

ORIGINAL ARTICLE

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The effect of COVID-19 pandemic on treatment compliance and process of chronic urticaria patients receiving omalizumab treatment **Gokhan Aytekin,**  **Emel Atayik***Konya City Hospital, Department of Clinical Immunology and Allergy, Konya, Turkey*

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**Abstract**

Social distancing, curfew restrictions, travel restrictions and quarantines were imposed in order to reduce the risk of transmission of SARS-CoV-2. These restrictions have caused a severe reduction in admissions to hospitals. Therefore, with this study, we aimed to investigate effect of the COVID-19 pandemic on treatment processes and adherence to therapy of the patients that require to receive omalizumab due to chronic urticaria and to address effect of the pandemic on anxiety level of this patient group. Among the patients who were being followed-up for chronic urticaria and receiving omalizumab for this, files of the patients were examined retrospectively. These patients were applied a mini survey and a validated coronavirus anxiety index. Ninety-eight patients (Female: 65; Male: 33) were recruited in the study. The patients' 3-month adherence to therapy during March-April-May 2020 was 42.9%. It was the lowest during April (56.1%). The curfew (51%) and the fear of contracting SARS-CoV-2 (50%) were the most common reasons. Although rates of admissions to emergency department, an increase in symptoms of urticaria and need for an additional treatment were higher in the patients with chronic urticaria who were nonadherent to omalizumab therapy, this difference was not statistically significant (p: 0.113, p: 0.216, p: 0.141, respectively). During the pandemic, patients' adherence to therapy has reduced due to both government-related and patient-related reasons. For patients with chronic urticaria, their adherence to therapy should be ensured by minimizing the risk of transmission of SARS-CoV-2. Furthermore, in order to enhance adherence to therapy of this patient group and make access to health institutions easier, it should be considered for these patients to provide some tolerances and privileges in pandemic-related restrictions.

Keywords: COVID-19, omalizumab, chronic urticaria**Introduction**

Coronavirus disease 2019 (COVID-19) (previously known as 2019-nCoV) is a disease with a high rate of transmission and mortality which leads to pneumonia and respiratory failure, was first reported from Wuhan, China, and caused by a zoonotic virus that belongs to the coronavirus family. This novel coronavirus was termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has spread to the whole world shortly after its identification [1, 2]. Due to the higher rate of transmission and fatal course, the disease has become a pandemic influencing the whole world [3, 4]. Although some vaccines have been introduced by 2021 for the prevention of transmission of SARS-CoV-2, it is obvious that several years are needed for an effective vaccine that includes all people. Due to the lack of an effective drug or vaccine especially during the first periods of the pandemic, social distancing, curfew restrictions, travel restrictions, and quarantines

were imposed to reduce the risk of transmission. Although these restrictions have reduced the transmission of SARS-CoV-2, it has caused a severe reduction in admissions to hospitals due to reasons other than COVID-19, significantly reducing admissions of the patients who need to be tested and treated at hospitals for their chronic diseases to health institutions [5-9]. Both challenges in accessing health institutions due to restrictions and patients' fear of contracting and transmitting SARS-CoV-2 to the loved ones have affected doctor-patient interaction, leading to exacerbations of chronic diseases and loss of control of chronic diseases. One of the patient groups which requires to be treated at hospitals at regular intervals is the patients with chronic urticaria. Chronic urticaria refers to the presence of urticaria for longer than 6 weeks as long as symptoms are present on many days of the week [10]. Many guidelines recommend subcutaneous administration of omalizumab at 4-week intervals for patients that have not have benefited from treatment with antihistamines [11-13]. Although Food and Drug Administration (FDA) allows the administration of omalizumab for chronic urticaria at home by self-administration during the pandemic, the patients with chronic urticaria have to admit to the hospital for omalizumab injection and management of potential adverse effects. Therefore, with this study, we aimed

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to investigate the effect of the COVID-19 pandemic on treatment processes and adherence to therapy of the patients that require to receive omalizumab due to chronic urticaria and to address the effect of the pandemic on the anxiety level of this patient group.

