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Safety of allergen immunotherapy in patients with SARS-CoV-2 infection

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ABSTRACT

Objectives: The aims of presenting study were trying to expose the course of SARS-CoV-2 (severe acute respiratory syndrome–related coronavirus) in patients with allergic rhinitis (AR), to compare the prevalence of SARS-CoV-2 infection, hospitalization and pneumonia rates in patients with AR receiving allergen immunotherapy (AIT) and patients did not receiving AIT (non-receivers) and to define possible risk factors for SARS-CoV-2 positivity in patients with AR.

Methods: A total of 419 patients with AR who were being followed-up in a tertiary allergy clinic between June 1, 2020 and December 31, 2020, were selected for the study.

Results: Seventy-nine (18.9%) patients became infected with the SARS-CoV-2 [32 (19.6%) patients in AR patients with AIT and 47 (18.4%) patients in non-receivers] and the rate of pneumonia was 2.4% [12.7% of SARS-CoV-2 (+) patients]. There was no significant difference was determined between the AR patients with AIT and the non-receivers in regard of the rate of SARS-CoV-2 infection, pneumonia and hospitalization (p = 0.864, p = 0.055 and p = 0.075; respectively). There was a significant difference between the groups in terms of gender, duration of disease, sensitivity to allergens (atopy) and serum IgE levels (p = 0.009, p = 0.001, p = 0.001 and p = 0.001; respectively). The accompanying comorbidities, eosinophil cout, AIT and duration of AIT were not found to be associated with an increased risk SARS-CoV-2 PCR positivity. However, female gender was shown to be associated with an decreased risk for SARS-CoV-2 PCR positivity (OR, 0.571; 95% confidence interval, 0.330-0.987; p = 0.045)

Conclusions: The course of SARS-CoV-2 is similar in patients with AR who underwent AIT and patients with AR who did not undergo AIT, and AIT does not seem to increase the risk for SARS-CoV-2 infection.

Keywords: Allergic rhinitis, allergy immunotherapy, subcutaneous immunotherapy, therapeutics

Although unprecedented efforts have been made all over the world to prevent the spread of and contain COVID-19, the number of cases continues to rise, and since it was first identified COVID-19 has become the most pressing health issue globally [1, 2]. There is still no effective treatment for the disease, and due to different virus variants and numerous socioeconomic inequalities, vaccination efforts against the virüs currently do not have the expected speed and effects. Therefore, in terms of both reducing mortality and morbidity, as well as for the efficient utilization of resources, it is very important to identify special patient groups, especially those with chronic diseases and who may be affected to a greater extent by COVID-19, and to investigate the effect of the treatment received by these patiet groups during the course

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of COVID-19.

Allergic rhinitis (AR) is a common allergic disease that affects approximately 10-30% of the pediatric and adult population [3, 4]. Among patients with AR, Allergen Immunotherapy (AIT) can be applied to those who do not possess sufficient clinical benefit despite minimal allergen exposure and optimal pharmacological treatment, or who have side effects related to these treatments. Patients with AR tend to produce lower levels of type 1 interferon (IFN) during upper respiratory viral infections than those without AR [5, 6]. This may put allergic patients at higher risk for COVID-19-related morbidity and mortality [7, 8]. In contrast, low expression of angiotensin converting enzyme (ACE) 2 was detected in airway cells of AR patients, and this is thought to be protective against COVID-19.

In patients with seasonal/perennial allergic rhinitis, AIT is the only therapy that demonstrates both disease-modifying and therapeutic potential, as well as inducing long-term tolerance of the immune system to allergens. AIT exerts these effects with an increase in B regulatory (Breg) and T regulatory (Treg) cell numbers and functions, and IL-10 levels in the foreground [9, 10]. AIT inhibits the activation of allergen-specific Th2 cells through B and T reg cells, as well as suppressing the T cell response directed by Th1 and Th17 cells. Besides causing a cytokine storm of dysregulated Th1 immune response and ARDS (Acute Respiratory Distress Syndrome), ARDS remains an prominent cause of SARS-CoV-2 related mortality [11]. It can therefore be argued that AIT may have a positive effect on the course of SARS-CoV-2. Moreover, the adenomatous and secretory structure of the nasal mucosa in AR patients due to allergen exposure, local anti-inflammatory effects of intranasal steroids used for treatment, type 2 inflammation dominance in AR and the effects of AIT on Breg and Treg suggest that the course of SARS-CoV-2 may differ in patients with AR.

