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REVIEW

Understanding and Managing Severe Asthma in the Context of COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19) continues to spread across the world. Since the beginning of the pandemic, the question of whether asthma is a risk factor for getting the infection or for poor outcomes motivated a great debate. In the field of severe asthma and its treatment during COVID-19 pandemic, several issues are also pending. A literature review focused on the management of severe asthma patients in the context of COVID-19 is performed. The available evidence suggests that severe asthma patients do not have an increased risk of poor COVID-19 outcomes and that it is safe to treat asthmatic patients with inhaled corticosteroids (ICS) and biologics during the pandemic, even though some studies indicate that high doses of ICS may predispose to COVID-19. The chronic use of oral corticosteroid (OCS) might be associated with poor COVID-19 outcomes, although there is no complete agreement. There is very limited evidence concerning the use of triple therapy for asthma in the context of this pandemic. Ultimately, severe asthma patients should maintain their medication during the COVID-19 pandemic, including biologic agents. More studies are needed to address the role of asthma medications and asthma's different phenotypes on the incidence and course of COVID-19.

Keywords: allergy, biologics, corticosteroids, COVID-19, SARS-CoV-2, severe asthma

Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), continues to spread across the world. As with other respiratory viruses, there were great concerns about the impact of COVID-19 in chronic respiratory diseases, particularly in asthmatics who might be at higher risk of infection and/or poor outcomes.

Contrary to some expectations, in most studies, asthma was not associated with an increased risk of severe COVID-19.[1] In the first studies, unlike old age and underlying morbidities such as cardiovascular diseases, in particular hypertension and metabolic disorders such as obesity and diabetes, asthma was not identified as a significant risk factor for COVID-19 morbidity or mortality.[2–4] Studies from many countries on multiple continents (France, China, Italy, Sweden, Spain, Belgium, Israel, Mexico, Brazil, Saudi Arabia, and India) reported a lower prevalence of asthma among patients hospitalized with COVID-19 than in the general population in each region.[1,5]

Consequently, the Centers for Disease Control and Prevention (CDC), which initially considered patients with asthma to be at high risk for severe illness and mortality from COVID-19, revised their recommendations and now only consider those with moderate or severe asthma to be at high risk.[6]

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Studies from the USA, the UK, Ireland, Korea, and Australia showed a higher prevalence of asthma among patients hospitalized with COVID-19 and suggested that severe asthma patients were at higher risk of in-hospital mortality from COVID-19.[1,5,7,8]

Thus, the question of whether asthma is a risk factor for contracting the infection or associated with severe disease or negative outcomes motivated a great debate. Recent publications on this matter revealed a variety of results, gaining even more complexity with increasing data indicating that different phenotypes of asthma may be associated with different COVID-19 outcomes.[1,9–12]

The asthma treatments themselves are also a topic of debate, namely immunomodulating drugs, such as corticosteroids and biologic therapies, which one might expect to be related to an increased risk of infection or poor outcomes.[13 – 15] Up to 10% of the asthmatics have severe asthma and a clear understanding of the risk/benefit of maintaining treatment with immunomodulating drugs is essential to support correct treatment of these patients, who are most at risk of clinical decompensation.[16] Currently approved biologics for the treatment of severe asthma are omalizumab (a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E [IgE]), mepolizumab (a monoclonal antibody directed against interleukin-5 [IL-5]), benralizumab (a humanized fucosylated monoclonal antibody against IL5 alfa receptor [IL5Ra]), reslizumab (a monoclonal antibody against IL-5), and dupilumab (a humanized monoclonal antibody directed against the alpha-chain of the interleukin 4 receptor [IL4Ra]). Biologic therapy raised some concerns, particularly anti-IL5 and anti-IL5 receptor blocking monoclonal antibodies that induce an eosinophil depletion, considering that eosinopenia is a biomarker of COVID-19 severity.[17]

Conversely, it has been suggested that biologics may be effective against COVID-19 related asthma exacerbations, by reducing baseline airway inflammation and possibly through specific antiviral properties.[18] In the PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study, omalizumab decreased the duration of rhinovirus infections, viral shedding, and the risk of rhinovirus illnesses in children with allergic asthma.[19] The question on whether the same is true for coronavirus disease remained unanswered.

