested positive for COVID-19 was confirmed by PCR test. There was no statistical difference in the rates of being positive for COVID-19 between contacted patients using oral isotretinoin and contacted patients using topical treatment (P = 0.391).

Of the 27 patients who were positive for COVID-19, 26 had symptoms, only one patient using oral isotretinoin was asymptomatic, and there was no statistical difference in the rates of asymptomatic COVID-19 positivity between patients using oral isotretinoin and patients using topical treatment (P = 0.593).

In order of frequency, the symptoms associated with COVID-19 were: taste\smell loss (15), headache (13), fever (12), malaise (12), arthralgia\myalgia (11), cough (8), sore throat (6), shortness of breath (4). There was no statistical difference between patients using oral isotretinoin and patients using topical treatment in terms of the incidence of symptoms other than headache. Headache was seen at a lower rate in patients using oral isotretinoin compared

to those using topical treatment (33.3%, 72.7%, respectively), and there was a statistically significant difference (P = 0.047). Taste\smell loss developed in 7 (46.7%) of 16 COVID-19-positive patients using oral isotretinoin and 8 (72.7%) of 11 COVID-19-positive patients using topical treatment, but there was no statistical difference (P = 0.246) (Table 2).

Among the gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (dyspnea, chest pain) associated with severe COVID-19, only shortness of breath was seen in 4 of our patients, other severe symptoms were not encountered. Dyspnea was observed in one patient (6.7%) using oral isotretinoin and 3 (27.3%) patients receiving topical treatment. There was no statistically significant difference between the two groups (P = 0.279).

No patient with COVID-19 needed hospitalization or intensive care. Of the 16 COVID-19-positive patients who took oral isotretinoin, 10 recovered with medical treatment at home and 6 without treatment. All 11 COVID-19-positive patients who received topical treatment recovered with medical treatment at home. There was no statistical difference between the two groups in terms of the need for medical treatment (P = 0.054).

Six of the patients with COVID-19 had partial taste\smell loss that continued 1 month after they had the disease,

Table 2. Symptoms of COVID-19-positive patients (comparison between oral retinoid users and topical treatment users)

Symptom	Oral retinoid users N (%)	Topical treatment users N (%)	P
Taste/smell loss	7 (46.7)	8 (72.7)	0.246
Headache	5 (33.3)	8 (72.7)	0.047
Fever	7 (46.7)	5 (45.5)	0.951
Malaise	7 (46.7)	5 (45.5)	0.951
Artralgia/myalgia	4 (26.7)	7 (63.9)	0.109
Cough	6 (40.0)	2 (18.2)	0.395
Sore throat	4 (26.7)	2 (18.2)	0.999
Shortness of breath	1 (6.7)	3 (27.3)	0.279

2 (12.5%) were receiving oral isotretinoin and 4 (36%) were receiving topical treatment. There was no statistical difference between the patients using oral isotretinoin and the patients using topical treatment in terms of taste/smell loss sequela ($P = 0.350$).

Discussion

It has been reported that the use of oral isotretinoin may have positive and negative effects on the course of COVID-19 and the risk of transmission (Table 3).

Mawson et al. found that COVID-19 disease is very similar to an endogenous form of a hypervitaminosis of vitamin A, that liver damage caused by the SARS-CoV-2 virus causes toxic concentrations of retinoic acid and stored retinyl esters to be released into the circulation, including the lungs, heart, blood vessels, and skin, without binding to protein. They claimed it caused damage to organs. They recommended that treatment strategies focus on reducing circulating retinoid concentrations. They argued that all nonessential drugs that are metabolized in the liver should be discontinued, and also that all drugs that damage the liver should be avoided during the acute phase of treatment [8]. However, the patients using oral isotretinoin included in our study did not need hospitalization or intensive care even though they continued their medication when they became COVID-19-positive.

Retinoic acid and carotenoids exert many physiological effects, along with the enhancement of T-cell function, which develops an inducible immune response against pathogens such as viruses [9]. Bioinformatics computational findings showed that vitamin A has anti-viral, anti-inflammatory, and immunomodulatory effects through different biological processes and cell signaling pathways. As a result of these findings, the therapeutic mechanisms of vitamin A for the clinical treatment of COVID-19 have been defined [7]. Therefore, contrary to Mawson et al, it is thought that vitamin A derivatives may have a protective role in the pathogenesis of ARDS, which is a complication of severe COVID-19 cases,

thanks to their antioxidant and surfactant-mediated properties [9]. We did not see ARDS symptoms in any of our patients. We could not associate this with the protective use of oral isotretinoin, because our patients had a low mean age and a very low rate of possible risk factors for ARDS.

Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) have been associated with severe COVID-19 [10]. Severe COVID-19-associated dyspnea was seen at a lower rate in patients using oral isotretinoin compared to patients receiving topical treatment (6.7%, and 27.3%, respectively), we thought that this might be related to the protection of oral isotretinoin against severe COVID-19, but we did not detect a statistically significant difference ($P = 0.279$).