Therefore, the aim of presenting this study was to attempt to expose the course of SARS-CoV-2 in patients with allergic rhinitis, to compare the prevalence of SARS-CoV-2/COVID-19 infection, hospitalization and mortality rates in patients with allergic rhinitis receiving AIT and in patients not receiving AIT (non-receivers), and finally to define possible risk factors for SARS-CoV-2 positivity in patients with allergic rhinitis.

METHODS

Selected for the study were 419 adult patients with allergic rhinitis who were being followed-up in a tertiary allergy clinic in Konya, located in the central Anatolia, Turkey, between June 1, 2020 and December 31, 2020, in a retrospective manner. Only patients who were receiving active-continuous treatment for allergic rhinitis during the study period were included in the study.

Patients with nasal discharge, sneezing attacks, burning, nasal congestion and stinging in the eyes, accompanying itching in the ears, eyes and palate were evaluated. Patients with skin prick tests or allergen-specific IgE measurement, which were found to be compatible with the patient's clinical condition, were included in the study. Patients with nasal discharge, sneezing attacks, burning, nasal congestion but not allergen sensitivity were not included in the study.

Demographic (age, gender, duration of allergic rhinitis and AIT, accompanying comorbidities, atopy) and clinical data (serum IgE and blood eosinophil counts in patients prior to initiation of treatment for allergic rhinitis and/or AIT) were retrieved from medical files. A skin prick test was performed using standardized inhalant allergens (ALK, Madrid, Spain), House dust mite (Dermatophagoides (D) farinae, D. pteronyssinus), cat (Felis domesticus), dog (Canis familaris), cockroach (Blatella germanica), fungi (Alternaria, Cladosporium, Aspergillus) and pollen mixtures (tree, weed, grass). It was performed subcutaneously with the conventional protocol in all patients undergoing AIT. Specific IgE measurement was carried out in patients where systemic atopy could not be demonstrated via skin prick tests. We did not have any patients who underwent sublingual immunotherapy, rush or ultra-rush immunotherapy. The diagnosis of SARS-CoV-2 was made by a positive Polymerase Chain Reaction (PCR) test in patients with consistent clinical presentation for COVID-19.

Venous blood samples for biochemical analyses were drawn after at least 10 h of fasting before taking any medication. Abbott Cell Dyn 3700 series (Sheath reagent) and Siemens BN II/ BN ProSpec system (using particle-enhanced immunonephelometry) were used for whole blood count and quantitative determination of serum immunoglobulin (IgE).

The study was approved by Karatay University Ethics Committee (Decision number 2021/36, date

19.11.21).

Statistical Analysis

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation and data that were not normally distributed were expressed as median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using a Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exact or Chi-square tests where appropriate. As a result of these statistical analysis, parameters with $p < 0.2$ between SARS-CoV-2 (+) patients and SARS-CoV-2 (-) patients were subjected to regression analysis. Binomial logisticegression analysis was performed to determine independent predictors for SARS-CoV-2 positivity.

RESULTS

A total of 419 patients with allergic rhinitis were included in the study [Female: 266 (63.5%), Male: 153 (36.5%)]. The mean age was 30 years (18 to 76 years). The mean duration of disease was 5 years (0.6-35). One hundred sixty-three (38.9%) patients were receiving AIT. In patients undergoing AIT, the duration of immunotherapy was 15 months (3-58 months). The most common allergen sensitivity in patients was found to be pollen mixture sensitivity (58.7%) and house dust mite sensitivity (23.2%).

Seventy-nine (18.9%) patients became infected with the SARS-CoV-2 virus during the study period [32 (19.6%) patients in allergic rhinitis patients with AIT and 47 (18.4%) patients in non-receivers]. There was no significant difference was determined between the allergic rhinitis patients with AIT and the non-receivers in regard to the rate of SARS-CoV-2 ($p = 0.864$). Clinical characteristics of the patients are summarized in Table 1.

