

## ORIGINAL CONTRIBUTION

# Is systemic isotretinoin use a risk factor for coronavirus disease 2019 (COVID-19)?

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**Abstract****Aim:** To investigate whether acne treatment agent systemic isotretinoin causes susceptibility to COVID-19 disease.**Material and method:** Patients admitted to a single center due to acne between March 2020 and December 2020 were included. A retrospective analysis was conducted on the medical records of acne patients receiving systemic isotretinoin or topical treatments. The patients with PCR-confirmed SARS-CoV-2 infection were recorded.**Results:** 302 patients who used isotretinoin and 329 patients who used topical treatment were included in the study. No statistically significant difference was found between the groups in terms of age ( $p = 0.151$ ). It was found that of the 302 patients who used isotretinoin, 33 had PCR test for SARS-CoV-2 and two of these had PCR positivity, while of the 329 patients who received topical treatment, 45 had PCR test and five of these had PCR positivity. No statistically significant difference was found between the groups in terms of having SARS-CoV-2 positivity with PCR ( $p = 0.692$ ).**Conclusion:** Susceptibility to COVID-19 disease was not observed in patients using systemic isotretinoin.**KEYWORDS**

acne, COVID-19, systemic isotretinoin

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it can cause severe respiratory system involvement. It has been shown to enter cells through angiotensin-converting enzyme-2 (ACE-2) receptors.<sup>1</sup>

COVID-19 disease caused a pandemic leading to the death of millions of people worldwide. Therefore, a large number of drugs used in other chronic diseases have begun to be assessed for their impact on the progress of COVID-19 infection with the thought that they can aggravate COVID-19. Dermatological diseases and drugs used in dermatological diseases have also been affected by this situation.<sup>2</sup> One of these diseases is acne vulgaris.<sup>3</sup> Acne vulgaris became the most common reason for referral to dermatology clinics during

the pandemic since personal protective equipment triggers acne.<sup>4,5</sup> Isotretinoin is a derivative of retinoic acid, and it is used in first-line treatment of nodulocystic acne. It is also commonly used in the treatment of acne vulgaris resistant to other treatments. The most common side effect of isotretinoin is mucosal xerosis.<sup>6,7</sup> For this reason, at the beginning of the pandemic isotretinoin has been suggested as an agent to increase vulnerability to COVID-19 infection by increasing the transmission of SARS-CoV-2 through the disrupted nasal mucosal barrier.<sup>8</sup> On the other hand, it was also stated that isotretinoin can be protective against COVID-19 since it decreases ACE-2 receptors, increases CD4 T lymphocytes and attends immunomodulatory effects.<sup>9</sup>

The aim of this study is to investigate whether systemic isotretinoin causes susceptibility to COVID-19 disease in a cohort of acne vulgaris patients.

## 2 | MATERIAL AND METHOD

Medical records of patients who administered isotretinoin for the first time due to acne between March 2020 and December 2020, patients who had previously started getting isotretinoin treatment and those whose treatments were continuing between March 2020 and December 2020 were examined retrospectively. Patients who were using topical treatments for acne between March 2020 and December 2020 were included to the control group. The number of patients who developed SARS-CoV-2 PCR positivity was recorded throughout the study population along with demographics. In addition, for isotretinoin group, the drug dose and duration of treatment were recorded. The disease course of COVID-19 PCR (+) cases was explained for the isotretinoin group.

The patients who were using immunosuppressive or immunomodulator drug treatment, those who had a chronic disease and women who were pregnant and breastfeeding were excluded. Ethical board approval was taken for the study.

### 2.1 | Statistical analysis

The data were analyzed in IBM SPSS Statistics 23 (Evaluation version) program. Descriptive statistics were shown as mean  $\pm$  standard deviation for normally distributed variables, while they were shown as median (min–max) for variables which were not normally distributed. Nominal variables were shown as number (%). The significance of the difference between means of the groups was analyzed with *t* test, and the significance of the difference in terms of median values was analyzed with Mann-Whitney test. The frequency of PCR-confirmed COVID-19 cases was compared with Pearson chi-square or Fisher's exact test. The results were accepted as statistically significant for  $p < 0.05$ .

## 3 | RESULTS

302 patients using isotretinoin and 329 patients using topical treatment were eligible for the study. Average age was  $21.40 \pm 5.22$  (16–55) in the isotretinoin group and  $20.79 \pm 5.39$  (14–47) in the control group. No statistically significant difference was found between the groups in terms of age ( $p = 0.151$ ). Table 1 shows the age distribution of the patients using isotretinoin and topical treatment. In the isotretinoin group, 209 of the patients were female, while 93 were male and in the control group, 218 were female, while 111 were male. No statistically significant difference was found between the groups in terms of gender ( $p = 0.430$ ).

