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ÖZGÜN ARAŞTIRMA /ORIGINAL ARTICLE

Effect of the SARS-CoV-2 Pandemic on Treatment Processes of Patients with Severe Asthma Who Were Receiving Monoclonal Antibody Treatment

Monoklonal Antikor Tedavisi Verilen Ağır Astımlı Hastaların Astım Kontrolüne ve Tedavi Süreçlerine SARS-CoV-2 Pandemisinin Etkisi

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Abstract

Objective: Patients with severe asthma are at particularly higher risk for SARS-CoV-2 infection and disease severity due to exacerbations of asthma caused by viral infections, SARS-CoV-2 viral load at hospitals and challenges in access to health¬care facilities due to some restrictions. Thus, we aimed to investigate effect of the SARS-CoV-2 pandemic on treatment and control of asthma in patients receiving monoclonal antibody (MAb) treatment.

Material and method: The patients, who were using MAb for treatment of for severe persistent asthma, were enrolled. Each patient was asked to fill in a validated Coronavirus anxiety scale and a mini survey.

Results: Sixty-two patients (Female: 44; Male: 18), who were given MAb therapy for asthma, were enrolled. Patients' treat¬ment compliance was 56.5% in March-April-May 2020. Curfew was the most common government-related factors that have influenced patients' compliance to treatment (35.5%). The most common individual factor was fear of contracting SARS-CoV-2 (40.3%). Exacerbated symptoms and need for additional treatment for asthma were significantly more common in patients, who were not compliant to treatment, compared to the patients adherent to MAb treatment (p= 0.034 and p= 0.013)

Conclusion: Treatment compliance has reduced in patients, who take MAb treatment, due to both governmental and individual reasons. This has led to more common admissions to emergency department with complaints of asthma and need for an additional treatment. All these findings indicate that patients should maintain their MAb treatments despite the pandemic and that they should minimize the risk of SARS-CoV-2 infection by following the recommendations published in the guidelines.

Öz

Amaç: Ağır astımı olan hastalar, viral enfeksiyonların neden olduğu astım alevlenmeleri, hastanelerdeki SARS-CoV-2 viral yükü ve bazı kısıtlamalar nedeniyle sağlık tesislerine erişimdeki zorluklar ve tedavilerindeki aksamalar nedeniyle özellikle SARS-CoV-2 enfeksiyonu ve hastalığın şiddeti açısından daha yüksek risk altındadır. Bundan dolayı monoklonal antikor (MAb) tedavisi alan hastalarda SARS-CoV-2 pandemisinin astım tedavisi ve kontrolü üzerindeki etkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Ağır persistan astım tedavisi için MAb kullanan hastalar çalışmaya dahil edildi. Her hastadan onaylanmış bir Coronavirüs kaygı ölçeği ve mini bir anket doldurması istendi.

Bulgular: Ağır astım nedeniyle MAb tedavisi alan 62 hasta (Kadın: 44; Erkek: 18) çalışmaya alındı. Mart-Nisan-Mayıs 2020'de hastaların tedaviye uyumu %56.5 idi. Sokağa çıkma yasağı, hastaların tedaviye uyumunu (%35.5) etkileyen en yaygın hükümetle ilgili faktör olarak saptandı. En yaygın bireysel faktör, SARS-CoV-2 kapma korkusuydu (%40.3). Tedaviye uyum sağlamayan hastalarda, MAb tedavisine uyan hastalara göre, semptomlarda artış ve astım için ek tedavi gereksinimi anlamlı olarak daha fazlaydı (p= 0.034 ve p= 0.013)

Sonuç: MAb tedavisi alan hastalarda hem resmi hem de bireysel nedenlerle tedaviye uyum azalmıştır. Bu durum acil servise astım şikayetleri ve ek tedavi ihtiyacı ile daha sık başvurulara neden olmuştur. Tüm bu bulgular, hastaların pandemiye rağmen MAb tedavilerini sürdürmeleri gerektiğini ve kılavuzlarda yayınlanan tavsiyelere uyarak SARS-CoV-2 enfeksiyon riskini en aza indirmeleri gerektiğini göstermektedir.