Table 1. Demographic, clinical and laboratory parameters of allergic rhitis patients

Parameters	Total (n = 419)	Allergic rhinitis patients with AIT (n = 163)	Allergic rhinitis patients without AIT (n = 256)	*p* value
Age (years), mean (range)	30 (18-76)	31 (18-69)	28 (18-76)	0.070
Gender, Female, n (%)	266 (63.5)	91 (55.8)	175 (68.4)	**0.009**
Duration of disease (years), mean (range)	5 (0.6-35)	6 (1-35)	4 (0.6-24)	**0.001**
Allergen sensivity, n (%)				**0.001**
Pollen mixtures	246 (58.7)	115 (70.6)	131 (51.2)	**0.001**
House dust mite	97 (23.2)	41 (25.2)	56 (21.9)	0.438
Mold	6 (1.4)	0	6 (2.3)	0.086
Animal dander	7 (1.7)	1 (0.6)	6 (2.3)	0.178
Venom	20 (4.8)	3 (1.8)	17 (6.6)	**0.032**
Multiple	43 (10.3)	3 (1.8)	40 (15.6)	**0.001**
IgE at diagnosis (IU/ml), mean (range)	90 (10-2020)	118 (17-2020)	78 (10-1143)	**0.001**
Eosinophil count (cell/ml), mean (range)	170 (3.40-1110)	160 (3.40-1110)	170 (10-980)	0.971
SARS-CoV-2, n (%)	79 (18.9)	32 (19.6)	47 (18.4)	0.745
Pneumonia, n (%)	10 (2.4)	7 (4.3)	3 (1.17)	0.055
Hospitalization (days), mean (range)	7 (1.7)	5 (3.1)	2 (0.77)	0.075

AIT = Allergen immunotherapy, Ig = immunoglobulin, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

Table 2. Demographic and clinical characteristics of allergic rhinitis patients according to SARS-CoV-2

Parameters	Total (n = 419)	SARS-CoV-2 (+) (n = 79)	SARS-CoV-2 (-) (n = 340)	*p* value
Age (years), mean (range)	30 (15-76)	32 (17-69)	29 (15-76)	0.244
Female gender, n (%)	266 (63.5)	58 (73.4)	208 (61.2)	**0.042**
Duration of disease (years), mean (range)	5 (0.6-35)	6 (2-32)	5 (0.6-35)	0.093
Comorbidities, n (%)	33 (7.9)	8 (10.1)	25 (7.4)	0.410
Hypertension	13 (3.1)	1 (1.3)	12 (3.5)	0.296
Type 2 diabetes mellitus	5 (1.2)	2 (2.5)	3 (0.9)	0.239
CAD	12 (2.9)	4 (5.1)	8 (2.4)	0.193
Hypothyroidism	3 (0.7)	1 (1.3)	2 (0.6)	0.112
Atopy, n (%)				0.752
Pollen mixtures	246 (58.7)	45 (57.0)	201 (59.1)	0.726
House dust mite	97 (23.2)	22 (27.8)	75 (22.1)	0.272
Mold	6 (1.4)	0	6 (1.8)	0.599
Animal dander	7 (1.7)	1 (1.3)	6 (1.8)	0.755
Venom	20 (4.8)	3 (3.8)	17 (5)	0.652
Multiple	43 (10.3)	8 (10.1)	35 (10.3)	0.965
IgE at diagnosis (IU/ml), mean (range)	90 (10-2020)	83 (15-2020)	96.5 (10-1380)	0.713
Eosinophil count (cell/ml), mean (range)	170 (3.40-1110)	180 (20-980)	165 (3.40-1110)	0.130
Immunotherapy, n (%)	163 (38.9)	32 (40.5)	131 (38.5)	0.745
Duration of AIT (months), mean (range)	15 (3-58)	14 (5-40)	17 (3-58)	0.714

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, Ig = immunoglobulin, CAD = Coronary artery disease, AIT = Allergen immunotherapy

In the 419 patients included in the study, the rate of pneumonia was 2.4% (10 patients) [12.7% of SARS-CoV-2 (+) patients]. During the study period, seven patients [21.9% of SARS-CoV-2 (+) patients] in AIT group and three patients [6.4% of SARS-CoV-2 (+) patients] in non-AIT group had pneumonia due to SARS-CoV-2. Five patients [15.6% of SARS-CoV-2 (+) patients] in AIT group and two patients [4.3% of SARS-CoV-2 (+) patients] in non-AIT group were hospitalized. No significant difference was determined between allergic rhinitis patients with AIT and the non-receivers in regard to the rate of pneumonia and hospitalization ($p = 0.055$ and $p = 0.075$). During the study period, there were no patients admitted to the intensive care unit or who had died.

