Evaluation of Patients Treated with Omalizumab (Anti-IgE) During the Pandemic Period

Pandemi Döneminde Omalizumab Tedavisi Alan Hastaların Değerlendirilmesi

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ABSTRACT

Objective: There are few studies investigating the impact of the COVID-19 pandemic on patients using omalizumab. In this study, it was aimed to investigate the effects of the COVID-19 pandemic on our patients who have been treating with omalizumab.

Material and Methods: From two centers, a total of 20 patients participated in the study. A questionnaire, consisting of 45 questions prepared by our department, and a visual analogue scale (0: minimum, 10: maximum) were applied face-to-face to the patients.

Results: It was observed that six patients (30%) did not continue their omalizumab treatment during the pandemic period. While 90% (n=18) of the patients were wearing masks, 85% (n=17) stated that they paid attention to social distance. In our study, the frequency of COVID-19 infection in patients using omalizumab was 10% (n=2). With the pandemic, while our patients' working-study habits were affected negatively (n=10, 50%), their appetite increased (n=8, 40%), and it was noted that there have been changes in their sleep patterns (n=8, 40%).

Conclusion: The COVID-19 pandemic has significantly affected our patients' treatments and follow-ups. Our results support the argument that the use of omalizumab does not increase the risk of SARS-CoV-2 infection.

Key Words: Asthma, COVID-19, Urticaria, Omalizumab

ÖZ

Amaç: Omalizumab kullanan hastalarda COVİD-19 pandemisinin etkisini araştıran az sayıda çalışma bulunmaktadır. Bu çalışmada, omalizumab tedavisi alan hastalarımızda COVİD-19 pandemisinin etkilerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışmaya iki merkezden toplam 20 hasta katıldı. Hastalara tarafımızca hazırlanan 45 sorudan oluşan anket ve görsel analog skala (0: minimum, 10: maksimum) yüz yüze uygulandı.

Bulgular: Altı hastanın (%30) pandemi döneminde omalizumab tedavisine devam etmediği görüldü. Hastaların %90'ı (n=18) maske takıyorken, %85'i (n=17) sosyal mesafeye dikkat ettiğini belirtti. Çalışmamızda omalizumab kullanan hastalarda COVİD-19 enfeksiyon sıklığı %10 (n=2)'di. Pandemi ile hastalarımızın ders çalışma alışkanlıkları olumsuz etkilenirken (n=10, %50), iştahlarının arttığı (n=8, %40) ve uyku düzeninde değişiklikler (n=8, %40) olduğu tespit edildi.

Sonuç: COVİD-19 pandemisi hastalarımızın tedavi ve takiplerini önemli ölçüde etkilemiştir. Sonuçlarımız, omalizumab kullanımının COVİD-19 enfeksiyonu riskini artırmadığı görüşünü desteklemektedir.

Anahtar Sözcükler: Astım, COVİD-19, Ürtiker, Omalizumab

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INTRODUCTION

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by World Health Organization on March 11, 2020. Although countries have developed rapid and effective strategies to prevent the virus, it spread worldwide (1,2). Studies have shown that children are much less affected by COVID-19 than adults, and their clinical symptoms are often milder (3).

Omalizumab is a recombinant human IgG1 anti-IgE monoclonal antibody and is widely used for the treatment of severe asthma and chronic urticaria (4,5).

During the COVID-19 pandemic, there has been confusion about the management of patients treated with monoclonal antibodies, e.g. omalizumab. It has been stated that especially for these patients if they are infected with SARS-CoV-2, an Allergy/Immunology Specialist should be consulted and it should be discussed whether omalizumab and other biological agents are safe for the continuation of their treatment (6-9).

Even though monoclonal antibodies are generally considered safe in adults; the data, which is from clinical studies, on long-term use of the drug is limited (10). It is recommended to continue using omalizumab during the COVID-19 pandemic, in spite of the fact that there are not enough studies on this subject (11). In our study, we aimed to evaluate the attitudes of our patients treated with Omalizumab during the COVID-19 pandemic and to determine whether the use of anti-IgE poses a risk for SARS-CoV-2 infection.

