Summary

Allergic rhinitis (AR) is a common disease affecting up to 40% of the general population worldwide. In the Coronavirus 2019 (COVID-19) pandemic era, many observational studies analysing the effect of asthma and chronic obstructive pulmonary disease on the risk of developing COVID-19 were conducted, while data on AR are limited.

In this paper, we review the risk of developing SARS-Cov-2 infection carried by AR patients, the outcomes of those with COVID-19 disease, and the COVID-19 influence on the allergic and nasal symptoms and the psychological status of AR patients, in both adult and pediatric populations.

AR patients seem to be protected from COVID 19 infection. Even if data about the influence of AR on the severity of COVID-19 disease are still not conclusive, it seems that being an AR patient does not increase the risk of poor COVID-19 prognoses. The clinical manifestation of AR can be distinguished by COVID-19 symptoms. Treating AR adequately is also strongly recommended, especially during pandemic.

Introduction

The COVID-19 pandemic caused by SARS-Cov-2 infection raised important questions as to whether some chronic comorbidities could favour the infectiveness or the prognosis of the disease. Concerning respiratory diseases, many studies were conducted analysing the effect of asthma and chronic obstructive pulmonary disease (COPD) on the risk of COVID-19 but data on allergic rhinitis (AR) are scarce, even if AR is a common disease affecting up to 40% of the general population (1).

In this review, we evaluate whether AR patients are at higher risk for SARS-Cov-2 infection or COVID-19 outcomes and whether COVID-19 can influence AR symptoms and the psychological status of AR patients, both in the adult and in the paediatric population.

Methods

This work was not intended to be a systematic literature review but a comprehensive narrative review. The literature search has been conducted consulting the most relevant scientific databases: PubMed/MEDLINE, Scopus, Web of Science. Controlled vocabulary supplemented with keywords was used to search for all type of articles on allergic rhinitis and COVID-19. The search strategy included different terms, i.e. allergic rhinitis, rhinitis, allergy, atopy, COVID-19 and SARS-CoV-2, and was restricted to English language articles.

Allergic Rhinitis and risk of non-SARS-CoV-2 viral infections

A high proportion of patients with AR and other atopic diseases have a predisposition to produce lower levels of type I interferon (INF) upon viral respiratory infections (2,3). Through different mechanisms, Type 2 inflammation may have an inhibitory effect on the induction of type I interferon (4). Intriguingly, defective production of IFNs by plasmacytoid dendritic cells (pDCs) and epithelial cells have been described in severe atopic patients (5) with a consequent delayed and inefficient antiviral defense. In this context, a cross-regulation mechanism between FceRI and TLRs in certain cell types such as pDCs has been described, which may explain why the crosslinking of IgE bound to FceRI by allergens may result in a reduced TLR expression and ultimately in a decreased capacity to secrete type I interferons for viral defense (4,6). Furthermore, IL-5-induced airway eosinophilia appears to be a negative regulator of TLR7 expression and antiviral responses (7). Such impairment of antiviral responses suggests that patients with asthma might be at high risk of COVID-19 morbidity and mortality.

Allergic Rhinitis and risk of SARS-CoV-2 infection

The prevalence of AR in the world is ranging from 10 to 40% varying according to different geographic areas (1). The spread of COVID-19 worldwide could have posed a significant psychological burden to patients suffering from AR, because some nasal and ocular manifestations of AR are also possible presenting symptoms of COVID-19 illness (Figure 1), therefore potentially leading to misinterpretation and anxiety.