Introduction

Following the initial identification on December 2019 in Wuhan, China, severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) has spread to the world, resulting with one of the most catastrophic pandemics in the history of mankind (1, 2). During approximately 1 year following the initial identification, it has caused death of approximately 1.900.000 people worldwide (3). The principle factor responsible for mortality in SARS-CoV-2 is the cytokine storm caused by abnormally activated immune system and resultant respiratory failure (2). Although some vaccines have been introduced for protection against the disease, vaccination of all people and achievement of an effective public immunity do not seem possible in the near future. Moreover, due to lack of a definitive treat¬ment for the disease, the best way for protection against SARS-CoV-2 includes hand washing, wearing a mask, social distancing and isolation of infected individuals (4). Due to very high infectivity of the disease, all countries have had to take some protective measures, particularly including curfew, as well as intercity- and international travel restrictions in order to prevent spread of the disease. Although these measures protect high-risk patients from SARS-CoV-2 infection to some extent, they have led to problems in their follow-up at hospital and access of the patients to healthcare facilities for inpatient treatment institutions as well as increased anxiety (5). Furthermore, these factors have led to SARS-CoV-2-related fear, worry and anxiety in patients (6). Patients with severe asthma are at particularly higher risk for SARS-CoV-2 infection due to exacerbations of asthma caused by viral infections, increased SARS-CoV-2 viral load at hospitals and challenges in access to healthcare facilities due to several restric¬tions (7-9). However, it has been revealed out that many patients hindered their treatments or did not present asthma outpatient clinics and that they, therefore, did not receive particularly their monoclonal antibody therapy due to the restrictions imposed during this period and fear of SARS-CoV-2 infection.

Thus, we aimed, in this study, to investigate effect of the SARS-CoV-2 pandemic on treatment and control of asthma in patients receiving monoclonal antibody therapy due to severe asthma and to demonstrate government- and/or patient-related reasons by determining patients' reasons for presenting late or not presenting for treatment. In addition, we planned to investigate effects of a delay in monoclonal antibody therapy on symptoms, asthma control and admission to emergency department to due asthmatic complaints and to examine effect of the SARS-CoV-2 pandemic on anxiety levels of these patients.

Material and Methods

The study enrolled the patients, who were being followed-up in our clinic between January 2015 and June 2020 for severe persistent asthma and using monoclonal antibody therapy, such as omalizumab or mepolizumab, for asthma control. Of these patients -admitted to outpatient clinic during March-April-May 2020, when the first case of SARS-CoV-2 from Turkey was reported and some restrictions were imposed in order to reduce the risk of transmission- a mini survey was applied that we have developed particularly for this examination. The mini survey was applied face-to-face in baseline outpatient clinic visit or by phone calls since June 2020 when the normalization process started in Turkey. The mini survey addressed demographics, including patients' age, gender, education status, history of comorbid diseases, presence of atopy, name and dosing frequency of the biological agent and whether an allergen-specific immunotherapy was administered. In addition, we also investigated whether they visited the hospital for monoclonal antibody treatment and whether they presented late or did not present on March-April-May 2020. Government-related reasons (curfew, intercity travel restriction, failure to schedule an outpatient clinic appointment, status of disability and pregnancy etc.) and patient-related factors (fear of viral infection, fear of transmitting the virus to family members, possibility of supplying the drug directly from pharmacies during this period, feeling no need for treatment in this period, Coronavirus disease 2019 (COVID-19) infection or COVID-19 quarantine etc.) were addressed. The patients, who did not present for outpatient clinic control visit at least once on March, April or May 2020 were considered non-compliant to monoclonal antibody therapy. Each patient was also asked to fill in a validated coronavirus anxiety scale (Annex-1) (10).

Annex I. Coronavirus Anxiety Scale (10)

1. I felt dizzy and dull or was about to faint when I read or heard news about coronavirus.
   a. Always b. Usually c. Sometimes
   d. Seldom e. Never

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2. I had problems with falling asleep or staying asleep because I thought about coronavirus.
   a. Always b. Usually c. Sometimes
   d. Seldom e. Never

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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

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4. I lost my appetite when I thought about coronavirus or I was subject to these issues.
   a. Always b. Usually c. Sometimes
   d. Seldom e. Never

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5. I had nausea or stomach discomfort when I thought about coronavirus or I was subject to these issues.
   a. Always b. Usually c. Sometimes
   d. Seldom e. Never

We also investigated their need for an additional treatment (systemic steroids, long-acting beta agonists, short-acting beta agonists, leukotrien receptor antibody, inhaled anticholinergic drug etc.) when they did not receive or received late the monoclonal antibody treatment; admissions to emergency department to due exacerbations of asthma; additional asthmatic complaints (shortness of breath, productive cough, severe expectoration etc.)); and use of a drug, food or herbal supplement during this period.

