INTRODUCTION

World Health Organization (WHO) declared that the outbreak of coronavirus disease 2019 (COVID-19) constituted a Public Health Emergency of International Concern in January 30th, 2020 and described the outbreak of COVID-19 as a pandemic in March 11th, 2020. Globally, as of January 15th, 2021, there have been almost 90 million confirmed cases of COVID-19 reported to WHO. The first COVID-19 case was reported in Turkey in March 15th, 2020, and more than 2.5 million cases and 23000 deaths have been reported.
by January 15th, 2021. The patient presentations to dermatology outpatient clinics have significantly reduced in Turkey and all around the world during COVID-19 pandemic. The pandemic has negatively affected dermatology patients especially those on systemic treatment due to interruption of follow-up in dermatology clinics and inability to perform monitoring laboratory tests. The pattern of the diseases presenting in dermatology outpatient clinics has changed; however, acne vulgaris has constituted one of the most common dermatologic disorders during the pandemic period as before the pandemic. Since isotretinoin treatment has an important role in the treatment of moderate to severe acne vulgaris, British Association of Dermatologists (BAD) and American Academy of Dermatology (AAD) have published guidelines and recommendations regarding the management of isotretinoin treatment in acne vulgaris during the current pandemic. Scheduled telemedicine appointments for side effect monitoring and blood monitoring and home-pregnancy testing for female patients have been advised to reduce face-to-face consultations during the pandemic. It has been speculated that drying effect of isotretinoin on the mucous membranes may pose a theoretically increased risk of COVID-19 viral load in patients on isotretinoin.

Therefore, the aim of this study was to compare the prevalence of COVID-19 in the acne vulgaris patients receiving oral isotretinoin treatment with the acne patients on topical treatment in order to provide an evidence for the management of acne vulgaris patients during the COVID-19 pandemic.

2 | MATERIAL METHODS

2.1 | Study design

This study was conducted as a retrospective cohort study of acne vulgaris patients presented to the dermatology outpatient clinics in Uşak Training and Research Hospital. Uşak University Training and Research Hospital is a tertiary care teaching hospital located in Uşak in which has a population over 370 thousand. After the first COVID-19 case was seen in Turkey, our dermatology outpatient clinic has limited the scheduled appointments to every 15 min in order to prevent overcrowding and the spread of the virus among the patients who applied to our clinic.

The patients diagnosed with acne vulgaris have been started to topical treatment or systemic treatment (isotretinoin or systemic antibiotics) regarding the severity of the disease, and have been monitored according to acne vulgaris guidelines before pandemic. Isotretinoin was started with low doses (0.3–0.5 mg/kg per day), continued with low doses, and sustained till the threshold dose, 120–150 mg/kg. The patients were recommended to stop taking isotretinoin for five to ten days if they tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and/or prescribed hydroxychloroquine or favipiravir treatment.

After the ethical approval of our local ethics committee (1.12.2020/602.03.99), 267 acne vulgaris patients who were under follow-up for acne vulgaris treatment after March 15, 2020, were evaluated within one and a half months period between December 1, 2020, and January 15, 2021. Patients older than 12 years of age who did not use any other treatment due to a dermatologic or systemic disorder were included in the study. 37 patients who were under systemic antibiotic treatment such as azithromycin or doxycycline and 3 patients infected with SARS-CoV-2 before the onset of the isotretinoin treatment were excluded.

Demographic data of the patients and clinical data associated with COVID-19 including history of a close contact to a patient with confirmed COVID-19 infection, real-time polymerase chain reaction (RT-PCR) testing for COVID-19, and results of COVID-19 RT-PCR testing were recorded according to statements of the patients and checked from e-Pulse (Turkish National Personal Health Record System). Clinical data including severity of acne vulgaris, treatment modality (topical treatment or oral isotretinoin), total cumulative dose, and the duration of isotretinoin treatment were collected using the database of the hospital where electronic medical records of the patients were recorded. Acne patients were divided into four groups according to acne severity: mild (simple non-inflammatory acne—comedones and a few papules), moderate (comedones, papules, and a few pustules), severe (larger inflammatory papules, pustules, and a few cysts), and very severe (more severe, with cysts becoming confluent). If the patient had tested positive for COVID-19 during treatment period, the time elapsed between the onset of acne vulgaris treatment and COVID-19 positivity was calculated, and the patients were asked for their COVID-19 symptoms, especially olfactory and gustatory dysfunction (loss of taste and smell).