Nevertheless, available evidence shows that is not difficult to recognize and discriminate between these two different conditions. Bruno et al. (8) compared 40 patients suffering from AR with a similar group of 43 subjects affected by mild-moderate COVID-19 disease using the Sino-nasal Outcome Test 22 (SNOT 22). The mean overall score was higher in patients with COVID-19 compared to AR ones (39,9 vs 27,2). There was a significant difference in sneezing and blow nose between AR and COVID-19 patients (p<0.016 and p<0.001, respectively), while the COVID-19 group most frequently reported cough, loss of smell, fatigue during the day, reduced productivity and concentration, sadness and feeling of shame compared to AR group (p<0.001). In a retrospective study, patients hospitalized with COVID-19 were interviewed via telephone by using the mini Rhino-conjunctivitis Quality of Life Questionnaire (9). Among these patients, for those who were also affected by allergic rhino-conjunctivitis (10,8%), clinical manifestations of COVID-19 were regarded as completely different from AR in 62.8% of cases, and similar only in 18,2% of cases. No differences were found between sino-nasal symptoms in COVID-19 allergic vs non-allergic patients (p= 0.288), particularly for the prevalence of smell disfunction. The authors concluded that patients with AR are very familiar with their symptoms, can distinguish AR from COVID-19 rhino conjunctival manifestations, and have the same upper airway COVID-19 manifestations of non-AR patients (9). Finally, the EUFOREA expert team statement evidenced that cough and fever were the most prominent symptoms of COVID-19, whereas conjunctivitis and itching were typical of AR (Figure 1) (10).

A multicentre questionnaire study conducted on 301 nurses with AR characterized the impact of face masks on AR symptoms (11). They used both surgical and N95 masks. Nurses with intermittent AR

symptoms showed a significant improvement in overall symptoms after wearing the mask, regardless of the type, but no change in specific ocular symptoms. The mechanism of protection could be a physical filtration of face masks and the potential physiological response to allergens by breathing humid and hot air (11).

The mandatory lockdown established by governmental authorities during the first wave of COVID-19 forced people to stay home for several months and this could have influenced the AR course in patients with house dust mite (HDM) allergy. Gelardi et al. (12) compared the results of SNOT-22 of years 2019 (pre-lockdown) and 2020 collected from 42 patients with AR to HDM (28% with asthma comorbidity). These authors showed that all SNOT-22 scores were higher in the lockdown period than the year before. However, only the scores relative to runny nose, need to blow nose, nasal obstruction were statistically different from 2019 to 2020 ($p<0.05$). Other non-specific parameters, such as difficulty falling asleep, waking up at night, being frustrated/restless/irritable, and sad were statistically significant ($p<0.05$). Of note, there was a significant increase in the use of systemic antihistamine, and nasal decongestants ($p<0.05$) to reduce nasal congestion but not in accordance with ARIA guidelines recommendations.

These findings may suggest that being quarantined at home for a long time may increase the exposure to HDM and focus on the importance of treating patients according to ARIA guidelines to control AR symptoms (13). Avoiding contact with allergens (indoor or outdoor) is the primary preventive measure in patients with respiratory allergies and a strategy with pharmacotherapy associated with allergen immunotherapy (AIT), when indicated, must be considered (12). Regarding pharmacologic therapy of AR, it is recommended to start early and use it regularly throughout the pollen season. None of the recommended therapy for seasonal AR is contraindicated in COVID-19 patients. In particular, it is not advised to suspend intranasal steroids as this therapy does not reduce immunity, is effective in normalizing the structure and function of the nasal mucosa, and reduces sneezing, one of the means for spreading the coronavirus (14). There are also preliminary data indicating that some

corticosteroids as mometasone may suppress coronavirus replication (15). Systemic steroids, however, should be avoided, if possible, as they may suppress the immune system (14).

AIT should be continued in non-infected individuals and in those who completely recovered from COVID-19, whereas it should be interrupted in patients diagnosed with COVID-19 or suspected of having SARS-Cov-2 infection (16). Subcutaneous immunotherapy can be continued under strict safety protocols considering injection intervals expansion. AIT start in eligible patients is preferred to be in the sublingual route of administration to minimize in-person encounters for subcutaneous injections. Sublingual immunotherapy offers the possibility of taking it at home, thus avoiding the need to travel to or stay in an allergy clinic or doctor's office, which would increase the risk of infection (16).