Materials and Methods

The authors performed a focused review on PubMed identifying the current data available on the management of severe asthma patients in the context of COVID-19. Case reports, prospective and retrospective studies and reviews concerning the treatment of severe asthma patients with COVID-19, published until June 2021, were included.

Results

COVID-19, ACE2 and TMPRSS2 Expression and Asthma

Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) mediate SARS-CoV-2 infection of host cells.[20] SARS-CoV-2 binds mainly to ACE2 receptors in host cells, which are abundant in the lungs, heart, blood vessels, and intestine.[1,20] It has been suggested that ACE may be just one of several factors influencing the virus infection of cells, since not all cells that express ACE2 are susceptible to infection by SARS-CoV-2,[21] namely club cells, which do not get infected by this virus.[22] Club cells have been reported to potentially express intrinsically high levels of some antiviral interferon (IFN)-stimulated genes, such as IFITMs (IFN-induced transmembrane proteins) and Ly6E (lymphocyte antigen 6E),[23] both described as coronavirus restriction factors.[24,25]

It has been questioned why children are less affected by SARS-CoV-2 infection even though they have similar seroprevalence rates.[21] Some publications showed an association between levels of ACE2 expression in nasal epithelium and age,[26] but in other studies, that was not found.[27]

Peters et al studied the relationship between demographic features and sputum ACE2 and TMPRSS2 gene expression in asthma by analyzing sputum cells from 330 participants in SARP-3 (Severe Asthma Research Program-3) and 79 healthy control subjects. They found that expression levels of ACE2 and TMPRSS2 were similar between subjects with asthma and healthy subjects. Among severe asthma patients, diabetes mellitus, male sex, and African American race were associated with higher expression of ACE2 and TMPRSS2, as was the use of inhaled corticosteroids (ICS). However, they found no difference in the expression of these genes before and after treatment with intramuscular triamcinolone acetonide.[28]

Asthma Phenotypes/Atopic Disease and COVID-19

A meta-analysis of 131 studies and 410,382 patients found that COVID-19 asthmatic patients had a lower risk of death compared to non-asthmatic patients.[10] Accordingly, other large studies and meta-analyses suggested that

asthma patients may have a lower risk of severe COVID-19.[1,9,29] This could be related to the effect of atopy and type 2 inflammation in allergic patients.[30] An Italian study found a decreased risk of severe COVID-19 disease in patients with atopic disease.[31] However, in another study, there was no difference between the atopic and non-atopic groups in terms of intensive care unit (ICU) admission, duration of the hospitalization or mortality, suggesting that atopy was unrelated to COVID-19 severity.[32]

Different phenotypes of asthma may be associated with different COVID-19 outcomes.[1,9,10] In particular, type 2 inflammation, mostly associated with asthma in the pediatric population or initiated during childhood, is characterized by a Th2 cells dominance and their hallmark cytokines IL-4, IL-5 and IL-13, together with eosinophilia. It has been shown that IL-13 downregulates the expression of ACE2 airway epithelial cells. Reduced levels of ACE2 transcripts have been associated with allergy, allergen exposure, and high IgE levels,[33,34] as well as to higher levels of fractional exhaled nitric oxide.[35] Eosinophilia has been negatively associated with COVID-19 susceptibility, whereas eosinopenia is a biomarker of severe COVID-19. Eosinophils express toll-like receptor 7, which recognizes single-stranded RNA, triggering an activation pathway that enhances the antiviral effects of eosinophils.[36] Mast cells, also allergy-associated effector cells, have high antiviral potential owing to their production of interferons and other antiviral mediators.[30]

In contrast, the mechanisms associated with non-type 2 asthma and chronic obstructive pulmonary disease (COPD) (Th1-type or type 1 cytotoxic T (Tc1)-type responses and Th17 cell activation) may predispose to a more severe course of the disease:[30]