MATERIALS and METHODS

Twenty patients with Omalizumab treatment, followed by Pediatric Allergy Departments of Uludağ University Medical Faculty Hospital and Sakarya University Medical Faculty Training and Research Hospital, participated in the study. The questionnaire consisting of 45 questions prepared by our department, which was applied face to face, questioned the lifestyle changes of the patients during the pandemic period, their anxiety levels about the risk of transmission, the protection methods they applied to prevent transmission, and the clinical course of the disease of the patients if they infected with COVID-19.

In addition to that to measure our patients' concerns about SARS-CoV-2 infection, a test consisting of 8 questions scored with a visual analogue scale (0: minimum, 10: maximum) was applied. Visual analogue scale scoring is a scale method used to digitize some values that cannot be measured quantitatively. In the VAS scoring system, scoring is done between 0-10. The increase in the numbers in the answers given to the questions indicates an increase in the anxiety-worry rate. Number zero indicates no concern, whereas number ten indicates very

severe anxiety. Our study was approved by Ethics Committee of Uludağ University Faculty of Medicine as a number of 2021-2/24.

Statistics

Statistical analyses were performed using the SPSS 23 (IBM corp.) statistical package. Categorical data were expressed as frequencies and percentages, continuous data as mean ± standard deviation (SD) or median (minimum and maximum). Kolmogorov-Smirnov test and histogram were used to test the normality of the data distribution. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test.

RESULTS

The mean age of the patients was 16 (8-21) years, and the female/male ratio was 9/11. The diagnosis of the patients was chronic urticaria (n=13, 65%) and asthma (n=7, 35%). Atopic dermatitis was seen in 5 (25%) patients, allergic rhinitis in 4 (20%) and allergic keratoconjunctivitis in 1 (5%) patients, in order of accompanying comorbid diseases. Other treatments received by the patients are shown in Table I. Antihistamine and montelukast treatment were used in three patients. Two patients were receiving immunotherapy treatment in addition to omalizumab treatment. There was an increase in patient complaints of five patients (25%) during the pandemic period. While three patients using omalizumab, one with asthma and two with urticaria, had symptoms; two patients with asthma and urticaria had an increase in their complaints who discontinued omalizumab.

Omalizumab was administered 150 mg/month in 4 (30.7%) and 300 mg/month in 9 (69.3%) patients with chronic urticarial. The mean duration of patients receiving omalizumab treatment was 15.6 (2-48) months. Treatment of 3 patients with chronic urticaria was increased from 150 mg/month to 300 mg/month due to the persistence of symptoms. The dose was increased to 600 mg/month in 2 asthmatic patients because of failure of asthma control with 300 mg/month of omalizumab treatment. All but one of the patients using omalizumab therapy (n=19, 95%) reported that they benefited from the treatment. The treatment doses in the last controls of 20 patients treated with

Table II: Other treatments used by patients.

Drugs	n (%)
Inhaled steroid	5 (25)
Montelukast	3 (15)
Long-acting Beta2 Agonist	0
Immunotherapy	2 (10)
Nasal steroid	0
Antihistamine	3 (15)