Individuals with AR commonly report a higher proportion of anxiety, depression, and psychological disturbance than healthy people. In a cross-sectional study, 222 adults with AR and 133 healthy control were asked to complete the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) questionnaires. The SAS and SDS scores were significantly higher in AR patients than control, with a prevalence of anxiety and depression of 25% and 19%, respectively, in the AR group (17). Interestingly, the same data obtained one week after the period of lockdown were lower than before the COVID-19 pandemic and correlate with AR symptoms. The authors conclude that the COVID-19 pandemic had no significant influence on the psychological status of patients suffering from AR and confirmed that symptom severity is an important factor affecting the anxiety and depression of AR patients (17).

On the contrary, a cross-sectional survey-based study, designed to assess the degree of depression and the risk of post-traumatic stress disorder using the patient's health questionnaires and the impact of Event Scale-Revised, evidenced that, during the period of quarantine due to COVID-19, the psychological impact in patients with allergic diseases (n=1650) was greater than in non-allergic controls (n=2450). There was no difference between allergic respiratory and non-respiratory groups but in the hyperarousal scale, respiratory patients had higher scores (mean 1,15 vs 0,99 p= 0.013).

Unfortunately, the authors didn't distinguish between patients with allergic asthma from patients with AR (18). Even if at the beginning of the COVID-19 pandemic asthma and allergy were considered as possible risk factors for COVID-19, subsequent statements from international societies and expert scientific bodies concluded that allergic respiratory diseases do not constitute risk factors for severe COVID-19 (10,14). Accordingly, in a study from China, Shi et al found that the rate of combined allergy was low in COVID-19 patients. The ratio of combined asthma and AR were far lower than those of domestic morbidity, which might suggest that asthma and AR may not be a susceptibility factor for SARS-CoV-2 (19).

Can Allergic Rhinitis influence the outcomes of COVID-19?

COVID-19 pandemic has caused many hospitalizations and intensive care unit admission with a high burden on health care resources. For this reason, many studies were conducted to identify risk factors for severe COVID-19 outcomes. Elderly age, cardiovascular diseases, obesity and diabetes have been associated with more severe disease (20). Available evidence about asthma are not conclusive and it seems that only non-atopic asthma might be a risk factor for the severity of COVID-19 (21).

Currently, there are only a few data about the risk of COVID-19 in patients with AR, and these are mostly indirect evidence from studies analysing the effect of atopy or asthma on COVID-19. In a retrospective study on 531 patients with SARS-Cov-2 induced pneumonia, Scala et al. (22) found that atopic subjects (n=57; 10,7%) had a significantly lower prevalence of severe COVID-19 pneumonia than non-atopic patients (33,3% vs 67,7%; $p<0.0001$). These authors concluded that atopic status may confer protection against COVID-19 infection, although but they didn't address what type of allergic disease participants suffered from (22). A recent American cohort study involving 1043 COVID-19 patients was designed to understand the association between atopic conditions and COVID- 19 severity. 257 (24,6%) had atopy and this condition was associated with a significantly lower odds of hospitalization for COVID-19 ($p<0.004$) and length of hospitalization ($p<0.008$). Patients suffering from AR (n=171;16.4%) had a lower rate of hospitalization ($p<0.02$), length of hospitalization ($p<0.001$), and lower duration of intubation ($p<0.039$). Also, eczema was associated with a significantly reduced risk of hospitalization (23).

Chhiba et al. (24) conducted a study to investigate if asthma could be a risk factor for the severity of COVID-19. Among 1526 patients with COVID-19, 220 (14.4%) had asthma. The prevalence of AR was 35.9% in the asthmatics and 7.7% in the non-asthmatic groups ($p<0.0001$), whereas rhinosinusitis was comorbidity in 35.9% of asthmatic patients vs 9.6% in non-asthmatic ones ($p<0.0001$). Asthma was not associated with an increased risk of hospitalization, particularly in patients with AR and rhinosinusitis. The authors outlined the potential protective effect of Type-2 inflammation and

perhaps of using inhaled corticosteroids, although the latter conclusion needs further investigation (24).