Study data was analyzed using IBM SPSS Statistics Version 22 software package (New York, United States). Parameters with normal distribution were expressed as mean ± standard deviation, while the parameters without normal distribution were expressed as median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using Chi-square test. Baseline characteristics were compared using independent Student t, Mann-Whitney rank-sum, Fisher exact or Chi-square tests, where appropriate.

The study was approved by Scientific Research Platform of Turkish Ministry of Health. In addition, an ethics committee approval was obtained from the Ethics Committee of Karatay University (Decision Nr. 2020/018 dated 15.12.2020, and numbered 41901325-050.99). The study was carried out in accordance with the principles of the Helsinki Declaration. Informed consent form was obtained from the patients.

Results

Sixty-two patients (Female: 44 (71%); Male: 18 (29%)), who were receiving monoclonal antibody for asthma, were enrolled. Mean age of the study population was 46.52 ± 14.50. Patients' demographics and clinical characteristics are summarized in Table 1.

Patients' compliance to treatment was 56.5% in March-April-May 2020. April was characterized with poorest compliance (59.7%; 80.6% in March; and 71% in May). The most common government-related factors that have influenced treatment compliance were curfew (35.5%) and travel restrictions (32.3%). The most common individual factors were fear of SARS-CoV-2 infection (40.3%) and transmitting SARS-CoV-2 to family members (32.3%) (Table 2). There was no significant difference between patients compliant and non-compliant to monoclonal antibody therapy during March-April-May 2020 in terms of answers given to the anxiety survey (Table 3). Compliant and non-compliant patients did not differ significantly in terms of age, gender, education status and type of the monoclonal antibody (Table 2). Rate of admission to emergency department on March-April-May 2020 due to symptoms of asthma during the pandemic was higher in non-compliant patients than the compliant ones. However, this difference was not statistically significant (p=0.077). Moreover, fear of SARS-CoV-2 infection and transmitting the virus to others was significantly more common in this patient group compared to the patients, who complied with the monoclonal antibody treatment (p=0.001 and p=0.001, respectively). Furthermore, exacerbated symptoms of asthma and need for additional treatment for asthma during the pandemic were significantly more common in non-compliant patients that compliant ones (p=0.034 and p=0.013, respectively, Table 2).

Table I. Demographics parameters of patients

Parameters	Results
Age, year,mean(SD)	46.52 ± 14.50
• Female	46.12 ± 14.35
• Male	47.50 ± 15.25
Gender, female, n (%)	44 (71%)
Education, n (%)	
• Illiterate	10 (16.1)
• Primary School	30 (48.4)
• High School	9 (14.5)
• University	13 (21)
Diagnosis, n (%)	
• Allergic asthma	42 (67.7)
• Non-allergic asthma	20 (32.3)
Atopy, n (%)	
• Non atopic	20 (32.3)
• House dust mite allergy	28 (45.2)
• Mold allergy	7 (11.3)
• Pollen allergy	4 (6.5)
• Animal dander allergy	3 (4.8)
Duration of the disease, year	10 (2-40)
Injections of monoclonal antibody (number)	8 (3-54)
• Omalizumab:	8 (3-54)
• Mepolizumab:	6 (4-10)
Monoclonal antibody, n (%)	
Omalizumab / 4 weeks,mg:	44 (71)
• 150 mg	6 (9.7)
• 300 mg	21 (33.9)
• 450 mg	9 (14.5)
• 600 mg	8 (12.9)
Mepolizumab / 4 weeks:	18 (29)
• 100 mg	18 (29)
Immunotherapy, n (%)	3 (4.8)
Treatment compliance, n (%)	35 (56.5)
• March	50 (80.6)
• April	37 (59.7)
• May	44 (71.0)
Government-related reasons, n (%)	
• Curfew	22 (35.5)
• Travel restriction	20 (32.3)
• COVID-19 disease	5 (8.1)
• COVID-19 quarantine	2 (3.2)
• Pregnancy / disability	1 (1.6)
Individual reasons, n (%)	
• Fear of SARS-CoV-2 infection	25 (40.3)
• Fear of transmitting SARS-CoV-2 to family	23 (37.1)
• Supplying drugs directly from pharmacies	7 (11.3)
• Not feeling need for treatment	3 (4.8)
• Administration of drug in another medical center	2 (3.2)
Need for additional treatment, n (%)	20 (32.2)
• Inhale steroid + SABA	13 (21)
• Systemic steroids	7 (11.3)
• Admission to emergency department, n (%)	3 (4.8)
• Exacerbation of symptoms, n (%)	38 (61.3)