Materials and Methods

Among the patients who were being followed up for chronic urticaria in our clinic and receiving omalizumab for this, files of the patients who required to receive omalizumab therapy during March-April-May 2020 were examined retrospectively. Additionally, these patients have applied a mini-survey designed by us in person-to-person during their first outpatient clinic visit or by phone calls from June 2020, when the normalization process began. This mini-survey included patients' demographic data (age, gender, education status, presence of comorbid disease, presence of personal atopy), as well as a validated coronavirus anxiety index (Annex-1) [14]. The patients were also asked about whether they came, came late, or did not come to the hospital for omalizumab therapy and, if they did not come, the government-related reasons (curfew, intercity travel restrictions, failure to arrange an outpatient clinic visit, status of disability and pregnancy, etc.) and patient-related reasons (fear of contracting the virus, fear of transmitting the virus to other family members, the possibility to access the drug directly during this period, not needing the therapy during

this period, COVID-19 infection or COVID-19 quarantines, etc.). The patients who did not come to outpatient clinic control visits at least once during March, April, or May 2020 were accepted as the patients nonadherent to omalizumab therapy. The patients were also interrogated about an increase in complaints of urticaria, the need for treatment for increased complaints, admissions to the emergency department, and the use of herbal supplements during the pandemic (March-April-May 2020).

Statistical analysis was performed with IBM SPSS Statistics Version 22 software package (New York, United States). Normally distributed parameters were presented as mean ± standard deviation and data that is not normally distributed were expressed as median (interquartile range: minimum-maximum). Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exacts, or Chi-square tests where appropriate.

For the study, permission was obtained from the Turkish Republic Ministry of Health Scientific Research Platform. In addition, an ethics committee approval was obtained from Karatay University Ethics Committee (with the decision dated 17.07.2020, number: 41901325-050.99 and decision numbered 2020/01).

Annex-1. Coronavirus Anxiety Scale [14]

1.	I felt dizzy and dull or was about to faint when I read or heard the coronavirus news.				
	a. Always	b. Usually	c. Sometimes	d. Seldom	e. Never
2.	I had problems with falling asleep or sleeping because I thought about coronavirus.				
	a. Always	b. Usually	c. Sometimes	d. Seldom	e. Never
3.	I felt like having a stroke or petrified when I thought about coronavirus or was subject to these issues.				
	a. Always	b. Usually	c. Sometimes	d. Seldom	e. Never
4.	I lost my appetite when I thought about coronavirus or was subject to these issues.				
	a. Always	b. Usually	c. Sometimes	d. Seldom	e. Never
5.	I had nausea or stomach discomfort when I thought about coronavirus or was subject to these issues.				
	a. Always	b. Usually	c. Sometimes	d. Seldom	e. Never

Results

Ninety-eight patients (Female: 65 (66.3%); Male: 33 (33.7%)) were recruited in the study, of the study population; the mean age was 41.18 ± 13.76 years, and the mean duration of therapy was 10 (2-48) months.

The patients' 3-month adherence to therapy during March-April-May 2020 was 42.9%. Monthly, it was the lowest during April (56.1%). The most common government-related reasons affecting adherence to therapy were curfew (51%) and travel restrictions (43.9%), whereas the most common patient-related reasons were fear of contracting SARS-CoV-2 and fear of transmitting SARS-CoV-2 to family members (48%).

During the pandemic, 65.3% of the patients had additional complaints and the most common complaint was itching (58.2%). The rate of patients who required an additional treatment during this period was 42.9% and the most commonly used treatment was oral antihistamines (41.8%). During this period, seven (7.1%) patients were admitted to the emergency department due to complaints of chronic urticaria, and 10.2% of the patients used herbal supplements in addition to their current treatments.

There was no significant difference in responses given in the anxiety scale between the patients adherent to omalizumab therapy during the pandemic and those nonadherent to the therapy (p: 0.492, p: 0.915, p: 0.601, p: 0.735, p: 0.786, respectively) (Table 2).

There were no significant differences in age, gender, education status, status of atopy, comorbidities, duration of omalizumab therapy, and status of receiving allergen immunotherapy between the patients adherent to omalizumab therapy during the pandemic and those nonadherent to the therapy (p: 0.437, p: 0.422, p: 0.467, p: 0.384, p:0.681, p: 0.391, p: 0.185, respectively). Although rates of admissions to the emergency department, an increase in symptoms of urticaria, and need for an additional treatment were higher in the patients with chronic urticaria who were nonadherent to omalizumab therapy compared to the patients adherent to omalizumab therapy, this difference was not statistically significant (p: 0.113, p: 0.216, p: 0.141, respectively). However, fear of contracting the virus and fear of transmitting the virus to the family members were statistically significantly higher in the patients with chronic urticaria who were nonadherent to omalizumab therapy compared to the patients adherent to omalizumab therapy (p: 0.001 and p: 0.001, respectively) (Table 3).

