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RESEARCH ARTICLE

Self-reported COVID-19 prevalence among isotretinoin users vs. non-users: a cross-sectional survey

Rukiye Yasak Güner[1], Mehmet Kayhan[2], Mustafa Tosun[1], Ahmet Turan Ünsal[1], Ahmet Turan İnce[3], Volkan Erguvanlı[4]

[1]Department of Dermatology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye
[2]Department of Internal Medical Sciences, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye
[3]Department of Cardiovascular Surgery, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye
[4]Department of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye

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ABSTRACT

Aim: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic, and effective drug treatments for COVID-19 remain unavailable. Isotretinoin (ISO), a retinoic acid derivative commonly used for severe acne, is a potent down-regulator of ACE2 receptors, which play a key role in the pathophysiology of COVID-19. This study aims to investigate the effect of ISO treatment on COVID-19 infection in patients with acne vulgaris.

Materials and Methods: Between January 2021 and April 2021, 520 ISO users with acne vulgaris and 400 controls were included in the study. Data were collected using an electronic questionnaire distributed via social media, e-mail and mobile phones.

Results: Among ISO users, 66 (12.7%) had COVID-19 compared to 89 (22.3%) in the control group, indicating a significantly lower infection rate in the ISO group ($p < 0.001$). The risk of COVID-19 infection was 1.76 times higher in the control group. COVID-19 rates decreased steadily during the first three months of ISO treatment, particularly at the 20 mg/day dose. However, loss of smell and taste was more common in the ISO group than in controls.

Conclusion: In this cross-sectional survey, isotretinoin use was associated with lower self-reported COVID-19 prevalence.

Keywords: ACE2 receptor, acne, COVID-19, isotretinoin, off-label use

Corresponding author: Rukiye Yasak Güner **E-mail:** rky.guner@gmail.com
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INTRODUCTION

The high mortality rate, global impact, and lack of effective treatments have made COVID-19 a major public health concern. Although the pandemic has moved into an endemic phase due to vaccines and viral mutations, as of August 2025, approximately 778,474,21 cases and 7 million deaths have been reported worldwide since the onset of the pandemic (1). Despite these advancements, an effective drug treatment remains unavailable.

Isotretinoin (13-cis-retinoic acid) (ISO), approved by the FDA in 1982 for the treatment of severe acne, has also been used off-label for various cancers, including cutaneous T-cell lymphoma, neuroblastoma, and squamous cell carcinoma prevention (2,3). Similarly, drugs approved for other indications are undergoing clinical trials for COVID-19 treatment.

Isotretinoin has demonstrated significant suppression of ACE2 receptors, key players in COVID-19 pathophysiology, and may inhibit the papain-like proteinase enzyme encoded by SARS-CoV-2 genes (4). Furthermore, as a metabolite of retinoic acid, isotretinoin has been reported to prevent disseminated intravascular coagulation (DIC), a severe COVID-19 complication, and to reduce lymphocyte counts (5). While these effects suggest potential benefits, isotretinoin's anti-inflammatory and immunomodulatory properties may position it as a candidate for reducing SARS-CoV-2-related mortality and morbidity.

This study explores whether isotretinoin use is associated with differences in self-reported COVID-19 infection rates in a real-world sample. Given isotretinoin's modulatory effect on ACE2 receptor, the analysis is hypothesis-generating and not designed to test a treatment effect.

MATERIAL AND METHOD

Although data were collected through a questionnaire, participants reported their history of COVID-19 infection rather than current disease status. For this reason, the study design was considered retrospective in nature, based on self-reported past medical events rather than real-time follow-up.

The questionnaire was carefully developed in line with the study objectives and distributed to a diverse group of participants. Due to pandemic restrictions, face-to-face interviews were not possible; therefore, data collection was conducted online between January and April 2021. A total of 520 isotretinoin users with acne vulgaris and 400 controls were included in the study.

The 29-item questionnaire covered demographic characteristics, comorbidities, the amount and duration of isotretinoin use, COVID-19 infection status, disease severity, hospitalization history, contact history, and COVID-19 cases within the family. Individuals with chronic diseases were excluded from the study.

Ethical approval was obtained from the Local Ethics Committee and the Ministry of Health (2021-01/41).