Table II: According to diagnoses; lifestyle changes, compliance with methods of protection against COVID-19 infection.			
	Asthma n (%)	Urticaria n (%)	p
Have you had a diagnosis with COVID-19?	0	2	0.270
Have you been hospitalized due to a COVID-19 infection?	0	0	-
Changes in treatment during the COVID-19 pandemic			
No	4 (57.1)	7 (53.8)	
Those whose treatment was interrupted	2 (28.6)	4 (30.8)	0.860
New drugs added to their treatment	0 (0)	1 (7.7)	
Changing the medication regimen	1 (14.3)	1 (7.7)	
Has there been an increase in complaints about your illness during the COVID-19 pandemic?			0.780
Yes	2 (28.6)	3 (23.1)	
No	5 (71.4)	10 (76.9)	
The use of mask outside,			
Yes	7 (100)	11 (86.4)	0.270
No	0 (0)	2 (15.4)	
Regular attendance at school,			
Yes	4 (57.1)	8 (61.5)	0.840
No	3 (42.9)	5 (38.5)	
Do you think your school success was affected during the COVID-19 pandemic?			
Yes	6 (85.7)	9 (81.8)	0.820
No	1 (14.3)	2 (18.2)	
Keeping a distance of at least 1.8 meters from people,			
No	0 (0)	0 (0)	
Yes	6 (85.7)	11 (84.6)	0.940
Sometime	1 (14.3)	2 (15.4)	
Keeping a distance of at least 1.8 meters from family members within the home,			
Yes	2 (28.6)	2 (15.4)	0.480
No	5 (71.4)	11 (84.6)	
Have you lived in the same house as the person diagnosed with Covid-19?			
Yes	1 (25)	1 (10)	0.490
No	3 (75)	9 (90)	
The use of mask in the home,			
No	7 (100)	13 (100)	-
Yes	0 (0)	0 (0)	
Have you had contact with a person who has been diagnosed with Covid-19?			
Yes	1 (14.3)	2 (15.4)	0.940
No	6 (85.7)	11 (84.6)	
Have you ever stopped going to the hospital for fear of contracting a SARS-CoV-2 infection despite your symptoms?			0.780
Yes	2 (28.6)	3 (23.1)	
No	5 (71.4)	10 (76.9)	
Have you used an herbal medicine during the COVID-19 pandemic period?			
Yes	0 (0)	2 (15.4)	0.270
No	7 (100)	11 (84.6)	
Do you believe that the COVID-19 pandemic will be over ?			
Yes	2 (28.6)	6 46.2	0.440
No	5 (71.4	7 53.8	
Have you ever been unable to receive omalizumab treatment due to the pandemic			
Yes	2 (28.6)	4 (30.8)	0.910
No	5 (71.4)	9 (69.2)	
Have you stopped taking omalizumab yourself due to the pandemic?			
Yes	2 (28.6)	2 (15.4)	0.480
No	5 (71.4)	11 (84.6)	
Do you think that omalizumab treatment can have a negative effect on SARS-CoV-2 infection?			0.160
Yes	1 (14.3)	0 (0)	
No	6 (85.7)	11 (100)	

	Asthma n (%)	Urticaria n (%)	p
Would you get the Covid-19 vaccine?			
Yes	5 (71.4)	10 (76.9)	0.780
No	2 (28.6)	3 (23.1)	
Did you have a hard time finding the medications you use constantly during the pandemic?			
No	7 (100)	13 (100)	-
Has there been any change in sleep patterns during the pandemic period?			
No	4 (51.7)	8 (61.5)	0.890
Prolongation of sleep time	1 (14.3)	1 (7.7)	
Shortening of sleep time	2 (26.8)	4 (30.8)	
Has your appetite changed due to the Covid -19 pandemic?			
No	4 (57.1)	8 (61.5)	
Increased appetite	3 (42.9)	5 (38.5)	0.840
Decreased appetite	0 (0)	0 (0)	
Has there been a change in your body weight?			
No	4 (57.1)	7 (53.8)	0.880
Yes	3 (42.9)	6 (46.2)	
Change in the economic situation?			
No	4 (51.7)	9 (69.2)	
Positively affected	0 (0)	2 (15.4)	0.270
Negatively affected	3 (42.9)	2 (15.4)	
Have you been affected by the pandemic in your relationship with your parents?			
No	5 (71.4)	10 (83.3)	0.530
Negatively affected	2 (28.6)	2 (16.7)	
Have you had a change in your study/work habits during the COVID-19 pandemic?			
No	2 (28.6)	5 (41.7)	0.820
Positively affected	1 (14.3)	1 (8.3)	
Negatively affected	4 (57.1)	6 (50)	