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Table II. Comparison of patients, who comply or do not comply with monoclonal antibody treatment

Parameters	Compliant Patients (n: 35)	Non-compliant Patients (n: 27)	P
Age, year	45.20 ± 13.23	48.31 ± 16.16	0.412
Gender, female, n (%)	24 (68.6)	20 (74.1)	0.636
Education, n (%) • Illiterate • Primary School • High School • University	 3 (8.6) 18 (51.4) 4 (11.4) 10 (28.6)	 7 (25.9) 12 (44.4) 5 (18.5) 3 (11.1)	0.125
Atopy, n (%) • Non atopic • House dust mite allergy • Mold allergy • Pollen allergy • Animal dander allergy	 16 (45.7) 14 (40) 3 (8.6) 1 (2.9) 1 (2.9)	 4 (14.8) 14 (51.9) 4 (14.8) 3 (11.1) 2 (7.4)	0.100
Duration of the disease, n (%)	5 (1-35)	4 (1-30)	0.078
Injections of monoclonal antibody (number)	7 (3-36)	9 (3-54)	0.198
Treatment, n (%) • Omalizumab • Mepolizumab	 25 (71.4) 10 (28.6)	 19 (70.4) 8 (29.6)	0.927
Immunotherapy, n %	2 (5.7)	1 (3.7)	0.715
Fear of SARS-CoV-2 infection	0	25 (92.6)	0.001
Fear of transmitting SARS-CoV-2 to family members	0	23 (85.2)	0.001
Need for additional treatment during pandemic, n (%)	6 (17.1%)	13 (48.1)	0.013
Admission to emergency department, n (%)	0	3 (11.1)	0.077
Exacerbation of symptoms, n (%)	17 (48.6%)	21 (77.8)	0.034

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

Table III. Answers of patients using monoclonal antibodies to the COVID-19 anxiety questionnaire

Questions	Answers	Compliant Patients (n: 35)	Non-compliant Patients (n: 27)	P
Question 1, n (%)	Always Usually Sometimes Seldom Never	0 4 (11.4) 2 (5.7) 2 (5.7) 27 (77.1)	0 4 (14.8) 4 (14.8) 5 (18.5) 14 (51.9)	0.163
Question 2, n (%)	Always Usually Sometimes Seldom Never	0 4 (11.4) 3 (8.6) 5 (14.3) 23 (65.7)	0 3 (11.1) 6 (22.2) 3 (11.1) 15 (55.6)	0.506
Question 3, n (%)	Always Usually Sometimes Seldom Never	0 4 (11.4) 2 (5.7) 1 (2.9) 28 (80)	0 2 (7.4) 5 (18.5) 3 (11.1) 17 (63)	0.196
Question 4, n (%)	Always Usually Sometimes Seldom Never	1 (2.9) 3 (8.6) 2 (5.7) 6 (17.1) 23 (65.7)	0 4 (14.8) 5 (18.5) 5 (18.5) 13 (48.1)	0.362
Question 5, n (%)	Always Usually Sometimes Seldom Never	0 4 (11.4) 3 (8.6) 3 (8.6) 25 (71.4)	0 3 (11.1) 6 (22.2) 5 (18.5) 13 (48.1)	0.213

Discussion

The SARS-CoV-2 pandemic has become a global public health issue that has influenced the whole world. Imposed restrictions and fear of contracting/transmitting SARS-CoV-2 have reduced admissions to medical centers, resulting with a major effect on physician-patient interaction. Due to pandemic-related reasons, the patients refrain from hospital visits, leading to loss of control for chronic diseases and/or delays in patients' access to appropriate treatments. Our study also found that patients' compliance to treatment reduced during the pandemic and, compared to the patients, who were compliant to monoclonal antibody treatment, the non-compliant patients suffered from asthma-related symptoms and needed an additional treatment more commonly and they were also more commonly admitted to emergency department, although the difference was not statistically significant. Furthermore, the non-compliant patients were determined to have higher fear of viral infection or transmitting the virus to others compared to compliant patients.