Another study retrospectively analysed the comorbidity of 1172 hospitalized COVID-19 patients in Wuhan. 115 (9,8%) reported AR and tended to have higher asthma comorbidities. There was no difference in the frequencies of severe cases, need of mechanical ventilation or other treatment or complications (including severe acute respiratory syndrome) between patients with and without AR. The authors conclude that there is not any association between AR comorbidity and COVID-19 severity (25).

On the contrary, Yang et al. (26) conducted a nationwide cohort study in South Korea involving 291,959 adult patients who were tested for SARS-Cov2 to determine the association of allergic disorders with the likelihood of a positive SARS-Cov-2 tests result and with clinical outcomes of the disease. The number of patients with positivity to SARS-Cov-2 was 7,340. The SARS-Cov-2 test positivity rate was 3,3% in individuals with AR compared to 2,8% in those without AR. Severe clinical outcomes from COVID-19 were observed in 4,7% and 3,7% of patients with and without AR, respectively. Also, patients with asthma had a significantly higher risk of severe COVID-19, but this data was particularly evident for non-allergic asthma, whereas atopic dermatitis didn't show an association with severe clinical outcomes. They concluded that patients with respiratory allergic diseases are at higher risk of worse clinical outcome and that AR is associated with an increased likelihood of SARS-Cov-2 test positivity and worse clinical outcomes as death, intensive care admission, non-invasive ventilation, and longer hospital stay.

The local immunologic environment in the respiratory system (impaired secretion of innate IFN) seems to be more important for SARS-Cov-2 infection than the systemic immunologic effects characteristic of atopic dermatitis (26). In a single-centre retrospective study with a small sample size (140 COVID-19 patients) in China, Shi et al. (19) observed a lower rate of comorbid allergy in patients with COVID-19 in comparison with the prevalence of allergic diseases in the general population. When excluding patients with other underlying diseases and stratifying COVID-19

patients into those with (n= 21) and without allergy history (n= 44), they found that patients with allergy demonstrated lower proportions of bilateral lung lesions on chest computed tomography scanning and severe illness and higher circulating total T-cell counts than those without allergy. Another study conducted in 949 COVID-19 patients showed that smell loss was associated with less severe COVID-19 and that a history of smell dysfunction ($p<0.001$), AR ($p<0.02$), rhinosinusitis ($p<0.02$) was associated with a greater risk of acute smell loss in patients with COVID-19. So indirectly AR and rhinosinusitis could be related to a better course of COVID-19 disease (27).

The host immune response is integral to determining susceptibility to SARS-CoV-2 infection and the severity of consequent COVID-19 (28). Recently, Larsson et al. (29) provide evidence to support that the genetic factors underlying predisposition to allergic disease are protective against COVID-19. They considered 136 uncorrelated ($r^2 < 0.02$) single nucleotide polymorphisms associated with a broad allergic disease phenotype (presence of at least one allergic disease, including AR, atopic dermatitis and asthma) at $p < 3 \times 10^{-8}$ in a meta-analysis of 13 genome-wide association studies with a total of 180129 cases and 180709 controls (without the three allergic diseases), all of European descent. Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19 but not clearly with the risk of being hospitalized with COVID-19. Secondary analyses based on genetic variants associated with different allergic diseases did not reveal associations with any particular allergic disease specifically, although the magnitude of the inverse association was most pronounced for AR albeit with broad confidence intervals (29).

Can Allergic Rhinitis be protective against poor outcomes of COVID-19?

As previously stated, some studies have suggested possible non-harmful or protective effects of AR on the clinical outcomes of COVID-19. Allergy is an immune response to allergen stimulation that is characterized by elevated Type-2 cytokines and eosinophilic inflammation. The above findings raise the possibility that allergy might be a protective factor for COVID-19. AR might protect against poor outcomes in COVID-19 due to several possible mechanisms, including altered viral entry receptor expression, chronic type-2 inflammation, younger age and/or absence of comorbidities, increased adherence to therapy and intranasal corticosteroids use (30).