Table III: Evaluation of anxiety levels about SARS-CoV-2 infection by VAS (visual analogue score).		
	Mean± Std	**Min.-max.**
How afraid are you of the COVID-19 infection in general?	5.15±2.207	0-10
Do you believe that COVID-19 will infect you more easily?	3.75±3.092	0-10
How afraid are you of going out during the pandemic period?	4.15±2.739	0-10
Are you worried about the spread of COVID-19 from market products coming from outside the home?	3.40±3.033	0-10
Have your concerns about your health increased during the pandemic period?	4.50±3.170	0-10
Are you afraid to go to the hospital during the pandemic period?	5.85±3.55	0-10
How sad is it for you not to go out during the pandemic period?	6.00±3.583	0-10
How much do you think the COVID-19 pandemic has affected your treatment?	3.90±3.905	0-10

omalizumab were 150 mg/month in 5 patients, 300 mg/month in 13 patients, and 600 mg/month in 2 patients.

For six patients (30%), omalizumab treatment was interrupted during the COVID-19 pandemic. Four of them had self-terminated the treatment. Four patients stated that they stopped treatment because they were worried to go to the hospital during the pandemic. On the other hand, the treatment of two patients diagnosed with chronic urticaria was stopped by us because symptom control was provided.

In our study, the incidence of SARS-CoV-2 infection was 10% (n=2). During the pandemic period, one patient infected with SARS-CoV-2 never took a break from his treatment, while the other took a break for 2 months by himself and then continued regularly. Patients infected with SARS-CoV-2 were monitored at home and no symptoms requiring hospitalization were observed. The first patient who used omalizumab for the diagnosis of asthma became infected with SARS-COV 2 at the 10th month of treatment. The patient stated having mild fatigue and fever during the COVID-19 infection, but asthma attacks increased and symptom control worsened following the Post-COVID-19 period. The other patient who was treated with omalizumab with the diagnosis of chronic urticaria became infected with SARS-COV-2 at the 4th month of treatment. Mild nasal discharge and fatigue were observed as symptoms, but

Tablo IV: Evaluation of anxiety levels about SARS-CoV-2 infection by VAS (visual analogue score) according to the diagnoses.

	Asthma (Mean± Std)	Urticaria (Mean± Std)	p
How afraid are you of the SARS-CoV-2 infection in general?	5.71±3.147	4.85±1.573	0.410
Do you believe that SARS-CoV-2 will infect you more easily?	4.14±3.532	3.54±2.961	0.680
How afraid are you of going out during the pandemic period?	4.29±3.773	4.08±2.178	0.870
Are you worried about the spread of SARS-CoV-2 from market products coming from outside the home?	2.71±2.360	3.77±3.370	0.470
Have your concerns about your health increased during the COVID-19 pandemic period?	4.14±3.716	4.69±2.983	0.720
Are you afraid to go to the hospital during the COVID-19 pandemic period?	4.71±3.251	6.46±3.688	0.300
How much do you think the COVID-19 pandemic has affected your treatment?	3.43 ± 3.457	4.15±4.240	0.700
How sad is it for you not to go out during the COVID-19 pandemic period?	6.00±3.606	6.00±3.719	1.000

Table V: Evaluation of anxiety levels related to SARS-CoV-2 infection by VAS (visual analogue scale) in patients with and without a change in sleep pattern.

	Sleep pattern changes (Mean± Std)	No change in sleep pattern (Mean± Std)	p
How afraid are you of the COVID-19 infection in general?	4.63±2.973	5.50±1.567	0.510
Do you believe that COVID-19 will infect you more easily?	3.63±2.973	3.83±2.887	0.410
How afraid are you of going out during the pandemic period?	4.63±3.292	3.83±2.406	0.720
Are you worried about the spread of COVID-19 from market products coming from outside the home?	3.75±3.284	3.17±2.980	0.860
Have your concerns about your health increased during the pandemic period?	6.00±3.505	3.17±2.167	0.170
Are you afraid to go to the hospital during the pandemic period?	6.00±4.375	5.75±3.108	0.110
How sad is it for you not to go out during the pandemic period?	6.00±4.243	6.00±3.275	0.330
How much do you think the COVID-19 pandemic has affected your treatment?	5.00±4.064	3.17±4.064	0.380

no urticaria attack was observed during and after the infection. Covid symptoms of both patients lasted for about 5 days.