- Th1 and Th17 are associated with an increased expression of ACE2, although the underlying mechanisms are not fully understood.[33,35,37]
- Patients with non-type 2 asthma or COPD commonly suffer from other comorbidities that may predispose them to a more severe course of COVID-19 disease.[18]

Systemic and Inhaled Corticosteroids Use and COVID-19

In hospitalized COVID-19 patients, the use of systemic dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.[38] Using the OpenSAFELY platform, Williamson et al analyzed asthmatic patients' outcomes during COVID-19. The authors reported an increased risk of death in asthma patients with recent use of an oral corticosteroid (OCS).[8] A study by Adir et al of COVID-19 asthma patients using the computerized database of Clalit Health Services also found that recent (within the previous 120 days) and chronic use of systemic corticosteroid in asthma patients was associated with a higher risk of moderate-to-severe COVID-19, all-cause mortality, and the composite endpoint of moderate-to-severe COVID-19 or all-cause mortality.[39]

The risk of getting COVID-19 in asthmatics taking OCS has also been analyzed. Hanon et al conducted an observational study using data from the Belgian Severe Asthma Registry. Of the 676 severe asthma patients surveyed, 58 were on maintenance OCS, none of whom was diagnosed with SARS-CoV-2 infection.[40] A study of 1365 patients from the UK Severe Asthma Registry found that maintenance treatment with OCS was not associated with COVID-19.[41]

Regarding the use of ICS, Schultze et al reported an increased risk of COVID-19 related death among people with asthma prescribed high-dose ICS compared to those prescribed only short-acting beta-agonists (SABA) and those on low- or medium-dose ICS. However, quantitative bias analysis confirmed that a hypothetical unmeasured confounder of moderate strength could explain the observed results rather than these representing a harmful effect of ICS.[42] In a large cohort of hospital admissions for COVID-19 across England, Scotland, and Wales, Bloom et al described different outcomes in patients with asthma or chronic pulmonary disease, according to whether or not these patients used ICS in the 2 weeks before hospital admission.[43] Asthma patients aged 50 years and older who were using ICS had a 14% reduction in mortality risk compared to patients with no underlying respiratory condition. It was interesting to note that the proportion of people with asthma admitted to hospital with COVID-19 in this study (8.6% aged <16 years, 20.9% aged 16–49 years and 12.2% aged ≥50 years) was higher than the national prevalence of asthma (approximately 7% for each age group). Patients with underlying respiratory conditions were more likely to present with dyspnea and cough, but wheeze was uncommon except for pediatric asthma patients (<16 years). In this group, no deaths

occurred, but 10 patients (6.6%) required admission to the ICU. Overall, patients with asthma aged 16–49 years and those aged 50 years and older were significantly more likely to receive critical care, non-invasive ventilation, and oxygen than non-asthmatic patients after adjusting for confounding factors. In these age groups, severe asthma patients had a significant increase in mortality compared to non-asthmatic patients. This increased risk was not observed in the other asthma patients.

Armentia et al conducted an observational study of 134 nursing home residents and 139 patients with uncontrolled asthma. The latter were all treated with ICS. Of the 139 asthma patients, 13 contracted COVID-19, none of whom became uncontrolled. Of the 134 nursing home residents, 80 were infected. Of these, 43% had previously received ICS for several health problems. Of the latter, 80% were asymptomatic, compared with 14% of deaths and 46% of severe disease in nursing home patients not on ICS. In the two study groups, prior allergic sensitization was associated with a good prognosis. The authors also found a significant difference in SARS-CoV-2 infections between asthma patients treated with ICS and nursing home residents not treated with ICS.[29]

A big-data retrospective study that analyzed 71,182 patients with asthma showed that the proportion of patients who used ICS was significantly reduced in asthmatics who required hospitalization due to COVID-19.[44]

Other authors found no difference between high-dose and lower dose of ICS in the risk of being infected. However, they found that hospitalized patients were on lower doses of ICS compared to ambulatory patients.[41]

