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Is Omalizumab Treatment Used During the COVID-19 Pandemic Effective on the Frequency and Severity of COVID-19?

COVID-19 Pandemisi Sırasında Kullanılan Omalizumab Tedavisi COVID-19 Sıklığı ve Şiddeti Üzerine Etkili midir?

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Abstract

Objective: The effects of drugs used in chronic spontaneous urticaria (CSU) and similar chronic dermatological diseases in COVID-19 continue to be the subject of many studies. The present study aimed to reveal the frequency and severity of COVID-19 infection in CSU patients treated with omalizumab and antihistamines.

Materials and Methods: CSU patients who were followed up and treated with omalizumab or antihistamines were evaluated retrospectively for clinical conditions with CSU and COVID-19 during the pandemic and compared with the control group regarding the incidence and severity of COVID-19 infection. In addition, urticaria disease severity was also compared with pre-pandemic scores for the CSU group.

Results: Real-time reverse transcription-polymerase chain reaction test positivity rate for SARS-CoV-2 was detected in 17.4%, 30.1%, and 34.8% of the patients in omalizumab, antihistamine, and control groups, respectively (p= 0.001). The disease activity scores were increased in both antihistamine and omalizumab treated compared to the pre-covid state CSU patients, while the increase was minor in patients using omalizumab.

Conclusion: The fact that COVID-19 infection was seen less frequent and urticaria activity scores were lower during the infection in the omalizumab group suggests that omalizumab treatment is safe and convenient to use during COVID-19 infection.

Keywords: Antihistamine, COVID-19, incidence, omalizumab, urticaria

Öz

Amaç: Kronik spontan ürtiker (KSÜ) ve benzeri kronik dermatolojik hastalıklarda kullanılan ilaçların COVID-19'un seyri üzerindeki etkileri halen pek çok araştırma için çalışma konusu olmaya devam etmektedir. Sunulan çalışmada omalizumab ve antihistaminikler ile tedavi edilen KSÜ hastalarında COVID-19 enfeksiyonunun sıklığını ve şiddetini ortaya koymak hedeflenmiştir.

Materyal ve Metot: Omalizumab veya antihistaminiklerle izlenen ve tedavi edilen KSÜ hastalarının, pandemi sırasında KSÜ ve COVID-19 ile klinik durumları retrospektif olarak değerlendirildi ve COVID-19 enfeksiyonunun insidansı ve şiddeti açısından kontrol grubu ile karşılaştırıldı. Ayrıca ürtiker hastalığının şiddeti, KSÜ grubu için pandemi öncesi skorlarla karşılaştırıldı.

Bulgular: SARS-CoV-2 için gerçek zamanlı ters transkripsiyon-polimeraz zincir reaksiyonu testi pozitiflik oranı omalizumab, antihistaminik ve kontrol gruplarındaki hastaların sırasıyla %17,4, %30,1 ve %34,8'inde tespit edildi (p= 0,001). Hastalık aktivitesi skorları covid öncesi duruma kıyasla hem antihistaminik hem de omalizumab ile tedavi edilen KSÜ hastalarında artarken, omalizumab kullanan hastalarda artış daha düşük oranda saptanmıştır.

Sonuç: Omalizumab grubunda COVID-19 enfeksiyonunun daha az görülmesi ve enfeksiyon sırasında ürtiker aktivite skorlarının daha düşük olması, omalizumab tedavisinin COVID-19 enfeksiyonu sırasında kullanımının güvenli ve uygun olduğunu göstermektedir.

Anahtar Kelimeler: Antihistamin, COVID-19, insidans, omalizumab, ürtiker

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INTRODUCTION

Since the first few months of 2020, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread rapidly around the world, causing the Coronavirus disease 2019 (COVID-19) pandemic. Worldwide, over 541 million cases of COVID-19 have been diagnosed caused by severe acute respiratory SARS-CoV-2, and more than 6 million have died in 188 countries.[1] COVID-19 causes various clinical symptoms, from asymptomatic cases to severe acute respiratory failure, and can affect multiple organ systems.[2]

The effect of chronic diseases and drugs on COVID-19 continues to be the subject of many studies, and chronic spontaneous urticaria (CSU) and medications for treating this disease are no exception. CSU is a chronic condition characterised by itchy hives, swelling, or both that persist for at least six weeks.[3] It is estimated to affect about 50 million people, with symptoms significantly affecting their quality of life.[4]

Omalizumab, a humanised monoclonal antibody that binds to the Cε3 domain of free IgE and prevents it from binding to Fc epsilon RI (FcRI), has been approved in Europe and the United States as a treatment option for CSU in patients aged 12 and older who do not respond to high-dose H1 antihistamines.[5] In addition to the classical therapeutic mechanism of this molecule, it also has various effects, including potential antiviral and anticoagulant effects.[6,7]

During the pandemic, it was recommended to use antihistamines and omalizumab while avoiding immunosuppressive treatments such as systemic corticosteroids and cyclosporine, if possible.[8,9] For the possible role of mast cells in COVID-19-related lung injury, it has been reported that antihistamines and omalizumab in COVID-19 patients can decrease mortality in patients with severe to critical pulmonary disease.[10,11]

The present study aims to reveal the frequency and severity of COVID-19 infection in patients with CSU treated with omalizumab or antihistamine. A literature review on this subject shows a few reports regarding the use of omalizumab in patients diagnosed with CSU and COVID-19. However, this study differs from these reports in that it includes the most extensive patient series in the literature and is the only study with a control group.