While 90% (n=18) of the patients were wearing masks, 85% (n=17) stated that they paid attention to social distance. The proportion of patients who followed the social distance rule with the mask was 85%.

For the "Do you get the COVID-19 vaccine?" question, 15 people (75%) answered yes. Among the questions asked about the sleep duration, change in appetite, and the effect of the pandemic on family relations of our patients, It was observed that among them, the ones most commonly negatively affected were study-working habits (n=10, 50%), appetite (n=8, 40%), and sleep duration (n=8, 40%). Four (20%) patients stated that their relationships with their parents were negatively affected by the pandemic. Only 5 patients (25%) stated that their economic situation was adversely affected.

According to the diagnosis, there was no significant difference between diagnoses, lifestyle changes, and compliance with methods of protection against SARS-CoV-2 infection (Table II).

Patients reported that their study/working habits were affected negatively, their appetite increased and sleep duration was shortened. The evaluation of patients' concerns about SARS-CoV-2 infection with VAS (visual analogue scale) is shown in Table III. The question "How sad is it not to go out during the pandemic period?" which was asked to the patients who had the highest score on the VAS. The situation they were least concerned about was that 'COVID-19' would be easy to infect them. There was no significant difference in the VAS scores of the patients according to the diagnoses (Table IV). No statistically significant difference was found between VAS anxiety scores in all patient groups based on whether or not they had sleep disorders (Table V).

DISCUSSION

In our study, the effects of the pandemic period on our patients who were treated with omalizumab for asthma and chronic urticaria were investigated. Recommendations are presented

for the management of allergic diseases, which are an important health problem worldwide during the COVID-19 pandemic.

Considering the balance between pros and cons, for patients receiving asthma treatment, if there is no opportunity for individualized treatment and the patient cannot be involved in the medical decision-making process, it has been recommended that the patient's disease-controller medication should not be "stepped down". In the follow-up of chronic urticaria, postponing the follow-ups, initiating antihistamine twice a day, and postponing laboratory tests in most of the patients were recommended as suggestions (12). It has been stated that more frequent follow-up or face-to-face visits should be considered, including initiation of omalizumab protocol in resistant urticaria; on the other hand, face-to-face visits of patients with well-controlled urticaria may be delayed (13,14).

After omalizumab treatment, the decrease in IL-33 levels and the increase in the production of proinflammatory cytokines (including IL-6, IL-1β, TNF-α, MCP-1, and prostaglandin D2) will affect the SARS-CoV-2 infection, where pro-inflammatory cytokines are already increased. (15,16). The American Academy of Allergy, Asthma, and Immunology (AAAAI) stated that biologic therapies can be continued in patients with proven efficacy unless there is any report showing the harmful potential of anti-IgE therapy during the pandemic period (17). In other guidelines that have been published so far, discontinuation of omalizumab treatment has not been recommended (18,19).

Because patients with severe asthma are at higher risk of severe SARS-CoV-2 infection, optimal control of chronic disease is extremely important (20). At this point, the continuation of the control status of the patients whose diseases were controlled with omalizumab is critical importance. Although the advantage of omalizumab treatment provides effective disease control, it also has the disadvantage of frequent hospital admissions requirements for injection and thus increasing the risk of viral exposure (21). To overcome this problem during the pandemic period, the option of self-administration at home has been brought to the agenda.

In another study an online questionnaire was applied to 41 patients who switched to at-home treatment with omalizumab in the hospital during the pandemic period. Ninety-three percent (93%) of the patients preferred self-injection at home. Concerns about the home environment were reported less frequently; 18% of patients fear of wrong injection (n = 7/40), 13% feared forgetting a dose (n = 5/38) and 15% feared developing an adverse reaction to omalizumab (n = 6/ 39) reported respectively (22). In a study evaluating patients with asthma who received omalizumab treatment in the hospital, only 44.7% of the patients reported that they preferred to switch to self-injection at home (23).