ACE2 receptor

The lack of susceptibility to COVID-19 in patients with pre-existing allergic asthma seems to be in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, particularly rhinoviruses (31). However, rhinovirus uses the intercellular adhesion molecule 1 (ICAM-1) molecule as an entrance into respiratory epithelial cells, which is overexpressed in allergic airways as a marker of allergic inflammation (32). In contrast, COVID-19 uses another host cell receptor abundantly present in the oral mucosa and within the (healthy) airways, i.e., the angiotensin-converting enzyme-2 (ACE2) (33)), which plays a crucial role in the disease development and associated lung injury (34). Cofactors facilitating SARS-CoV-2 infectivity are transmembrane peptidase serine 2 (TMPRSS2), which cleaves the SARS-CoV-2 spike protein, and possibly protease furin (35). A lower expression of ACE2 has been described in airway cells of patients with AR and/or asthma. Jackson et al found that nasal cat allergen led to a significant reduction in ACE2 mRNA expression in nasal brush samples in adult AR patients allergic to cats (36). Furthermore, Kimura et al. reported that IL-13 exposure reduced ACE2 expression in airway epithelial cells from patients with asthma and atopy (37). These findings suggest that patients with

AR and allergic asthma might be protected from COVID-19 because of the low expression of ACE2 in their epithelial cells (38).

Inflammatory endotypes and COVID-19

Certain aspects of type 2 immune response, including type 2 cytokines (IL-4, IL-13, etc.), could therefore provide potential protective effects against COVID-19. In a retrospective study on patients with SARS-CoV-2-induced pneumonia, hospitalized in several Italian hospitals, atopic subjects showed a much lower occurrence of severe or very severe COVID-19 pneumonia (33.3% vs. 67.7%, $p<0.0001$) (22).

Eosinophilic inflammation

Further, the role of eosinophils, foes in asthma but possibly friends in COVID-19 infected lungs, needs to be established (39). Previous experimental studies indicated a potential role of eosinophils in promoting viral clearance and antiviral host defense (40). The capacity of eosinophils to protect against viral infection might therefore account for a low prevalence of asthmatic individuals among patients with COVID-19. Eosinophils are reduced in peripheral blood of SARS-CoV-2-infected patients, (41) therefore, it is tempting to speculate that increased numbers of eosinophils in the airways of asthmatic patients might be protective against the exaggerated inflammatory responses of the severe COVID-19 phenotype (39). The severity of AR is typically classified into a mild and a moderate-severe form based on symptom severity according to the ARIA guidelines (13). The clinical severity of AR correlates with the levels of eosinophils in the blood and nose. Recently, Chen et al found that the eosinophil levels in the blood were significantly higher in mild and moderate-severe AR compared to healthy controls (42). Severe COVID-19 occurring in susceptible individuals may be associated with cytokine-mediated hyper-inflammation and associated coagulopathy with

multisystem involvement and death (43). Markers of worsening disease include hypoxemia, lymphopenia, thrombocytopenia, and raised levels of IL-6, C reactive protein, ferritin, lactate dehydrogenase, and D-dimers. Eosinopenia may also be part of the overall cytopenic process in the early phase of severe COVID-19, with the later resolution of eosinophil counts being associated with clinical recovery (44). Peripheral blood eosinophil counts may, therefore, be an effective and efficient indicator in the diagnosis, evaluation, monitoring, and prognosis of COVID-19 patients (45).

Younger age and/or absence of comorbidities

Susceptibility and severity of COVID-19 infection increase with age (46), therefore, age is an important confounder in the assessment of the risk of contracting severe COVID-19. Expression of ACE2, the co-receptor for SARS-CoV-2, varies with age (47). Because Type-2 asthma sufferers tend to be younger than those with other comorbidities, the age factor probably explains why patients with asthma may not be at greater risk. However, to better address this question, age-adjusted models need to be formulated.