Biologic Therapies

Table 1 summarizes published studies regarding the outcomes of COVID-19 infected asthma patients treated with biologics. Using an artificial intelligence platform, Izquierdo et al examined a total of 71,182 asthmatics patients' electronic health records and identified 865 patients (1.21%) on biologic treatment. A total of 1006 patients were infected with COVID-19; 20 patients were being treated with a biologic. Two patients were hospitalized, both on treatment with mepolizumab, and one had a fatal outcome, a 52-year-old man with hypertension, diabetes mellitus and dyslipidemia.[44]

Rial et al studied 545 asthmatic patients on biologic treatment, 35 of whom were infected with SARS-CoV-2. Among eight hospital-admitted patients, one needed intensive care and one died because of COVID-19, an 82-year-old patient with hypertension, diabetes and ischemic cardiopathy. Comparing the different treatment groups, the authors found a higher probability, but not significant, of COVID-19 infection in patients treated with reslizumab. The authors also grouped the patients treated with the three anti-IL5 biologic drugs (mepolizumab, reslizumab and benralizumab) and compared with the ones under omalizumab: no statistical difference was observed regarding severity of the disease, presence of comorbidities, ICU admissions or mortality. The same result was obtained when comparing patients in this study and a cohort of patients with mild and moderate asthma with no biological treatment.[45]

In an Italian study, which included 473 severe asthma patients on ongoing treatment with a biologic, the prevalence of confirmed SARS-CoV-2 infection was of 0.846% and no difference was observed in comparison to data in the geography-matched general population, which presented a prevalence of 0.8%.[46]

Similar results were found in a Belgium study that included 676 severe asthma patients, 434 of these on a biological drug. Fourteen patients were infected with SARS-CoV-2 and 11 of these were under biologic treatment (4 with omalizumab and 7 with an anti-IL5 or anti-IL5R therapy). Five patients were hospitalized (one with no biologic treatment and four under anti-IL5/-IL5R treatment) but there was no need of non-invasive or invasive ventilation or ICU admission in either group of patients. There were also no reported deaths. Despite the low number of confirmed cases, the authors found no difference in the incidence of COVID-19 between patients treated with biologics and patients not receiving any biologic treatment.[40] The study was unpowered to discriminate any differences regarding distinct biologic treatments.

A study in the population of the Severe Asthma Network in Italy (SANI) and in an additional Italian Centre included 1504 patients, 65% of whom were treated with biologics. The authors reported 26 confirmed or highly suspected COVID-19 cases, 21 of whom were on biological treatment. Four patients were hospitalized and one of them was admitted to the ICU. Two patients died, which accounted for a COVID-19 related mortality of 7.7%, lower than in the general Italian population (14.5%).[47]

Another Italian study involving 41 centers of the Italian Registry of Severe Asthma (IRSA) network included 558 patients, 7 of whom contracted COVID-19. Two of them were hospitalized, but none was admitted to the ICU.

Table 1 Studies on COVID-19 Outcomes in Asthmatic Patients Treated with Biologics