Statistics

The data were evaluated using the SPSS version 22.0 package program. Data were analyzed using logistic regression analysis and the chi-square test. P-values less than 0.05 were considered statistically significant.

RESULTS

The study included 520 patients with acne vulgaris using ISO and 400 healthy controls. Of the participants using ISO, 68 (13.07%) were male and 452 (86.9%) were female. In the control group, 165 (41.25%) were male and 235 (58.75%) were female.

The mean age was 22.79 ± 4.90 in the ISO group and 22.18 ± 4.72 in the control group. There was no statistical difference between the two groups in terms of age and gender.

A total of 148 (16.1%) of all participants were married and 772 (83.9%) were single. As for the education level, 878 (95.4%) of all participants were high school graduates or above and 42 (4.56%) were primary school graduates.

Of the participants, 66 (12.7%) were from the ISO-using group and 89 (22.3%) from the control group had COVID-19 infection. When the patient and control groups were compared, the probability of having COVID-19 was lower in the group using ISO (p <0.001). In the group using isotretinoin, 189 patients tested for COVID -19, and 66 patients tested positive for SARS-CoV-2 PCR (+) (Table 1).

The cumulative dose was 34.35 ± 10.44 mg for the use of ISO. The cumulative dose in the ISO group was 35 ± 9.65 mg in those with COVID-19 infection, while it was 34.25 ± 10.56 mg in the group without COVID-19 infection. There was no statistically significant difference between the groups. The isotretinoin use period was 5.18 ± 2.4 months.

When both groups were evaluated together, 49 (21%) of the individuals who had COVID-19 were male, and 106 (15.4%) were female. When all groups were evaluated, the rate of COVID-19 transmission in men was statistically more significant than in women (p < 0.05). While 8 (11.8%) of 66 participants who used ISO and had COVID-19 infection were men, 58 (12.8%) were women. There was no statistically significant difference between them. While 41 (24.8%) of the 89 patients in the control group who had COVID-19 infection were men, 48 (20.4%) were women. There was no statistically significant difference between them.

When the treatment durations were evaluated, there was a consistent decrease in the rate of COVID-19

Table 1. The risk of having COVID-19

		Have you had Covid-19?		Total	p	OR
		Yes	No			
Group	Patient	66	454	520	<0.001	1,76
		12,7%	87,3%	100,0%		
Control	Control	89	311	400		
		22,3%	77,8%	100,0%		
Total		155	765	920		
		16,8%	83,2%	100,0%		

Table 2. The risk of having COVID-19 associated with the duration and dose of systemic ISO treatment

Variable	Category	Have you had COVID-19?		p
		Yes	No	
Group	Patient	66 (%12,7)	454 (%87,3)	<0,001
	Control	89 (%22,3)	311 (%77,8)	
Systemic ISO use time	0	89 (%22,3)	311 (%77,8)	0,002
	0-1 month	10 (%15,4)	55 (%84,6)	
	1-3 months	12 (%9,4)	116 (%90,6)	
	3-6 months	27 (%14,6)	158 (%85,4)	
	Over 6 months	17 (%12)	125 (%88)	
Systemic ISO dosage per day	0	89 (%22,3)	311 (%77,8)	0,002
	20 mg	12 (%9,8)	111 (%90,2)	
	30 mg	19 (%13,2)	125 (%86,8)	
	40 mg	25 (%15,9)	132 (%84,1)	
	Over 40 mg	10 (%10,4)	86 (%89,6)	

ISO: isotretinoin

infection with the use of ISO for the first 3 months. After a slight increase in the rate of COVID-19 infection between 3 and 6 months of treatment, the rate of COVID-19 decreased at the 6th iteration. The rate of COVID-19 infection significantly decreased with the use of ISO at 20 mg/day. Although there was a slight increase in the incidence of COVID-19 infection with the use of ISO at 30–40 mg/day, the rate tends to decrease again at doses above 40 mg (Table 2).

Multiple complaints were not observed in receiving drug treatment. Loss of smell and taste stood out compared to other complaints. Headache, joint, and muscle pains, and multiple complaints were more common in those who were not on drug treatment.

Of the participants, 51 continued ISO use during the COVID-19 pandemic, whereas 13 discontinued it. In total, 10 participants from the control group were hospitalized, but there were no hospitalizations among participants in the ISO group.