2.2 | Statistical analysis

The data were analyzed with the IBM SPSS v18.0 (SPSS Inc.) statistical package program. Descriptive categorical data were presented as frequencies and percentages, and continuous data were presented as mean ± standard deviation. Shapiro-Wilk test for normality was used to check the distribution of continuous data. Independent samples t test was used to analyze normally distributed data. Pearson's Chi-squared test or Fisher's exact test was performed in order to compare differences between patients receiving oral isotretinoin treatment and topical acne treatment for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported as parameters of association. Adjusted logistic regression analyses (in which age, gender, body mass index (BMI), and acne severity were considered) were performed taking COVID-19 prevalence and olfactory and/or gustatory dysfunction as dependent variables. p-values below 0.05 were considered statistically significant.

3 | RESULTS

A total of 267 patients with clinical diagnosis of acne vulgaris were screened within one and a half month period between December 1,
2020, and January 15, 2021. 227 patients with acne vulgaris receiving isotretinoin or topical treatment were included in the study. The mean age of the patients was 20.2 ± 4.0 (min: 13 max: 39) years. Female patients constituted 74% of the patients. The mean BMI was 21.6 ± 3.1 (min: 15.1 max: 33.5) kg/m². The mean length of follow-up of the acne treatment in all patients was 3.1 ± 2.0 months. The patients were categorized into two groups according to the treatment modality. 141 of them (62.1%) were under oral isotretinoin therapy for at least a month, while 86 patients (37.9%) were treated with topical agents during the pandemic period. There were no significant differences in terms of age, gender, BMI, or the length of follow-up between the two groups (P = 0.557, P = 0.463, P = 0.493, and P = 0.063, respectively). The mean total cumulative dose of the 141 patients receiving oral isotretinoin treatment was 2822 ± 2125 mg (min: 600 max: 9300). The demographics and the clinical characteristics of the patients were shown in Table 1.

Of 227 acne vulgaris patients, 51 (22.5%) had a history of close contact to a patient with confirmed COVID−19. The polymerase chain reaction (PCR) test for SARS-CoV-2 had been performed in 36 patients who had mild symptoms and 29 of them were positive for COVID-19. Unadjusted OR 0.612; 95% CI; 0.280–1.341; P = 0.220). 18 out of 29 patients (9 patients, 64.3% in isotretinoin group vs. 9 patients, 60% in topical treatment group) had reported loss of taste and smell among these mild symptoms with no significant difference between the two groups (unadjusted OR 0.833; 95% CI; 0.1852–3.750; P = 0.812). Of the patients who have positive RT-PCR test results for SARS-CoV-2 during acne treatment had pulmonary involvement or hospitalization due to COVID-19. The demographics and clinical characteristics of acne vulgaris patients with the history of COVID-19 positivity were shown in Table 2.

There were no significant differences in terms of gender, age, BMI, acne severity, length of isotretinoin treatment, and total cumulative doses between the acne vulgaris patients who had COVID-19 infection and the patients who did not (Table 3). The mean age was 20.7 ± 5.1 in patients with a history of COVID-19 during the acne treatment. The mean total cumulative dose of isotretinoin in acne patients was 2340 ± 1988 mg when they tested positive for COVID-19. The elapsed time between the onset of isotretinoin treatment and COVID-19 positivity was 13.3 ± 10.3 (min: 1 max: 36) weeks.

According to the adjusted logistic regression model, presence of isotretinoin treatment did not associate with a significant increased risk of getting COVID-19 (OR, 0.671; 95% confidence interval, 0.247–1.823; P = 0.434). When we tested the impact of isotretinoin treatment on prevalence of olfactory and/or gustatory dysfunction, the results showed that isotretinoin treatment did not significantly reduce the risk of olfactory and/or gustatory dysfunction compared to topical treatment (OR, 0.645; 95% confidence interval, 0.069–6.033; P = 0.701).

**4 | DISCUSSION**

Limited access to dermatology outpatient clinics during the pandemic and fear of getting infected with SARS-CoV-2 has