Table 1. Demographic features of the patients

Parameters	Results
Age, year	41.18 ± 13.76 Female: 41.46 ± 13.53 Male: 40.64 ± 14.39
Gender, female, n (%)	65 (66.3)
Education, n (%)	
Illiterate	6 (6.1)
Primary School	38 (38.8)
High School	28 (28.6)
University	26 (26.5)
Atopy, n (%)	No Atopy: 54 (55.1) House dust mite allergy: 19 (19.4) Pollen allergy: 17 (17.3) Venom allergy: 2 (2.0) Food allergies: 6 (6.1)
Comorbidities, n (%)	No comorbidities: 80 (81.6) Diabetes mellitus: 9 (9.2) Hypertension: 4 (4.1) Coronary artery disease: 1 (1.0) Hypothyroidism: 3 (3.1)
Duration of the disease, year	10 (2-48)
Omalizumab, dose	300 mg/ 4w: 96 (98) 300 mg/2w: 2 (2)
Immunotherapy, n (%)	4 (4.1)
Adherence to therapy, n (%)	42 (42.9)
March	64 (65.3)
April	55 (56.1)
May	55 (56.1)
Government-related reasons, n (%)	
Curfew	50 (51)
Travel restriction	43 (43.9)
COVID-19 disease	5 (5.1)
COVID-19 quarantine	2 (2.0)
Individual-related reasons, n (%)	
Fear of SARS-CoV-2 transmission	49 (50)
Fear of transmitting SARS-CoV-2 to family	47 (48)
Accessing drugs directly from pharmacies	12 (12.2)
Not feeling the need for treatment	9 (9.2)
COVID-19 quarantine	3 (3.1)
Need for additional treatment, n (%)	42 (42.9) Anti-histamines: 41 (41.8) Oral steroids: 4 (4.1) Leukotriene inhibitors: 4 (4.1)
Admission to emergency department, n (%)	7 (7.1)
Increase in symptoms, n (%)	64 (65.3) Pruritus: 57 (58.2) Wheals: 21 (21.4) Angioedema: 8 (8.2)
Those receiving alternative treatments, n (%)	10 (10.2)

COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Table 2. Comparison of groups adherent and not adherent to treatment

Parameters	Patients adherent to treatment (n: 42)	Patients not adherent to treatment (n: 56)	p
Age, year	39.93 ± 12.83	42.13 ± 14.46	0.437
Gender, female, n (%)	26 (61.9)	39 (69.6)	0.422
Education, n (%)			
Illiterate	1 (2.4)	5 (8.9)	0.467
Primary School	15 (35.7)	23 (41.1)	
High School	13 (31.0)	15 (26.8)	
University	13 (31)	13 (23.2)	
Atopy, n (%)			
No Atopy	27 (64.3)	27 (48.2)	0.384
House dust mite allergy	7 (16.7)	12 (21.4)	
Pollen allergy	4 (9.5)	13 (23.2)	
Venom allergy	1 (2.4)	1 (1.8)	
Food allergies	3 (7.1)	3 (5.4)	
Comorbidities, n (%)			
No comorbidities	35 (83.3)	45 (80.4)	0.681
Diabetes mellitus	3 (7.1)	6 (10.7)	
Hypertension	1 (2.4)	3 (5.4)	
Coronary artery disease	1 (2.4)	0	
Hypothyroidism	2 (4.8)	2 (3.6)	
Duration of the disease, month	9.50 (2-48)	10 (3-40)	0.391
Immunotherapy, n %	3 (7.1)	1 (1.8)	0.185
Fear of SARS-CoV-2 transmission	0	49 (87.5)	0.001
Fear of transmitting SARS-CoV-2 to family	0	47 (83.9)	0.001
Need for additional treatment during pandemic, n (%)	15 (35.7)	27 (48.2)	0.216
Admission to emergency department, n (%)	1 (2.4)	6 (10.7)	0.113
Increase in symptoms, n (%)	24 (57.1)	40 (71.4)	0.141
Those receiving alternative treatments, n (%)	5 (11.9)	5 (8.9)	0.630

COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Table 3. Responses of patients using monoclonal antibodies to the COVID-19 anxiety questionnaire