The risk of having COVID-19 infection in those who received drug treatment was calculated to be 1.76 times higher than the risk of having it in those who did not receive drug treatment (Table 1).

These findings suggest a statistically significant reduction in COVID-19 incidence among isotretinoin users. This aligns with previous studies on isotretinoin's role in ACE2 receptor modulation and immunomodulatory effects, emphasizing its potential as a preventive measure.

DISCUSSION

Our findings support the hypothesis that the downregulation of ACE2 receptors by isotretinoin may reduce susceptibility to SARS-CoV-2 by inhibiting viral entry, a critical step in COVID-19 pathophysiology (5,6). Consistent with previous studies, isotretinoin also has immunomodulatory properties that may attenuate inflammatory responses and potentially reduce the risk of severe outcomes. The absence of hospitalizations in the isotretinoin group in our cohort further supports a possible protective effect. By suppressing ACE2 receptors, isotretinoin may interfere with viral entry (7,8), while additional protective effects may arise from its regulation of immune responses and suppression of the mTORC1 pathway, which promotes inflammation (9- 13). Such mechanisms suggest that isotretinoin merits further investigation as a potential preventive agent against COVID-19.

Male patients typically experience higher COVID-19 mortality due to androgen-driven TMPRSS2 expression (14,15). The ability of isotretinoin to reduce DHT levels may therefore provide additional protection in males, consistent with our observation of no gender differences within the isotretinoin group. However, isotretinoin-related side effects such as nasal mucosa dryness could theoretically disrupt the nasal barrier and increase viral susceptibility (16,17), which may explain the transient mid-treatment increase in COVID-19 rates.

In line with this, Karadag et al. reported a suppression of Th1, Th2, and Th17 functions with isotretinoin treatment via reductions in TNF-α, IL-4, IL-17, and IFN-γ after three months (18). This immunosuppressive effect could explain the decline in COVID-19 rates during the first three months of isotretinoin use observed in our data. Loss of smell and taste was more frequent in the isotretinoin group, possibly related to disruption of the nasal barrier and ACE2/TMPRSS2 receptor expression in olfactory epithelial cells (19). Upregulation of genes such as LCN2, KRT23, and SERPINA3 has also been described in association with isotretinoin and in COVID-19 studies, which may contribute to inflammatory responses and could account for the transient increase in cases between the 3rd and 6th months of treatment (20,21).

Our current study further reveals that isotretinoin use does not increase the risk of contracting COVID-19 and may exert a protective effect. Acar et al. reported no increase in COVID-19 incidence or severity and no lung involvement in 186 patients on systemic retinoids (isotretinoin and acitretin) (22). Kuş et al. similarly found comparable infection rates between isotretinoin users and controls but with milder symptoms in the isotretinoin group (23). Demirel et al. also demonstrated the safe continuation of isotretinoin therapy during the pandemic (24). Havet et al. confirmed through larger epidemiological data that isotretinoin did not increase COVID-19 risk, despite reporting decreased drug access

during lockdowns (25). Our results are also supported by an interventional clinical trial by Shirvani et al., which demonstrated that isotretinoin use in COVID-19 patients accelerated clinical recovery and improved respiratory symptoms compared to controls (26). This study provides further evidence that isotretinoin may not only be safe during the pandemic but could also exert therapeutic benefits in infected patients.

Overall, these findings support the safety of isotretinoin under pandemic conditions and align with our observations.

Limitations of this study include its retrospective, questionnaire-based design, reliance on self-reported COVID-19 histories, and a relatively modest sample size. Nonetheless, in combination with previous evidence, our results provide further real-world support for the safe use of isotretinoin during the COVID-19 pandemic.

CONCLUSION

In light of these findings, isotretinoin use was not associated with increased COVID-19 risk. Its ability to modulate inflammatory responses warrants larger, controlled randomized trials to evaluate whether retinoid pathways merit clinical testing in COVID-19.

Ethical approval

This study has been approved by the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval date 13.01.2021, number 2021-01/41). Written informed consent was obtained from the participants.

Author contribution

Design: RYG; Data Collection: ATÜ, ATİ, VE; Analysis: MK, MT; Literature Search: RYG; Writing: RYG, MK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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