| TABLE 1 Demographics and clinical characteristics of the acne vulgaris patients |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Gender                          | Total (n 227) | Isotretinoin (n 141) | Topical (n 86) | χ²    | p²      |
| Male                            | 59 (26)      | 39 (27.7)        | 20 (23.3)      |      |        |
| Female                          | 168 (74)     | 102 (72.3)       | 66 (76.7)      |      |        |
| Acne severity                   |               |                  |                |      |        |
| Mild                            | 15 (6.6)     | 0 (0)            | 15 (17.4)      | 26.869 | .000   |
| Moderate                        | 73 (32.2)    | 30 (21.3)        | 43 (50)        | 21.142 | .000   |
| Severe                          | 116 (51.1)   | 90 (63.8)        | 26 (30.2)      | 24.413 | .000   |
| Very severe                     | 23 (10.1)    | 21 (14.9)        | 2 (2.3)        | 9.662  | .002   |
| History of a close contact to a patient with confirmed COVID−19 | 51 (22.5) | 28 (19.9) | 23 (26.7) | 1.454 | .228 |
| History of PCR testing for COVID−19 | 36 (15.9) | 19 (13.5) | 17 (19.8) | 1.585 | .208 |
| Positive PCR test result        | 29 (12.7)    | 15 (10.6)        | 14 (16.3)      | 1.525  | .217   |

Note: Significant p values are marked in bold.
Abbreviations: COVID-19, Coronavirus disease; PCR, Polymerase chain reaction.
*Chi-squared test for the comparison between study groups.
resulted in disruptions in dermatology care, especially for whom under systemic treatments. However, acne vulgaris patients have been showing more likely to have a continuation of the treatment among other diagnoses during this period.\(^8\) Moreover, increased frequency of patients with acne vulgaris and flares of acne probably caused by stress burden of the pandemic as well as long-time mask wearing\(^15\) has been observed in our dermatology outpatient clinic.\(^9,10\) Therefore, the treatment with an appropriate modality and follow-up of these patients have sustained in our clinic during the pandemic. In our study, topical treatment was initiated in patients with mild to moderate acne vulgaris while oral isotretinoin treatment was initiated to patients with severe and very severe acne vulgaris as expected. During the decision of treatment modality, there was a question raising in patients’ minds whether oral isotretinoin treatment had an effect on COVID-19. Since we did not have certain knowledge supported by literature on this issue, we could not give enough information to the patients that could answer this question.

There are inconsistent hypotheses related to the effect of isotretinoin on COVID-19. It has been stated that due to the side effects of isotretinoin treatment such as reducing normal and regenerated mucosal thickness and disturbing nasal mucociliary clearance, the use of isotretinoin can facilitate the transmission of the COVID-19 through ACE-2 receptors which are found in the basal layer of the non-keratinizing squamous epithelium in nasal mucosa.\(^16\) On the other hand, it has been claimed that the use of isotretinoin might prevent the cellular entry of SARS-CoV-2, since isotretinoin is one of the strongest down-regulator of ACE-2 receptors. Moreover, immunomodulatory effects of isotretinoin through inhibition of papain-like protease, encoded by SARS-CoV-2 and a potential target protein in the treatment of

| Gender | Age | Acne severity | Treatment | Cumulative dose | Duration (week) | Taste and smell loss |
|--------|-----|---------------|-----------|----------------|-----------------|---------------------|
| 1      | Female | 19 | Mild | Topical | N/A | N/A | Yes |
| 2      | Female | 23 | Mild | Topical | N/A | N/A | No |
| 3      | Female | 17 | Mild | Topical | N/A | N/A | Yes |
| 4      | Female | 23 | Moderate | Topical | N/A | N/A | No |
| 5      | Female | 21 | Moderate | Topical | N/A | N/A | Yes |
| 6      | Female | 25 | Moderate | Topical | N/A | N/A | No |
| 7      | Female | 19 | Moderate | Topical | N/A | N/A | Yes |
| 8      | Female | 31 | Moderate | Topical | N/A | N/A | No |
| 9      | Female | 24 | Moderate | Topical | N/A | N/A | Yes |
| 10     | Female | 19 | Moderate | Topical | N/A | N/A | Yes |
| 11     | Female | 19 | Moderate | Topical | N/A | N/A | No |
| 12     | Female | 25 | Moderate | Topical | N/A | N/A | Yes |
| 13     | Female | 20 | Severe | Topical | N/A | N/A | Yes |
| 14     | Male   | 21 | Severe | Topical | N/A | N/A | Yes |
| 15     | Male   | 14 | Moderate | Isotretinoin | 2100 | 14 | Yes |
| 16     | Female | 34 | Moderate | Isotretinoin | 300 | 2 | Yes |
| 17     | Female | 22 | Moderate | Isotretinoin | 1800 | 9 | Yes |
| 18     | Female | 18 | Moderate | Isotretinoin | 5100 | 8 | No |
| 19     | Male   | 16 | Severe | Isotretinoin | 1500 | 8 | Yes |
| 20     | Female | 16 | Severe | Isotretinoin | 6900 | 36 | No |
| 21     | Female | 19 | Severe | Isotretinoin | 4200 | 22 | Yes |
| 22     | Male   | 20 | Severe | Isotretinoin | 6900 | 32 | Yes |
| 23     | Male   | 17 | Severe | Isotretinoin | 2700 | 14 | No |
| 24     | Female | 22 | Severe | Isotretinoin | 2400 | 3 | Yes |
| 25     | Female | 25 | Severe | Isotretinoin | 1500 | 8 | No |
| 26     | Male   | 20 | Severe | Isotretinoin | 3300 | 9 | Yes |
| 27     | Female | 18 | Severe | Isotretinoin | 600 | 1 | No |
| 28     | Female | 27 | Severe | Isotretinoin | 5100 | 20 | Yes |
| 29     | Female | 22 | Very severe | Isotretinoin | 2400 | 14 | No |