Our study as being the first in Turkey to evaluate patients using omalizumab during the pandemic period, omalizumab treatment was applied in the hospital during the pandemic period, as it was in the pre-pandemic period, since the at home-use preparation of omalizumab has not yet been approved for use on our patients. In our country, at home-omalizumab treatment is not applied yet. For six patients (30%), omalizumab treatment was interrupted during the pandemic period. Four of them had self-terminated treatment. There was no hospitalization under omalizumab therapy.

In the joint recommendation of European Allergy Societies (German Society of Allergy and Clinical Immunology, Austrian Society of Allergy and Immunology, European Academy of Allergy and Clinical Immunology, Luxembourg Society of Allergy and Clinical Immunology, Austrian Pneumology Society), suggested that children who have mild SARS-CoV-2 infection and treated with biologic agents, their treatment can be continued. However, the treatment should be postponed until recovery in adults or children who develop severe COVID-19 symptoms (24). Among the patients in our study, omalizumab treatments were not administered during the disease in patients with SARS-CoV-2 infection as a precaution.

In a study, it was determined that the COVID-19 pandemic caused anxiety in adolescents (25). As Ding et al. conducted in a study, in the adolescent group, anxiety scores were found to be high (26). Likewise, in our study, an increase in anxiety rates against COVID-19 infection and a negative impact on study habits were found in our patients, most of who were in the adolescent age group, in line with studies that have been done before.

Anxiety developing due to any reason, including the pandemic period, and sleep disturbance as a result of depression are expected situations (27). In a randomly selected adult survey conducted in Spain during the pandemic period, 39.7% of the participants stated that they had lower quality sleep, most often with difficulty falling asleep (28). In a study on lifestyle changes in asthmatic patients of the pandemic, changes in sleep patterns were found in 38.7% of asthmatic patients and 42.9% of controls. In addition, it has been determined that asthmatic patients with changes in sleep patterns have a higher fear of contagion against SARS-CoV-2 infection (29). In our study, changes in sleep patterns were detected in 40% of our patients. In addition, there was no statistically significant difference in the evaluation of anxiety levels related to SARS-CoV-2 infection by VAS (visual analogue scale) between our patients with and without a change in their sleep pattern. In general, we thought that the patients did not have much worry and anxiety due to the below-average scores of the answers given to the VAS scoring.

In a survey study on the disruptions in the education of university students in Romania; lack of communication with teachers, lack of opportunity to carry out practical applications, and high probability of passing online exams (e.g. probability of cheating); it was stated that their desire and motivation to study decreased (30). In a study, which conducted in India, the

survey questioned about the quality of the instructor, course design, student expectations, satisfaction, and performance in an online platform of 544 university students and it showed that among the factors that are studied, the most important factor affecting student satisfaction in online courses was found to be the quality of the instructor. When all factors were evaluated, they concluded that both teachers and students have equal responsibility for better performance in lessons (31). Similarly, it was determined that 50% of our patients had a worse effect on their study habits, and it was thought that this could be the factor of the first encounter with online education, low motivation due to pandemic anxiety and the trainer. Questioning the patients about the underlying reason for the decline in their study habits was not done in this study.

In conclusion, our patients using omalizumab had a mild clinical course of SARS-CoV-2 infection. Although no adverse effect was observed in 2 patients who received omalizumab treatment during COVID-19 infection, this is insufficient to generalize. The widespread use of home treatment will facilitate the treatment of patients in difficult conditions such as the COVID-19 pandemic. In our patients participating in the study; lifestyle changes, disruption in sleep patterns, changes in eating habits and study habits, and an increase in anxiety levels due to the risk of infection have been detected. Anxiety that develops as a result of deterioration in the quality of life and lifestyle changes, especially in adolescent patients, should be further investigated during physician visits.

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