MATERIALS AND METHODS

Ethics Committee Approval: The research protocol was submitted to and approved by the Sakarya University Ethics Committee and was conducted according to the ethical regulations of the Declaration of Helsinki and adherence to Turkish law and regulations (E-71522473-050.01.04-136957-160).

Design: It is a retrospective case-control study.

Participants: Patients with CSU and treated with omalizumab or antihistamines in Sakarya University Training and Research Hospital, Dermatology and Venereology Department between March 2020 and July 2022 created the CSU treatment group. Individuals without CSU and any chronic disease and similar to the study group in age and sex were selected as the control group. Patients with immunosuppression, morbid obesity, incomplete file records, and who did not accept informed consent, combined therapy of omalizumab and antihistamines for the CSU group, patients who did not receive medical treatment for CSU during the pandemic, and medical history of urticaria for the control group were accepted as exclusion criteria.

Instrumentation: Real-time reverse transcription-polymerase chain reaction (rRT-PCR) test results for the SARS-CoV-2 between March 2020 and July 2022 were evaluated through the Public Health Management System of all of the participants, and the cases with positive rRT-PCR tests were recorded. We have done a telephone interview including standard questions with the patients who were followed up with the diagnosis of CSU and whose RT-PCR results were positive. Informed consent was obtained from all participants at the beginning of the interview. As a result of this interview, patients' COVID-19 symptoms, medical treatment methods applied to them for COVID-19, and chronic urticaria activity scores were determined. In addition, the patients were evaluated for COVID-19 disease severity as non-severe, severe, and critical diseases with the medical information retrieved from the patients and their medical information retrieved from hospital records.[12] The chronic urticaria activity score results of the patients evaluated in the pre-Covid period were compared with those in the Covid period.

The vaccination status of the patients was also obtained from the hospital records and compared to determine the comparability of the groups.

Statistical Analysis: Statistical analyses were performed using IBM SPSS version 20.0 for Windows statistical software (IBM Corporation, Armonk, New York, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed in percentage. For distribution normality analyses, Kolmogorov-Smirnov analysis was performed, and parametric and non-parametric tests were preferred according to the results of this analysis. The Independent sample t -test was used for the pairwise comparisons between groups. The Chi-square test was used for the comparison of the categorical variables. P values less than 0.05 were assigned significantly.

RESULTS

In all, 537 patients with CSU who were treated with omalizumab and/or antihistamines were reviewed for the study. However, 78 were excluded because they needed to meet the study eligibility criteria. Finally, the omalizumab group included 276 participants, of which 195 (70.7%) were female and 81 (29.3%) were male, with a mean age of 44.79 ± 14.83 years (17–84). In the antihistamine group, there were 183 patients in total, and of them, 130 (71.0%) were female, and 53 (29.0%) were male, with a mean age of 40.87 ± 15.03 years (17–78). The control group consisted of 400 participants, of which 272 (68.0%) were female, and 128 (32.0%) were male, with a mean age of 42.00 ± 15.17 years (14–90). The differences were not statistically significant when the groups were compared regarding age and gender distribution characteristics (p= 0.670, 0.941). COVID-19 rRT-PCR test positivity rates for omalizumab, antihistamine and control groups were 17.4% (48 patients), 30.1% (55 patients), and 34.8% (139 patients), respectively. The Chi-square test showed a statistically significant difference between the groups, favouring the omalizumab group (p= 0.001). The patients were also investigated for the COVID-19 infection disease severity characteristics.12 According to the WHO classification, most patients in both groups were in the non-severe category. Only four patients were in the critical category, and six were in the severe category. When the groups were compared regarding severity characteristics, the differences were not statistically significant (p= 0.690) (Table 1).

Table 1. Demographics characteristics and rRT-PCR positivity rates of the groups.