Abbreviations: N/A, Not applicable.
COVID-19,\textsuperscript{17} might lower risk of getting COVID-19 in patients with acne vulgaris.\textsuperscript{18} These reports were only comments on the possible effect of isotretinoin on COVID-19 mostly based on in vitro studies,\textsuperscript{17,19} and not supported by real-world experiences with clinical studies.

In a retrospective analysis evaluating adherence to isotretinoin therapy during the pandemic, none of the 34 acne vulgaris patients receiving isotretinoin were reported to have COVID-19.\textsuperscript{20} However, this study has not provided sufficient evidence on the effect of isotretinoin on COVID-19, since the number of patients was small, data were obtained only from patient statements, and there was no control group. In our study, we further assessed the possible effect of isotretinoin on COVID-19 through comparing acne vulgaris patients receiving isotretinoin with patients on topical treatment and found no significant difference between two groups. None of the 29 patients who had been tested positive for COVID-19 had been admitted to hospital due to severe infection and respiratory failure, as expected in young COVID-19 patients.\textsuperscript{21} Although it was not statistically significant, the frequency of those who had COVID-19 was lower in acne vulgaris patients who received isotretinoin compared to the topical treatment group (10.6% vs. 16.3%) in our study. This result may support the immunomodulatory and preventive action of isotretinoin on COVID-19. Moreover, absence of severe infection requiring hospitalization in patients with acne vulgaris receiving isotretinoin treatment may be associated with the down-regulatory effect of isotretinoin on ACE-2 receptors, apart from the younger age of patients with acne vulgaris. Further studies are required to provide more information related to effect of isotretinoin on COVID-19 through ACE-2 receptors.

Olfactory and gustatory dysfunction is one of the most common neurologic symptoms represented early stages of COVID-19 or an isolated symptom of COVID-19.\textsuperscript{22} Olfactory and gustatory effects of isotretinoin treatment have not studied well previously. Heise et al. (1990) were reported a case of olfactory and taste disturbances in a patient with acne vulgaris receiving isotretinoin treatment.\textsuperscript{23} On the contrary, it has been recently reported that isotretinoin treatment has an improving effect on olfactory functions in a clinical study.\textsuperscript{24} From this point of view, it could be expected that olfactory dysfunction due to COVID-19 might be less in patients taking isotretinoin, however, 9 of 15 (64.3%) patients with acne vulgaris receiving isotretinoin treatment were found to have loss of taste and smell symptom of COVID-19 in our study. Therefore, we recommend that question of loss of taste and smell should be added to routine examinations in acne vulgaris patients receiving isotretinoin treatment in the pandemic period, since it will be useful to identify possible COVID-19 prior to disease transmission.

The limitations of this study can be listed as retrospective design, short time period for the collection of patients who examined for control visit, and that those who discontinued treatment could not be included in the evaluation. Nevertheless, we aimed to evaluate the prevalence of COVID-19 in acne vulgaris patients under oral isotretinoin treatment. We reported that there was no increased risk related to transmission of SARS-CoV-2 in patients who were under oral isotretinoin treatment for the first time in the literature. Further studies are needed in order to provide additional support for these results.

In conclusion, low-dose oral isotretinoin treatment was not associated with an increased risk of developing COVID-19 infection. The result of our study encourages dermatologists and acne vulgaris patients to initiate oral isotretinoin treatment safely during the pandemic period. We believe that our results are important to inform acne vulgaris patients to continue the follow-up and to provide treatment compliance.

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**CONFLICT OF INTEREST**

The authors report no conflict of interest.

**IRB APPROVAL STATEMENT**

Approved by local ethics committee with the date/number: 1.12.2020/602.03.99.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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