ACE2 has been shown to be a functional receptor for SARS-CoV to enter host target cells [11]. ACE2 receptor expression has been found in the basal layer of the squamous epithelium in the nasal mucosa. The use of oral isotretinoin, which causes dryness in the nasal mucosa, causes mucosal fragmentation, and may facilitate the adhesion of the coronavirus to the nasal mucosa by exposing the basal layer [4,5]. On the other hand, since isotretinoin is one of the strongest down-regulators of ACE-2 receptors, it was thought that the use of isotretinoin may be protective against the transmission of COVID-19 in that it reduces the possibility of cellular entry of the virus [6]. To evaluate these hypotheses, we looked at the rates of being positive for COVID-19 after contact with a COVID-19(+) person, and we did not find any difference in the rates of being COVID-19-positive between contact patients using oral isotretinoin and contact patients using topical treatment ($P = 0.391$). Ögüt et al also found that oral isotretinoin treatment was not associated with an increased risk of contracting COVID-19 [12]. These results suggest that oral isotretinoin use increases the risk of transmission by exposing ACE2 receptors, while reducing the risk of transmission by down-regulating ACE2 receptors, leading to a similar risk of transmission with people who do not use isotretinoin.

Table 3. Possible associations between oral isotretinoin and COVID-19

COVID-19 transmission risk and oral isotretinoin use	Oral isotretinoin may increase the risk of transmission by exposing ACE-2 receptors in the nasal mucosa.
	Oral isotretinoin can reduce the risk of transmission by down-regulating ACE-2 receptors.
Severe COVID-19 and use of oral isotretinoin	Because COVID-19 disease resembles an endogenous form of hypervitaminosis of vitamin A, the use of oral isotretinoin may worsen the disease severity.
	Thanks to its antioxidant and surfactant-mediated properties, oral isotretinoin may be protective in the pathogenesis of ARDS, which is a complication of severe COVID-19 cases.
COVID-19 treatment and oral isotretinoin use	Oral isotretinoin can be used in the treatment of COVID-19 as it has anti-viral, anti-inflammatory, and immunomodulatory effects.
Symptoms due to COVID-19 and use of oral isotretinoin	Oral isotretinoin can alleviate COVID-19-related headache with its down-regulating effect on ACE-2 receptors and anti-inflammatory-immunomodulatory effects.
	Since oral isotretinoin increases the sense of smell and improves the lost sense of smell, it can reduce the level of taste-smell loss due to COVID-19 and accelerate its recovery.

During the course of COVID-19, the most common clinical symptoms were reported as fever, cough, headache, and sore throat, in decreasing order of frequency [13]. In our patients, this order was taste\smell loss, headache, fever, malaise, arthralgia\myalgia, cough, sore throat, and shortness of breath. We found that the headache symptom decreased with the use of oral isotretinoin ($P = 0.047$). Various mechanisms have been described for headaches due to COVID-19. The first of these mechanisms has been reported to be the invasion of the trigeminal nerve endings of the virus that is bound to ACE2 receptors in the nasal cavity. We thought that the use of oral isotretinoin may cause a less frequent occurrence of headache due to COVID-19, with the down-regulating effect of isotretinoin on ACE2 receptors [6,11,14].

Although taste\smell loss is one of the most commonly known symptoms of COVID-19 in the non-medical community, its incidence varies between 0% and 98% [15]. We found the rate of taste\smell loss to be 55%, this rate was higher in patients using a topical treatment (72.7%).

It has been reported that the loss of taste\smell is resolved in most cases within an average of 14 days from the full recovery of COVID-19. However, in some of the patients, it was observed that the loss of taste\smell partially improved after months or did not improve at all [15].

It was found that retinoic acid treatment in mice increased the number of macrophages expressing retinoic acid receptors, and this increase was associated with a faster recovery of olfactory function [16,17]. Oral isotretinoin has been shown to improve the sense of smell in humans according to the olfactory function test evaluated before starting oral isotretinoin treatment and at the third month of treatment [18]. According to the data of our study, loss of smell\ taste was lower in patients using oral isotretinoin compared to patients receiving topical treatment (46.7% and 72.7%, respectively.), this may be related to the improvement of the sense of smell by oral isotretinoin use, but we found no statistically significant difference ($P = 0.246$). Partial

loss of taste\smell, which persisted 1 month after recovery, was lower in patients using oral isotretinoin compared to patients receiving topical treatment (12.5% and 36%, respectively), which may be related to the faster recovery of olfactory function by isotretinoin, but again, no statistical difference was observed ($P = 0.350$). The main weakness of this study is that the small number of patients. Smell\ taste loss levels could not be evaluated objectively because it is a retrospective study.

In conclusion, the use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission. Headache symptom was seen less frequently in oral isotretinoin users. In patients using oral isotretinoin, the rates of taste\smell loss were lower, although not statistically significant. The rates of complete recovery of taste\smell loss were higher in oral isotretinoin users, although it was not statistically significant.

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