		Omalizumab group (n=276)	Antihistamine group (n:183)	Control group (n=400)	p
Gender	Female	195(70.7%)	130(71.0%)	272 (68.0%)	0.670
	Male	81 (29.3%)	53 (29.0%)	128 (32.0%)	
Age		44.79 ±14.83	40.87 ±15.03	42.00 ±15.17	0.941
PCR test positivity rate		48 (17.4%)	55 (30.1%)	139 (34.8%)	0,001 $P^{\dagger-\ddagger}$: <0.002 $P^{\dagger-\S}$: <0.001 $P^{\ddagger-\S}$: >0.212
WHO Classification	Mild	38 (79.2%)	41 (74.5%)	101 (72.7%)	0.690
	Moderate	8 (16.7%)	13 (23.6%)	31 (22.3%)	
	Severe	2 (4.2%)	-	4 (2.9%)	
	Critical	-	1(1.8%)	3 (2.2%)	

PCR: SARS-CoV-2 rRT – PCR test positivity rate; †: Omalizumab group; ‡: Antihistamine group; §: Control group.

The vaccination status of the CSU and control group before the COVID-19 infection was examined. Thirty-eight patients (69.1%) in the antihistamine group, thirty patients (62.5%) in the omalizumab group, and eighty patients (61.9%) in the control group were unvaccinated. The most common form of vaccination among the vaccinated was two doses of BNT162b2 mRNA (Pfizer-BioNTech) followed by two doses of the Sinovac vaccine. Although there are rare forms of vaccination, these groups were not included in the statistical analysis because of the limited number of patients in these groups. When the groups were compared with the chi-square analysis according to the most common type of vaccination, the difference was not statistically significant (p= 0.610). These results also showed the comparability of the groups (Table 2).

Table 2. The vaccination status before COVID-19 Infection of the groups.

	Antihistamines (n:55)	Omalizumab (n:48)	Control (n:139)	Statistics
Unvaccinated	38 (69.1%)	30 (62.5%)	80 (57.6%)	
2 dose Sinovac	5 (9.1%)	5 (10.4%)	11 (7.9%)	p=0.610
2 dose BNT162b2 mRNA (Pfizer-BioNTech	10 (18.2%)	10 (20.8%)	38 (27.3%)	
2 dose Sinovac + 3 dose BNT162b2 mRNA (Pfizer-BioNTech)	2 (3.6%)	0	3 (2.2%)	
1 dose BNT162b2 mRNA (Pfizer-BioNTech)	0	1 (2.1%)	2 (1.4%)	
3 dose BNT162b2 mRNA (Pfizer-BioNTech)	0	2 (4.2%)	5 (3.6%)	Statistically non-comparable

In the pre-pandemic period, 89.1% of the patients in the antihistamine group were well-controlled, and 10.9% were in the mild urticaria category. In the same period, 91.7% of patients in the omalizumab group were well-controlled, and 8.3% were mild urticaria. The group comparisons on this topic did not constitute a statistically significant difference (0.660). During the COVID-19 pandemic, 79.2% of the patients in the omalizumab group were well-controlled, 6.3% mild, 6.3% moderate, and 8.3% severe urticaria. In the same period, 61.8% of patients in the antihistamine group were well-controlled, 29.1% had mild urticaria, and 9.1% had moderate urticaria. There were no severe COVID patients in the omalizumab group. The difference was statistically significant when the groups were compared (0.004). In total, 26.1% (120 patients) of the patients in CSU showed an increase in disease severity during COVID-19 infection, which is 34.5% of the patients in the antihistamine group and 20.8% in the omalizumab group. The difference was not statistically significant (p= 0.123). (Table 3)

Table 3. Disease activity statuses in the COVID-19 and pre-COVID-19 period.

		Omalizumab group (n=276)	Antihistamine group (n:183)	p
UAS Score - prepandemic period	Well-controlled	91.7%	89.1%	0.660
	Mild	8.3%	10.9%	
	Moderate	-	-	
	Severe	-	-	
UAS Score -pandemic period	Well-controlled	79.2%	61.8%	0.004
	Mild	6.3%	29.1%	
	Moderate	6.3%	9.1%	
	Severe	8.3%	-	
Disease Worsening Rate		20.8%	34.5%	0.123

UAS: Urticaria activity score.

DISCUSSION AND CONCLUSION

Viral infections, which play a role in both triggering and exacerbating the disease in the course of CSU, may lead to T-cell activation followed by induction of inflammatory mediators (interferon, IL-1, IL-2, and TNF-alpha). This increased cytokine environment induces degranulation of mast cells, considered the most important effector cells in chronic spontaneous urticaria and have receptors for TNF-α and IL-1, which cause urticaria formation[13,14]. Based on this basic information, Kritas and colleagues showed that coronavirus infection invades mucosal mast cells and exacerbates the inflammatory state by stimulating the secretion of pro-inflammatory cytokines (TNF - α, IL - 1, IL - 6, IL - 33, and proteases).[15] In this clinical pro-inflammatory scenario, it can be thought that chronic spontaneous urticaria may worsen during COVID-19 disease.[12-15] As Kocatürk et al. state, exacerbation is observed in 36% of CSU patients, especially in severe COVID-19 patients.[16] The data of our study also showed an increased incidence rate for disease activity in 26.1% of the patients, similar to the literature.[16]