Ref.	Study Type	Publication Date	Time Period	Database	Asthmatic Population Studied	COVID-19 Diagnosis	Biologic Treatment/Main Results	Study Location
[44]	Multicentre, retrospective and observational study	Oct 2020	January 1 to May 10, 2020	Electronic health records in the region of Castilla La-Mancha using the SAVANA Manager clinical platform	- 71,182 Asthmatic patients - 1006 w/ COVID-19 diagnosis - 263 hospitalized after COVID-19 diagnosis	Rapid serological tests or clinical, radiological and/or analytical evaluation.	- 865 (1.21% of all asthmatic patients) were being treated with biologics: omalizumab, n=641; mepolizumab, n=308; benralizumab, n=98; reslizumab, n=26. - From 20 patients w/ asthma treated with biologicals w/ COVID-19 2 were hospitalized (mepolizumab) and 1 died.	Guadalajara, Spain
[45]	Multicentre retrospective cohort study	Jan 2021	March to June, 2020	9 University hospitals (Spanish Network of Asthma)	- 545 Adult patients with severe asthma under biological treatment	PCR, antibodies test and compatible clinical symptoms	- 545 Patients treated w/ biologics: omalizumab, n=263(48.3%); mepolizumab, n=154 (28.2%); benralizumab, n=98 (18.0%); reslizumab, n=26 (4.8%); dupilumab, n=4 (0.7%). - 35 Patients (6.4%) were diagnosed with COVID-19: 14 treated w/ omalizumab; 11 treated w/ mepolizumab; 7 treated w/ benralizumab; 3 treated w/ reslizumab. - 8 patients (22.9%) were hospitalized: 1 in ICU (omalizumab) and 1 died (mepolizumab).	Spain
[46]	Cross-sectional telephone-based survey	July 2020	April 1 to 20, 2020	Patients contacted by telephone of 6 asthma centers in Northern and Center Italy (Emilia-Romagna, Liguria, Lombardy, Tuscany, Veneto)	- 473 Adult severe asthma patients, with ongoing treatment with biological therapy	Nasopharyngeal swab (PCR test)	- 473 Patients treated w/ biologics: omalizumab, n=145 (30.6%); mepolizumab, n=200 (42.3%); benralizumab, n=124 (26.2%); dupilumab, n=4 (0.8%). - 4 Patients (0.846%) were diagnosed with COVID-19: 3 treated w/ omalizumab (1 critical, 1 severe and 1 mild case) and 1 treated w/ benralizumab (mild case).	Italy

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Table 1 (Continued).

Ref.	Study Type	Publication Date	Time Period	Database	Asthmatic Population Studied	COVID-19 Diagnosis	Biologic Treatment/Main Results	Study Location
[40]	Observational study telephone-based survey	Sept 2020	April 30 to July 8, 2020	9 Asthma centers from BSAR	- 676 Severe asthma patients	Nasopharyngeal swab (PCR) or serology (SARS-CoV-2 IgG)	- 242 Patients w/ no biologics - 3 confirmed COVID-19 (1.2%). - 434 Patients w/ biologics (mepolizumab, n=182; benralizumab, n=98; reslizumab, n=25, 129 omalizumab). - 11 Patients were diagnosed with COVID: 4 were treated w/ omalizumab (3.1%) and 7 were treated w/ anti-IL5 or anti-IL5R (2.3%).	Belgium
[47]	Multicenter, non-interventional, retrospective study	Aug 2020	-	Severe Asthma Network in Italy (SANI) and University Center in Ferrara	- 1504 Severe asthmatic patients	Confirmed or highly suspect cases of COVID-19	- 978 (65%) Patients were treated with biologicals: 52.9% w/ anti-IL5 or anti-IL5R agents and 47.1% w/ anti-IgE. - 26 (1.73%) Patients were considered COVID positive and 21 were on biologicals: mepolizumab, n=13 (1 death); benralizumab, n=2; omalizumab, n=6.	Italy
[48]	Observational study	Aug 2020	February 24 to May 18, 2020	A questionnaire submitted to clinicians of 41 centers of the Italian regions (65.5% of total subjects of IRSAN)	- 558 Severe asthma patients	PCR and specific IgG	- 68.2% of the subjects were treated w/ biologics: omalizumab (46.9%), mepolizumab (39.1%), - benralizumab (14%). - 7 Patients were diagnosed w/ COVID-19: 3 treated w/ omalizumab (1 hospitalized) and 4 treated w/ mepolizumab (1 hospitalized).	Italy
[41]	Retrospective and observational study	Jan 2021	June 2020	UK Severe Asthma Registry	- 1365 Severe asthma patients - 97 with COVID-19	PCR/serology test and compatible clinical symptoms	- 918 Patients were treated with biologics: anti-IgE, n=166; anti-IL5 or anti-IL5R agents, n=735; and anti-IL-4/13, n=16. - 64 Patients were diagnosed with COVID-19: 55 treated w/ anti-IL5 or anti-IL5R agents (6 hospitalized) and 9 treated w/ anti-IgE (1 hospitalized).	UK