Questions	Answers	Patients adherent to therapy (n: 42)	Patients not adherent to treatment (n: 56)	p
Question 1, n (%)	Always	1 (2.4)	1 (1.8)	0.492
	Usually	4 (9.5)	4 (7.1)	
	Sometimes	1 (2.4)	6 (10.7)	
	Seldom	12 (28.6)	11 (19.6)	
	Never	24 (57.1)	34 (60.7)	
Question 2 n (%)	Always	1 (2.4)	2 (3.6)	0.915
	Usually	3 (7.1)	4 (7.1)	
	Sometimes	3 (7.1)	6 (10.7)	
	Seldom	12 (28.6)	12 (21.4)	
	Never	23 (54.8)	32 (57.1)	
Question 3 n (%)	Always	1 (2.4)	2 (3.6)	0.601
	Usually	1 (2.4)	5 (8.9)	
	Sometimes	4 (9.5)	3 (5.4)	
	Seldom	6 (14.3)	10 (17.9)	
	Never	30 (71.4)	36 (64.3)	
Question 4 n (%)	Always	0	2 (3.6)	0.735
	Usually	3 (7.1)	5 (8.9)	
	Sometimes	3 (7.1)	5 (8.9)	
	Seldom	13 (31.0)	14 (25)	
	Never	23 (43.4)	30 (56.6)	
Question 5 n (%)	Always	1 (2.4)	1 (1.8)	0.786
	Usually	3 (7.1)	4 (7.1)	
	Sometimes	4 (9.5)	2 (3.6)	
	Seldom	9 (21.4)	11 (19.6)	
	Never	25 (59.5)	38 (67.9)	

COVID-19: Coronavirus disease 2019

Discussion

COVID-19 pandemic has influenced the whole world not only in the medical aspect but also in several aspects including economic, social, and cultural. The extremely high rate of transmission has affected international and intercity travels and curfews and social isolation has come with many mental and psychological problems [15, 16]. The leading group of the groups most commonly affected by these restrictions is the patients who require to admit to health institutions at regular intervals due to their chronic diseases and to receive regular treatment. The patients who require receiving omalizumab due to chronic urticaria are also included in this chronic patient group. In our study, adherence to therapy of the patients with chronic urticaria who were receiving omalizumab during the 3 months of the pandemic had reduced to 42.9%. Furthermore, fear of contracting SARS-CoV-2 and fear of transmitting SARS-CoV-2 to family members were determined to be higher in patients with low adherence to omalizumab therapy compared to the patients adherent to omalizumab therapy.

During the COVID-19 pandemic, reductions in admissions to many outpatient clinics and emergency departments and many outpatient services have been carried on with telemedicine method or through consultations by phone calls [5, 7, 9]. Perez et al. reported that there was a reduction by 81.7% in admissions to hospitals, by 64.6% in hospitalizations, and by 53.5% in admissions to pediatric emergency departments in Spain between 15th March 2020 and 15th April 2020 [17]. In Italy, a reduction by 73-88% in admissions to hospitals between 1 to 27 March was reported [18]. During the same period, a 70%-increase was reported in the use of telemedicine [19]. In a study conducted in Turkey by Ozturk et al., the use of telemedicine by allergy clinics ranged between 22% to 73%, depending on the allergic patient groups, and treatment with biological agents was terminated in 25% of the patients receiving a biological agent [9]. In our study, the reduction of adherence to therapy up to 42.9% in the 3 months and 56.1% in one month is consistent with the literature. In our study, a higher rate of fear of contracting and transmitting the virus to other family members in the patients nonadherent to omalizumab therapy compared to those with higher adherence to therapy may have led to, in addition to some restrictions, avoidance from environments with a high risk of transmission such as hospitals by this patient group and, hence, a reduction in their adherence to therapy.

Omalizumab is a monoclonal anti-immunoglobulin E antibody that is quite effective in the treatment of chronic urticaria [11, 12]. In addition, studies are showing that omalizumab is effective in the treatment of chronic urticaria in the COVID-19 pandemic [20, 21]. Although complaints of urticaria, need for additional treatment, and admission to the emergency department were increased in the patients nonadherent to omalizumab therapy during the 3 months of pandemic compared to the group adherent to therapy, this difference was not significant. The smaller study population may have led to this situation. In addition, consideration of the patients who did not come to the hospital for at least one month during March-April-May as nonadherent to therapy and the fact that some patients continued to therapy after a one- or two-month interval may have contributed to taking the symptoms under control and to the reduction of the need for treatment.

In conclusion, during the pandemic, patients' adherence to therapy

has reduced due to both government-related and patient-related reasons. For patients with chronic urticaria, their adherence to therapy should be ensured by minimizing the risk of transmission of SARS-CoV-2 following recommendations by international guidelines because of anxiety about the transmission of the virus. Furthermore, to enhance adherence to therapy of this patient group and make access to health institutions easier, it should be considered for these patients to provide some tolerances and privileges in pandemic-related restrictions.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

For the study, a permission was obtained from Turkish Republic Ministry of Health Scientific Research Platform. In addition, an ethics committee approval was obtained from Karatay University Ethics Committee (with decision dated 17.07.2020, number: 41901325-050.99 and decision numbered 2020/015).

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