The pathophysiology of CSU is partially understood, but the excessive histamine discharge from local basophils and mast cells and the fact that anti-H1 antagonists are highly effective in the treatment indicate that histamine is the primary mediator for it.[4] It provides immunomodulation by acting on T cells and may cause cytokine release and damage to tissues such as the lung by stimulating inflammation.[17] Dual histamine receptor blockade with the combined use of histamine-1 (H1) receptor antagonist and histamine-2 (H2) receptor antagonist is reported to be a safe and effective method to reduce progression in pulmonary symptom severity in patients with COVID-19, possibly by minimising histamine-mediated cytokine storm[17]. However, we did not show a similar protective effect of antihistamines for getting the COVID-19 infection and its severity.

In addition to the classical therapeutic mechanisms of omalizumab, it has anti-viral and anticoagulant effects[6,7]. The anti-viral effect occurs through down-regulating the high-affinity IgE receptors on plasmacytoid dendritic cells, essential for anti-viral immune responses. It also shows that it restores ex-vivo IFN-α responses to rhinovirus and influenza viruses.[18] A study by Alizadeh et al. showed that omalizumab reduced the FcεRI expression on the surface of basophils, plasmacytoid and myeloid dendritic cells in CSU patients, increasing interferon production[14]. The current scientific literature on COVID-19 provides the information that the levels of interferon-1, which confers anti-viral activity to host cells, were lower in severe or critical COVID-19 patients than in controls.[19]

Because of these reasons, we can interpret that

omalizumab treatment, which increases anti-viral immunity and interferon production, may protect against COVID-19 infection. There is a case report that supports this interpretation.[7] A patient under omalizumab treatment for severe asthma was presented in that report. In that report, it is stated that one of the reasons for the mild overcoming of the COVID-19 infection and the absence of asthma exacerbation as a result of the SARS-CoV-2 infection is because of the treatment of omalizumab and its antiviral effectiveness.[7] However, Kocatürk et al. reported that 96% (n=79) of the CSU patients showed a mild course of COVID-19 and that the severity of COVID-19 was not affected by urticaria treatment.[16] Similarly, Bostan et al. could not find a statistically significant relationship between the symptoms of COVID-19 and treatment types.[20] In the present study, the frequency of COVID-19 disease was found to be statistically significantly lower in the omalizumab group compared to both the antihistamine and control groups. This may be related to the fact that omalizumab reduces the risk of contracting COVID-19 infection, or it may be related to the fact that it causes a low-severity infection and does not cause any complaints in the patient; therefore, the PCR test is not performed. When the severity of the COVID-19 disease was examined, it was seen that the patients in the non-severe category were mostly in the omalizumab group. However, it did not create statistical significance. In addition, no critical patients were observed in this group. The discrepancy between the current literature and our study on this subject highlights the need for further research and more extensive studies to validate the findings and determine the true impact of omalizumab on the COVID-19 outcomes observed.

It is known that omalizumab inhibits inflammatory cells, such as neutrophils and coagulation, in patients with CSU.[6] In an experimental study, Wang et al. noted that intramuscular injection of omalizumab small peptide segment into female mice might inhibit IL-6, IL-1β, and TNF-α synthesis in bronchoalveolar lavage fluid, thereby alleviating acute inflammation.[15] In severe COVID-19 infection, vascular skin symptoms may occur due to multi-organ failure and hypercoagulopathy, which is associated with cytokine storm. With this mechanism of action, omalizumab treatment may promise a good prognosis during COVID-19 infection. However, the limited number of patients in the critical category did not permit the statistical analysis.

The major limitation of our study is that the possibility of different behaviours of the patients in the groups regarding the pandemic, such as wearing a mask, social isolation, etc., could not be determined. In addition, although our study included more patients than studies in the current literature, our study group could only be Expanded a little more due to the exclusion criteria used for forming the study group and the patient group being studied from rare dermatology diseases. The small sample size can limit the generalizability of the findings.

In conclusion**,** the fact that COVID-19 infection was less frequent in the omalizumab group and the lower urticaria severity scores during the infection make omalizumab treatment safe during the COVID-19 pandemic. Considering that COVID-19 infection may continue with different variants in the coming years, if additional studies support these data, using omalizumab in COVID-19 and similar viral diseases may be more straightforward.

Ethics Committee Approval: All procedures performed in studies involving human participants followed the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. - The research protocol was approved by the Sakarya University Non-Invasive Trial Ethics Committee (approval number: E-71522473-050.01.04-14802-82)

Conflict of Interest: No conflict of interest was declared by the authors.

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