[39]	Retrospective cohort study	August 2021	March 1 to December 7, 2020	Database of Clalit Health Services	- 80,602 Asthmatic patients - 8242 tested positive to SARs-CoV-2	Nasopharyngeal swab (PCR test)	- 514 Patients were treated w/ biologics: omalizumab, n= 224; benralizumab, n=78; mepolizumab, n=135; reslizumab, n=20; dupilumab, n=57. - 50 Patients tested positive to SARS-CoV-2: omalizumab, n=24 (48%); benralizumab, n=7 (14%); mepolizumab, n=13 (26%); reslizumab, n=3 (6%); dupilumab. n=3 (6%)	Israel
[49]	Retrospective and observational study	November 2020	March 1 to April 30, 2020	6 Cities major hospitals in the North and Center of Italy	- 42 Asthmatic patients hospitalized due to COVID 19		-2 Patients were treated w/ biologic (5%) – 1 with a worse outcome	Italy
[50]	Retrospective study	March 2021	March 14 to April 27, 2020	Albert Einstein College of Medicine/Montefiore Medical Center	- 951 (77.5%) Asthma patients - 737 with COVID-19 diagnosis. 581 were admitted in the ED	Nasopharyngeal swab (PCR test)	- 8 Patients were treated w/ biologics and 6 were admitted from the ED	USA
[51]	Retrospective and observational study	September 2020	April 2021	Patients interviewed from the Allergy Unit of Infanta Leonor University Hospital, Madrid	- 80 Severe asthmatic patients 3 with COVID-19	Nasopharyngeal swab (PCR test)	- 29 Patients were treated w/ a biologic: omalizumab, n=9 (11.2%); mepolizumab, n=9 (11.2%); Benralizumab, n=1 (1.2%). - 1 w/ COVID-19 (mepolizumab). No hospitalizations.	Spain
[52]	Prospective cohort study	November 2020	March 15 to April 15, 2020	Bicêtre Hospital, University Paris-Saclay	- 37 Asthmatic patients with COVID-19	Nasopharyngeal swab (PCR test) and/or typical CT abnormalities	- 2 Patients were treated w/ omalizumab - 1 was admitted in ICU.	France
[53]	Retrospective and observational study	June 2020	-	Patients of La Paz University Hospital contacted by telephone	- 71 Severe asthmatic patients on biologic treatment	Nasopharyngeal swab (PCR test) and/or high suspicion of COVID-19	- Patients were treated w/: omalizumab, n=46; Mepolizumab, n=14; benralizumab, n=6, reslizumab, n=5. - 7 were diagnosed w/ COVID-19 (0 death): omalizumab, n=5; mepolizumab, n=1; reslizumab, n=1 (1 hospitalization).	Spain

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Table 1 (Continued).

Ref.	Study Type	Publication Date	Time Period	Database	Asthmatic Population Studied	COVID-19 Diagnosis	Biologic Treatment/Main Results	Study Location
[54]	Multicenter prospective study	December 2020	March 17 to April 30, 2020	Dutch Severe Asthma Registry RAPSODI (15 hospitals)	- 707 Severe asthma	Positive PCR or/ and typical symptoms <10 days after contact with a confirmed	- 634 Patients were treated w/ a biologic for asthma omalizumab, n=121 (19%), mepolizumab, n=247 (39%); reslizumab, n=247 (16%); benralizumab, n=121 (19%); dupilumab, n=44 (7%) - 9 were diagnosed w/ COVID-19: omalizumab, n=2 (2 ICU); mepolizumab n=3 (2 in ICU; 1 death); reslizumab, n=1; benralizumab, n=2 (1 ICU); dupilumab n=1.	Netherlands

Abbreviations: Ref., Reference; w/, with; n, number; PCR, polymerase chain reaction; BSAR, Belgian Severe Asthma Registry; IRSAN, Italian Registry of Severe Asthma network; ED, emergency department; CT, computerized tomography; ICU, Intensive care unit; RAPSODI, Registry of Adult Patients with Severe asthma for Optimal Disease management.