We divided the study participants into two groups, as the allergic rhinitis patients on AIT and allergic rhinitis patients not receiving AIT; no significant difference was determined between the groups in terms of age, baseline eosinophil count and frequency of infection with SARS-CoV-2 virus, SARS-CoV-2 related pneumonia and SARS-CoV-2 related hospitalization. However, there was a significant difference between the three groups in terms of gender, duration of disease, sensitivity to allergens (atopy) and serum IgE levels ($p = 0.009$, $p = 0.001$, $p = 0.001$ and $p = 0.001$, respectively) (Table 1).

When SARS-CoV-2 positive and SARS-CoV-2 negative allergic rhinitis patients were compared, there were no significant differences between both groups in terms of age, duration of disease, accompanying comorbidities, sensitivity to allergens (atopy), serum IgE levels, eosinophil counts, rate of patients receiving AIT and duration of AIT. A significant difference was determined in terms of gender ($p = 0.042$) (Table 2).

It was found that according to univariant and mul-

Table 3. Logistic regression analysis of possible risk factors associated with SARS-CoV-2 in allergic rhinitis patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender	0.571 (0.331-0.984)	**0.043**	0.571 (0.330-0.987)	**0.045**
Duration of disease	1.041 (1.000-1.083)	0.048	1.040 (0.999-1.082)	0.056
CAD	2.213 (0.649-7.543)	0.204		
Eosinophil count	1.001 (1.000-1.002)	0.073		
Immunotherapy	1.086 (0.659-1.790)	0.745		
Duration of immunothrapy	0.987 (0.953-1.022)	0.470		

CAD = Coronary artery disease

tivariant regression analysis, the accompanying comorbidities (coronary artey disease), eosinophil count, AIT and duration of AIT were not found to be associated with an increased risk SARS-CoV-2 PCR positivity. On the other hand, female gender was shown to be associated with an decreased risk for SARS-CoV-2 PCR positivity (OR, 0.571; 95% confidence interval, 0.330-0.987; $p = 0.045$) (Table 3).

DISCUSSION

To the best our knowledge, our study is the only study evaluating the course of COVID-19 in patients undergoing AIT, and this study highlights three important findings: (1) Allergic disease duration, sensitized allergen types, and IgE levels at the time of diagnosis are higher in allergic rhinitis patients undergoing AIT. (2) There is no significant difference between the patients who underwent AIT and the non-AIT patient group in terms of SARS-CoV-2 prevalence, SARS-CoV-2-associated pneumonia, and SARS-CoV-2-associated hospitalization. (3) Although female gender is protective for SARS-CoV-2 positivity in allergic rhinitis patients, AIT or duration of AIT is not a risk factor for SARS-CoV-2 (+) in this patient group.

AIT is recommended for patients who use optimal pharmacological treatment for allergic respiratory diseases and minimize allergen exposure but do not get enough benefit from these treatments or have side effects related to these treatments. Thus, AIT can be considered as the next step of pharmacological treatment in patients with AR. It is therefore expected that the duration of illness in patients with AR who underwent AIT would be longer than in patients without AIT. In patients with a long disease duration, higher serum IgE levels may be achieved due to increased allergen exposure.

In our study, the prevalence of SARS-CoV-2, SARS-CoV-2-associated pneumonia, and hospitalizations between patients with and without AIT were found to be normal between groups. In a retrospective study conducted in Wuhan, no difference was found between patients with AR and non-AR patients in terms of severe cases, need for mechanical ventilators, and complications [12]. Ren *et al*. [13] reported that AR has a protective effect for COVID-19 infection in all age groups and that drugs used in the treatment of AR (antihistamines and intranasal steroids) do not affect COVID-19 severity and mortality. A study conducted in Turkey showed that there was no significant difference between patients with and without allergic rhinitis in terms of SARS-CoV-2-related hospitalizations and COVID-19 severity [14]. It was reported by Vezir *et al*. [15] that COVID-19 is more asymptomatic/mild in pediatric patients with aeroallergen sensitivity. A number of hypotheses have been proposed in these studies to explain the relatively positive effect of AR on the course of COVID-19. The first of these is on nasal steroids. Intranasal steroids are the most commonly used drugs in allergic rhinitis patients. In an ARIA-EAACI statement, it has been suggested that patients infected with COVID-19 can use intranasal steroids at recommended doses, since there is no evidence that the immune system is suppressed by these agents, patients with allergic rhinitis should not discontinue the use of intranasal steroids [16]. Moreover, some nasal steroids such as mometasone have been