Paediatric Allergic Rhinitis and COVID-19

Beken et al. conducted a study in 107 pediatric patients after hospitalization for COVID-19 (48). Questionnaires investigating environmental factors and an allergic evaluation, including allergy testing and spirometry, were conducted. The authors concluded that asthma and AR were not risk factors for hospitalization in children due to COVID-19. The presence of a pet in the environment might have a protective effect. Dul and colleagues (49) evaluated the data extracted from electronic medical records of 182 children hospitalized for COVID-19 and showed that allergic diseases do not increase the susceptibility to SARS-Cov-2 infection and hardly influenced the course of COVID-19 in children. Finally, Jackson et al. (36) reported that high levels of allergic sensitization are associated with a reduction in the expression of the ACE-2 receptor which is the gateway to the virus.

Regarding inhaled corticosteroid therapy, Bousquet et al. (14) report that out of 40 children with AR admitted to the Wuhan children's hospital for Covid 19, about one third regularly used intranasal steroids as before, the other two-thirds did not: in these two groups of patients there was no difference in severity and prognosis COVID-19 and everyone has recovered well (unpublished data). Also, Cardinale et al. (50) stress the importance of continuing treatment with intranasal steroids and antihistamines both to control the symptoms and to avoid superinfections potentially dangerous for the lower respiratory tract. Furthermore, these authors also underline how the failure to control rhinitis with the classic symptoms, in particular sneezing, can favor the transmission of the virus. Some authors also suggested that montelukast could be also considered in pediatric age to treat AR during the COVID-19 pandemic, considering the potential anti-inflammatory action of this medication (51). Recommendations for AIT during the COVID-19 pandemic for adults with AR also apply to children (16,50).

In the period of lockdown, allergic patients inevitably remained more confined to the home environment. Yucel et al (52) raised the question of relapses in patients allergic to HDM. This study carried out during 75 days of lockdown on 81 children showed an improvement in lung function and consequently in asthma symptoms, probably due to the reduction of respiratory tract infections and

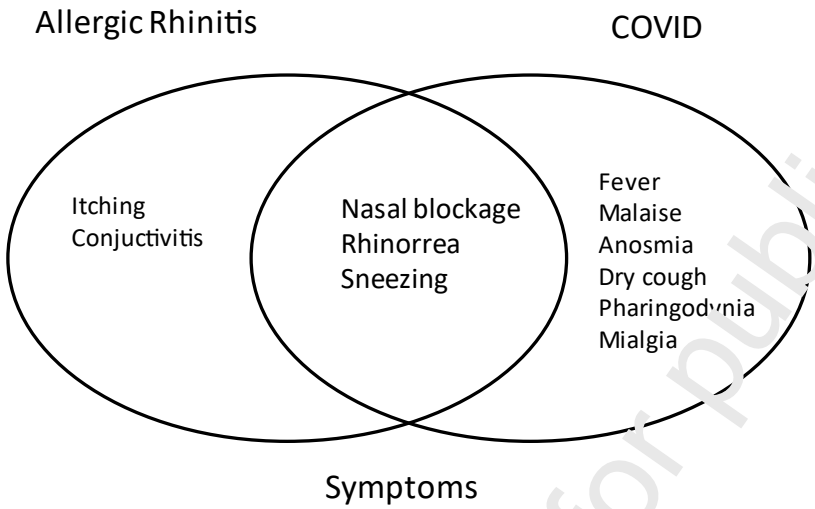
exposure to outdoor pollution. On the contrary, the nasal symptoms were significantly worsened in subjects with allergic rhinitis, underlining the importance of environmental remediation measures indoors.

In conclusion, it seems that COVID-19 affects childhood and adolescence, fortunately in a modest way (53). However, for this very reason, allergic children must continue the therapies for their allergies and scheduled visits as must be the case for all chronic diseases.

Conclusion

AR patients seem to be protected from COVID 19 infection. Even if data about the influence of AR on the severity of COVID-19 disease are still not conclusive, it seems that being an AR patient does not increase the risk of poor COVID-19 prognoses. The clinical manifestation of AR can be distinguished by COVID-19 symptoms. Treating AR adequately is also strongly recommended in the COVID-19 pandemic era,

Figure 1: "Similarities and differences between allergic rhinitis and COVID-19 symptoms (adapted from Scadding et al., WAO Journal 2020)



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