There were no reported deaths. The authors found no significant difference in COVID-19 frequency between severe asthma patients on biologics compared to those not on biologics.[48]

Smith et al studied 1365 patients from the UK Severe Asthma Registry, 97 of whom had suspected or confirmed COVID-19. Of the 1365 severe asthma patients, 918 were treated with biologics. The authors also found no association between biological treatment and the risk of COVID-19. Neither did they find an association between the type of biologic and COVID-19.[41]

In the study by Adir et al of COVID-19 asthma patients, the authors found that biologics use was not associated with an increased risk of the studied endpoints: moderate-to-severe COVID-19, all-cause mortality and the composite endpoint of moderate-to-severe COVID-19 or all-cause mortality.[39]

Caminati et al reviewed the medical records of patients admitted to COVID-Units of six Italian cities' major hospitals. Of the 2000 COVID-19 patients, 42 (2.1%) had asthma. Of these, 24% had severe asthma. Only 5% of asthma patients were treated with biologics. The authors found that GINA step 4–5 asthma was significantly associated with the probability of a worse outcome.[49]

In a study of 4558 COVID-19 patients of the Albert Einstein College of Medicine/Montefiore Medical Center, 951 patients had asthma, 8 of whom were on biologics. The authors did not find an association between treatment with biologics and the odds of being admitted from the emergency department.[50]

Haroun-Díaz et al reported on 80 severe asthma patients from the Infanta Leonor University Hospital, 23.7% of whom were treated with biologic agents. Of the total 80 patients, 3 had COVID-19, one of them being on mepolizumab. None of the patients required admission to the ICU and there were no reported deaths.[51]

Beurnier et al conducted a prospective cohort of COVID-19 asthma patients hospitalized in the Bicêtre Hospital, University Paris-Saclay, France. Of the total 768 COVID-19 patients, 37 were asthmatic. Eleven asthma patients were GINA step 5 and two of them were on omalizumab. Three patients died, none of whom were being treated with omalizumab. One of the patients on omalizumab required admission to the ICU.[52]

Domínguez-Ortega et al studied 71 severe asthma patients on therapy with biologics, most of them (n=63) treated at home on a self-administration program. Of these, seven had a COVID-19 diagnosis. This rate of infection

(9.85%) was similar to that of the general population. Only one of the patients required hospitalization and all recovered.[53]

Eger et al conducted a prospective study on the Dutch Severe Asthma Registry RAPSODI (Registry of Adult Patients with Severe asthma for Optimal Disease management) population. Of the 707 patients included, 634 were treated with biologics, 9 (1.42%) of whom were diagnosed with COVID-19. Seven of these nine patients were hospitalized and 5 of these were admitted to the ICU for mechanical ventilation, one (14%) of whom died. The authors found that, compared to the general population, the RAPSODI population on biologics had a higher risk of being infected by SARS-CoV-2 and of COVID-19 related hospitalization, intubation and death. However, the authors suggested that this could be explained by the higher prevalence of obesity in biologic-treated patients. They also pointed out that, compared to other studies, the RAPSODI population had a higher proportion of patients who had adult-onset asthma, were non-atopic and had been previously on chronic OCS treatment.[54]

There were also a few published case reports. An asthmatic patient on omalizumab became infected by SARS-CoV-2 and had a mild disease course[55]; four severe asthma patients treated with benralizumab had COVID-19 and only one required hospitalization but recovered.[56–58] Azim et al reported on another four patients on mepolizumab who had COVID-19, one of whom was hospitalized, but there were no deaths.[59] Aksu et al also reported the case of a COVID-19 severe asthma patient on mepolizumab who had mild disease.[60] Bhalla et al reported the case of a patient on dupilumab who had mild COVID-19.[61]