shown to inhibit SARS-CoV-2 replication [17]. It has been suggested by Straus *et al*. that the use of nasal steroids reduces COVID-19-related hospitalizations, intensive care admissions, and mortality [18]. Another hypothesis is about eosinophils. With experimental studies, eosinophils have been shown to have a potential role in viral clearance and antiviral host defense [19]. Clinical prevalence in patients with AR correlates with blood and nasal eosinophil counts [20]. Therefore, it can be speculated that increased eosinophil counts in the respiratory tract may be protective against COVID-19 [21]. Another hypothesis proposes that ACE2 expression is decreased due to Type 2 inflammation in airway cells of patients with AR, and that allergen-specific T cells show a rapid and effective memory response to heterogeneous SARS-CoV-2 epitopes [13]. It has been shown by Kimura *et al*. [22] that IL-13 exposure reduces ACE2 expression in patients with asthma and AR. Contrary to these data, Yang *et al*. [23] suggested that allergic rhinitis has an increased risk in terms of SARS-CoV-2 positivity and more severe disease, and that hospitalizations are longer in patients with allergic rhinitis.

As another result of our study, it was found that female gender is protective in terms of SARS-CoV-2 (+) in patients with AR. Many reasons have been suggested in the differences of pathophysiology between genders in COVID-19 [24-26]. Many studies have shown that since the beginning of the pandemic male gender is a risk factor for COVID-19-related morbidity and mortality. The reason for these differences between genders may be immunological, hormonal or genetic differences or a combination of these. The effects of sex hormones on pattern recognition receptor and type I IFN responses are different. Sex hormones may affect immune cells in different ways. Estrogen is immunosuppressive at high doses and activates the immune system at low levels. On the other hand, testosterone suppresses natural immunity at all levels. Also, estrogen has been shown to inhibit ACE2, a functional receptor of SARS-COV-2, but androgens upregulate ACE2 activity [27].

As a result of the study, we found that AIT or AIT duration in patients with AR is neither a risk nor protective factor for SARS-CoV-2 (+). There is no study in the literature on the course of COVID-19 in patients with allergic rhinitis who underwent AIT. There is increasing evidence that AIT induces IgG4-positive regulatory B cells (Bregs), and regulatory B cells suppress antigen-specific T cell proliferation by producing IL-10. Also, AIT induces Treg cell formation [10, 28]. Treg cells are an indispensable subset of T cells that weaken the excessive immune response to pathogens, develop immune tolerance against environmental proteins, cancer cells and transplanted organs, and prevent and control the occurrence of autoimmune and allergic diseases [29]. Treg cells can inhibit ongoing inflammation in various steps by secreting suppressive mediators such as IL-10, TGF-β, and IL-35, by suppressing and/or cytolyzing dendritic cells through membrane molecules such as CTLA-4, PD-1, and enzymes such as granzymes A and B [9, 30, 31]. T reg cells use these mechanisms to suppress all effector cell types (directly or indirectly), eosinophils, B cells, DCs, T cells as well as inflamed resident tissue cell [29]. Therefore, despite the fact that it is thought that AIT can contribute positively to the course of COVID-19 by preventing the exaggerated cytokine response via Treg, we could not obtain such a result in our study, and we found the COVID-19 course of patients with AR who underwent AIT and patients with AR who did not receive AIT to be similar. We believe that more comprehensive studies should be conducted on this subject.

Limitations

Our study has some limitations. The first of these is the cross-sectional design. Secondly, the age range of the study population is much younger compared to older patients who are vulnerable to COVID-19, and they have fewer accompanying comorbid non-allergic comorbidities. Another thing that may have negatively affected the prevalence of SARS-CoV-2 is that rapid diagnostic tests like PCR tests were not widely used at the beginning of the pandemic.

CONCLUSION

In conclusion, we would like to highlight that in patients with AR who underwent AIT and in patients with AR who did not undergo AIT, the course of COVID-19 is similar, and AIT does not seem to increase the risk for COVID-19 infection. As such, it could be safely used in patients with AR, compatible with the data in the literature.