Reduction in hospital admissions and adherence to treatment during the COVID pandemic is unsurprising. In countries with higher prevalence of COVID-19, such as Italy and United States of America (USA), physical consultations reduced by 80% along with number of open offices (11). Similarly, Jeffrey et al. reported that admissions to emergency departments due to non-COVID conditions have been by 41.5-63.5% in 5 states of the U.S. (Colorado, Connecticut, Massachusetts, New York, and North Carolina) in first 4 months of the pandemic (12). In a study by Ozturk et al., they reported that they have terminated monoclonal antibody therapy due to allergic diseases in 25% of the patients (11). In our current study, rate of outpatient clinic admissions was 56% on March-April-May 2020, with lowest rate in April (59.7%). The most common government-related reasons for the reduction in hospital admissions were curfew and travel restrictions (35.5% and 32.3%, respectively), while the most common patient-related factors were fear of SARS-CoV-2 infection and transmitting the virus to family members (40.3% and 37.1%, respectively). Thus, exemptions for curfew or travel restrictions later during the pandemic for patients with asthma, who need visit a hospital for monoclonal antibody therapy, may be beneficial for easier access to medical centers.

Monoclonal antibodies used for treatment of asthma, such as omalizumab and mepolizumab, have been shown to have some antiviral effects in various studies (13-17). Omalizumab downregulates high-affinity IgE receptors on plasmocytoid dendritic cells; reduces expression of TLR7, a receptor that recognizes virus and induces innate immunity; leads to an increase in levels of other immunoglobulins; and reduces synthesis of IL-6, IL-1β and TNF-α and level of periostin in bronchoalveolar lavage as well as lipopolysaccharide-induced acute lung injury (13-16, 18). Mepolizumab, however, inhibits entry of SARS-CoV-2 virus into epithelial cells, leads to an increase in NK cell counts and local IgA levels, and reduces SARS-CoV-2-induced epithelial injury by decreasing eosinophil counts and eosinophil-derived cytokines and chemokines (17). Due to cumulative antiviral effectiveness of omalizumab, many guidelines on asthma, especially The European Respiratory Society (ERS), The European Academy of Allergy and Clinical Immunology (EAACI) and The Allergic Rhinitis and its Impact on Asthma Foundation (ARIA) guidelines, have reported that treatment for asthma should not be terminated or switched due to SARS-CoV-2-related concerns, or otherwise, asthma control may be lost or systemic steroids may be required for asthma control, and continuation of anti-IgE and anti-IL-5 treatments may reduce virus-induced exacerbations of asthma (7, 19, 20). Our results support the recommendations by the aforementioned guidelines. In our study, asthmatic patients with complete adherence to monoclonal antibody treatment had no admission to emergency department due to asthma during the pandemic. In addition, compared to those with poorer adherence, they had less asthma-related symptoms and needed an additional treatment less commonly during the pandemic. Although home-use of omalizumab has not yet been approved in Turkey, Timmerman et al. reported that 47% of the patients receiving omalizumab for severe asthma would prefer self-administration at home and this rate was 77.6% among teenagers and young adults (21). In similar studies, it has been revealed out that omalizumab can be self-administered at home after appropriate training and it is both cost-effective and time-saving (22, 23). Therefore, especially for Turkey, home-use of omalizumab may be an appropriate treatment option in the future for reduction of adherence to treatment due to some restrictions and individual reasons.

Rapid spread of COVID-19 infection all over the world has influenced both physical and mental health (24). Social distancing, curfews, periods of isolation and quarantine, fear of contracting or transmitting SARS-CoV-2 to loved ones and future concerns affect patients' mental health (5). Vindegaard et al. found a significant increase in depressive and posttraumatic stress symptoms in COVID-19 patients. In the same study, increased depression/depressive symptoms, anxiety and impaired sleep quality were reported in healthcare professionals, and increased anxiety and depression scores in general population (25). In a previous Chinese study, anxiety scores of students with Covid-19 positive relatives, friends and loved ones were higher (26). In our study, anxiety levels regarding the fear of contracting or transmitting the virus to others were lower in patients, who were compliant to monoclonal antibody therapy, than non-compliant patients, indicating potential benefits of the treatment. Furthermore, increased anxiety and fear of transmitting the virus in non-compliant patients may have caused avoidance from environments with higher risk of COVID-19, such as hospitals, leading to a reduction in their adherence to treatment.

The limitation of our study was to evaluate the treatment progress of patients who received monoclonal antibody therapy, it was not compared with patients with severe asthma who did not receive this therapy.

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Conclusion

In conclusion, patients' compliance to monoclonal antibody therapy has reduced because of both governmental and individual reasons. This has led to more common admissions to emergency departments with complaints of asthma and need for an additional treatment. In addition, concerns about transmitting the virus were higher in non-compliant patients compared to compliant ones. All these indicate that patients should continue their monoclonal antibody treatments despite the pandemic, while the risk of transmitting SARS-CoV-2 should be minimized by following the recommendations by the guidelines and science committees.

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