Triple Therapy with ICS, LAMA, and LABA

Triple therapy with ICS, LAMA (long-acting muscarinic antagonists) and LABA (long-acting beta2 agonists) has gained importance as a potential treatment for asthma patients. GINA guidelines recommend LAMA as add-on therapy in steps 4 and 5.[62] Triple therapy has been reported to improve lung function and decrease exacerbations in uncontrolled asthma compared to treatment with ICS and LABA.[63,64] There is limited evidence about the role of triple therapy in asthmatic patients in the context of SARS-CoV-2 infection. Liang et al reported the case of a 54-year-old man with asthma and allergic rhinitis who contracted COVID-19 and required admission to the ICU and tracheal intubation. After extubation and during systemic glucocorticoids treatment and ICS/LABA combination, the patient remained very symptomatic and was therefore treated with inhaled budesonide/glycopyrrolate/formoterol fumarate, with a good response. This case suggested that triple therapy can be beneficial in SARS-CoV-2-infected asthmatic patients. However, this is only a case report. Furthermore, this patient had a smoking history and emphysema visible in the computed tomography scan, which supports the diagnosis of COPD and therefore makes it difficult to interpret these results.[65]

It has been suggested, from a study with primary human nasal and tracheal epithelial cell cultures, that a combination of glycopyrronium, formoterol and budesonide inhibit Coronavirus 229E (HCoV-229E) replication and modulate infection-induced inflammation in the airway. It is possible that these drugs also have an effect against SARS-CoV-2 infection, although that has not been studied.[66]

Discussion

Despite some controversy, the reviewed evidence suggests that severe asthma patients do not have an increased risk of COVID-19 poor outcomes. It also suggests that it is safe to treat asthmatic patients with ICS and biologics during the COVID-19 pandemic, even though some studies pointed to high doses of ICS being detrimental.[41,42] The chronic use of OCS might be associated with poor COVID-19 outcomes,[39] although that is not consensual. There is very limited evidence concerning the use of triple therapy for asthma in the context of COVID-19. The latter is, so far, promising, but it is impossible at this point to take any definite conclusions on this matter.[65]

Issues regarding the ideal dose and timing of corticoids administration in the treatment of COVID-19 asthma patients remain to be clarified. Several randomized controlled trials are underway to address the role of ICS in treating COVID-19 once patients have become infected with SARS-CoV-2 (NCT04355637, NCT04331470, NCT04377711, NCT04330586, and NCT04416399).[43]

Several organizations, as the Global Initiative for Asthma (GINA), the National Institute for Health and Care Excellence (NICE), and the British Thoracic Society (BTS) recommend not stopping treatment with biologics in asthmatic patients during the COVID-19 pandemic.[62,67,68]

Although Eger et al found that patients on biologics had an increased risk of COVID-19 and poor related

outcomes, this study had some confounding factors, namely the higher prevalence of obesity in the population treated with biologics.[54] Several studies on this subject refer as a methodological limitation the fact that in the beginning of the pandemic there was a restriction in the number of diagnostic tests available. The milder cases were most often quarantined and not tested. This may have resulted on a non-identification of many asthmatic patients with or without biological treatment and may bias the results.[40,44,46,53,54] The number of asthma admissions particularly in children may also been influenced by the social distancing and the use of face masks.[69]

Although the self-administration option of biologics treatment was not mentioned on most of the presented studies, Domínguez-Ortega et al[53] referred that the majority of patients on biologics (89%) were treated at home. Self-administration of biologic treatments should be increasingly available and encouraged, as it decreases the need of hospital visits which could be beneficial in the present pandemic situation, avoiding withholding the medication.

There are still many doubts surrounding this topic, namely regarding the effects of asthma phenotypes on COVID-19. It has been suggested that T2-low patients with asthma may have a higher risk for COVID-19 severe outcomes.[50]

Conclusion

Current evidence supports that severe asthma patients should maintain their medication during the COVID-19 pandemic, including biologic agents. It is recommended that, along with all the efforts to avoid exposure to the SARS-CoV-2 virus together with COVID-19 vaccination, regular asthma treatments should be optimized to maintain asthma control.[6,62,70] In particular, the evidence suggests that ICS and biologics do not increase the risk of SARS-CoV-2 infection or of poor related outcomes, while doubts remain about dosing and timing. The evidence regarding OCS is contradictory and that on triple therapy in this context is insufficient.

More studies are needed to address the role of asthma medications and asthma's different phenotypes on the frequency and course of COVID-19.

Disclosure

The authors report no conflicts on interest in this work.

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