Authors' Contribution

Study Conception: EA, GA; Study Design: EA; Supervision: EA, GA; Funding: EA; Materials: EA; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: EA, GA; Literature Review: GA; Manuscript Preparation: EA, GA and Critical Review: EA, GA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

1. Aboubakr HA, Sharafeldin TA, Goyal SM. Stability of SARS-CoV-2 and other coronaviruses in the environment and on common touch surfaces and the influence of climatic conditions: a review. Transbound Emerg Dis 2021;68:296-312.
2. Rostami A, Sepidarkish M, Leeflang MMG, Riahi SM, Nourollahpour Shiadeh M, Esfandyari S, et al. SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. Clin Microbiol Infect 2021;27:331-40.
3. Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. Allergy Asthma Proc 2001;22:185-9.
4. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010;126:778-83 e6.
5. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol 2012;130:489-95.
6. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;201:937-47.
7. Novak N, Cabanillas B. Viruses and asthma: the role of common respiratory viruses in asthma and its potential meaning for SARS-CoV-2. Immunology 2020;161:83-93.
8. Gill MA, Bajwa G, George TA, Dong CC, Dougherty, II, Jiang N, et al. Counterregulation between the FcepsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. J Immunol 2010;184:5999-6006.
9. Blaser K, Akdis CA. Interleukin-10, T regulatory cells and specific allergy treatment. Clin Exp Allergy 2004;34:328-31.
10. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol 2013;131:1204-12.
11. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020;80:607-13.
12. Wang H, Song J, Yao Y, Deng YK, Wang ZC, Liao B, et al. Angiotensin-converting enzyme II expression and its implication in the association between COVID-19 and allergic rhinitis. Allergy 2021;76:906-10.
13. Ren J, Pang W, Luo Y, Cheng D, Qiu K, Rao Y, et al. Impact of allergic rhinitis and asthma on COVID-19 infection, hospitalization, and mortality. J Allergy Clin Immunol Pract 2022;10:124-33.
14. Guvey A. How does allergic rhinitis impact the severity of COVID-19?: a case-control study. Eur Arch Otorhinolaryngol 2021;278:4367-71.
15. Vezir E, Hizal M, Cura Yayla B, Aykac K, Yilmaz A, Kaya G, et al. Does aeroallergen sensitivity and allergic rhinitis in children cause milder COVID-19 infection? Allergy Asthma Proc 2021;42:522-9.
16. Bousquet J, Akdis CA, Jutel M, Bachert C, Klimek L, Agache I, et al. Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: An ARIA-EAACI statement. Allergy 2020;75:2440-4.
17. Lipworth B, Chan R, RuiWen Kuo C. COVID-19: Start with the nose. J Allergy Clin Immunol 2020;146:1214.
18. Strauss R, Jawhari N, Attaway AH, Hu B, Jehi L, Milinovich A, et al. Intranasal corticosteroids are associated with better outcomes in coronavirus disease 2019. J Allergy Clin Immunol Pract 2021;9:3934-40 e9.
19. Rosenberg HF, Dyer KD, Domachowske JB. Respiratory viruses and eosinophils: exploring the connections. Antiviral Res 2009;83:1-9.
20. Chen Y, Yang M, Deng J, Wang K, Shi J, Sun Y. Elevated levels of activated and pathogenic eosinophils characterize moderate-severe house dust mite allergic rhinitis. J Immunol Res 2020;2020:8085615.
21. Carli G, Cecchi L, Stebbing J, Parronchi P, Farsi A. Is asthma protective against COVID-19? Allergy 2021;76:866-8.
22. Kimura H, Francisco D, Conway M, Martinez FD, Vercelli D, Polverino F, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. J Allergy Clin Immunol 2020;146:80-8 e8.
23. Yang JM, Koh HY, Moon SY, Yoo IK, Ha EK, You S, et al. Allergic disorders and susceptibility to and severity of COVID-19: a nationwide cohort study. J Allergy Clin Immunol 2020;146:790-8.
24. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 2021;76:428-55.
25. Rashedi J, Mahdavi Poor B, Asgharzadeh V, Pourostadi M, Samadi Kafil H, Vegari A, et al. Risk factors for COVID-19. Infez Med 2020;28:469-74.
26. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. Cardiovasc Res 2020;116:2197-206.
27. Liu J, Ji H, Zheng W, Wu X, Zhu JJ, Arnold AP, et al. Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17beta-oestradiol-dependent and sex chromosome-in-

dependent. Biol Sex Differ 2010;1:6.
28. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014;133:621-31.
29. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. Immunol Rev 2017;278:219-36.
30. Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J. Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. Eur J Immunol 1997;27:1131-9.
31. Francis JN, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 2003;111:1255-61.