Mean systemic isotretinoin dose was found as  $30.76 \pm 8.59$  (10–50). The mean follow-up time for patients using isotretinoin was  $4.29 \pm 1.16$  months. Of the 302 patients in the isotretinoin group, 33 had PCR test for SARS-CoV-2 and 2(0.66) of these had PCR positivity, while of the 329 patients who received topical treatment, 45 had PCR test and 5(1.51) of these had PCR positivity. No

TABLE 1 Age distribution of the patients using isotretinoin and topical treatment

Age (years)	Number of patients	
	Isotretinoin	Topical treatments
<20	161	211
20–40	138	114
>40	3	4
Total	302	329

statistically significant difference was found between the groups in terms of SARS-CoV-2 positivity with PCR ( $p = 0.692$ ).

One of the two patients who had PCR positivity in the isotretinoin group was a 21-year-old woman, and she only presented with mild fever. She has been using 30 mg/day dose of isotretinoin for 6 months. The other patient was 22-year-old woman who presented with mild fever and headache. She has been using 40 mg/day dose of isotretinoin for 4 months. Isotretinoin treatment was ceased for 2 weeks during the active disease course and thereafter reintroduced to both of these patients upon shared treatment decision making. Table 2 shows the clinical information of patients who were found to have PCR positivity.

## 4 | DISCUSSION

The first case in Turkey was reported on March 11, 2020. During COVID-19 pandemic, several treatments, especially immunosuppressive drugs, have raised concerns for the potential of increasing vulnerability to COVID-19 infection. While drugs which can be used in the treatment of COVID-19 disease are being investigated on the one hand, drugs which can aggravate the disease are being avoided on the other hand. It is not known for sure worldwide which drugs are effective in COVID-19 disease and which drugs aggravate the disease.<sup>10</sup>

One of the drugs with this confusion is isotretinoin. Isotretinoin is a drug commonly used in acne treatment and its most common side effect is dryness in mucosa. There are studies reporting that dryness in mucosa will increase SARS-CoV-2 colonization.<sup>8</sup> On the contrary, there are also studies which show that isotretinoin can protect against COVID-19 disease with a few mechanisms (by decreasing ACE-2 receptors, by increasing CD 4 T lymphocytes and immunomodulatory effects).<sup>9</sup> However, there are no patient-based studies supporting these hypotheses.

In this study, we examined whether isotretinoin predisposes to COVID-19 disease in a large number of acne patients using systemic isotretinoin.

In our study population, isotretinoin and control groups were similar in terms of age and gender. No statistically significant difference was found in isotretinoin and control groups in terms of the rate of having SARS-CoV-2 PCR test and PCR positivity ( $p > 0.05$ ). We attribute the low rate of having SARS-CoV-2 PCR

TABLE 2 Clinical information of patients who were found to have PCR positivity

Patients	Treatment subgroups	Age	Gender	Isotretinoin dose (duration)	Symptoms	Lung involvement	Hospitalization
1.	Isotretinoin	21	Female	30 mg/day (sixth month)	Mild fever	no	no
2.	Isotretinoin	22	Female	40 mg/day (fourth month)	Mild fever, headache	no	no
3.	Topical treatment	27	Female	-	Fatigue	no	no
4.	Topical treatment	18	Female	-	Sore throat, fever	no	no
5.	Topical treatment	22	Female	-	Mild fever	no	no
6.	Topical treatment	22	Male	-	Sore throat, fever	no	no
7.	Topical treatment	19	Male	-	Fatigue, muscle aches	no	no

test in both groups to the fact that both groups consisted of young patients.

In Turkey, PCR test for SARS-CoV-2 is performed for patients revealing at least two significant COVID-19 symptoms (fever, sore throat, loss of smell or taste etc.) and patients with a high-risk COVID-19 contact restricted to PCR (+) household members. Due to this health policy restricting the testing of the population to a smaller extent, we might overlook the cases with an asymptomatic or subclinical disease course. This stands as a major limitation as COVID-19 disease frequently has an asymptomatic or subclinical course in the young population. In our study, the patients with a positive COVID-19 PCR test result also revealed mild symptoms.

However, we can say that isotretinoin is not a risk factor for COVID-19 disease since the rate of SARS-CoV-2 PCR positivity was not high or it did not cause severe infection that requires hospitalization when compared to the control group.

## 5 | CONCLUSION

Isotretinoin does not seem to cause vulnerability to COVID-19 infection. In our study population, two patients who had been using isotretinoin treatment for a long period revealed only mild symptoms during COVID-19 infection.

### CONFLICT OF INTEREST

None.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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