



COVID-19, asthma, and biological therapies: What we need to know

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ABSTRACT

Managing patients with severe asthma during the coronavirus pandemic and COVID-19 is a challenge. Authorities and physicians are still learning how COVID-19 affects people with underlying diseases, and severe asthma is not an exception. Unless relevant data emerge that change our understanding of the relative safety of medications indicated in patients with asthma during this pandemic, clinicians must follow the recommendations of current evidence-based guidelines for preventing loss of control and exacerbations. Also, with the absence of data that would indicate any potential harm, current advice is to continue the administration of biological therapies during the COVID-19 pandemic in patients with asthma for whom such therapies are clearly indicated and have been effective. For patients with severe asthma infected by SARS-CoV-2, the decision to maintain or postpone biological therapy until the patient recovers should be a case-by-case based decision supported by a multidisciplinary team. A registry of cases of COVID-19 in patients with severe asthma, including those treated with biologics, will help to address a clinical challenge in which we have more questions than answers.

Keywords: Asthma, Biologics, COVID-19, Pandemic, SARS-CoV-2, Severe, Treatment

HOW TO MANAGE SEVERE ASTHMA DURING A PANDEMIC?

Managing severe asthma during the coronavirus pandemic and COVID-19 is challenging, particularly due to safety concerns regarding the use of

oral corticosteroids (OCS). Although recent developments in, and the approval of, biological therapies offers a promising and more personalized treatment option in severe asthma, we do not know their current safety status during the SARS-CoV-2 pandemic. Thus, the question remains in our clinical practice: biologics treatment for whom and when?

WHAT DO WE KNOW ABOUT COVID-19 AND ASTHMA?

Authorities and physicians are still learning how COVID-19 affects people with underlying diseases,

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and severe asthma is not an exception. Even though respiratory viruses are one of the most common triggers for asthma exacerbations, not all of these viruses affect patients equally. There is no clear evidence that patients with asthma are at a higher risk of being infected with SARS-CoV-2,¹⁻³ although recent reports from the United States suggest that asthma is much more common in children and adults with COVID-19 than it was previously reported in China and Europe.²⁻⁵

It is more likely for an asthma patient to have an exacerbation caused by other triggers, including allergens or other virus exposures, or even by stopping the regular use of their prescribed medication. However, an asthma exacerbation, in general, requires patients to visit a healthcare facility, which now puts them at an increased risk of exposure to SARS-CoV-2.⁶ Ongoing prospective cohort studies (SARP, NHLBI and others) provide a unique opportunity to examine the effects of COVID-19 on severe asthma and potential interactions with therapy, including inhaled and oral corticosteroids, as well as targeted treatment with biologics.

Bhatraju et al., from Seattle, USA, reported 24 patients with COVID-19, admitted to the intensive care unit (ICU), with a mortality rate of 50%. As coexisting disorders, 14% had asthma, corresponding to three cases with mild asthma who were treated with systemic steroids in the week before ICU admission, as outpatients, for a presumed asthma exacerbation. These patients were subsequently admitted to the ICU with severe respiratory failure that required invasive mechanical ventilation.⁷ These data, although limited, are in accordance with previous studies during other coronavirus outbreaks showing that systemic steroids can be associated with a higher viral load.^{8,9} Clinicians in the initial work up of a patient with "shortness of breath", that can overlap COVID-19 and asthma clinical manifestations, must be aware and recognize the differences between hypoxic respiratory failure and bronchospasm on physical examination to judge the need for a course of OCS.

HOW SAFE ARE INHALED CORTICOSTEROIDS IN THE COVID-19 ERA?

In addition, therapeutic questions still exist, including whether treatment with inhaled corticosteroids (ICS) influences susceptibility to SARS-CoV-2, as well COVID-19 severity and mortality.

Unless relevant data emerge that change our understanding of the relative safety of such medications in patients with asthma in the COVID-19 era, clinicians must follow the recommendations of current evidence-based guidelines for preventing loss of control and exacerbations.¹⁰

SHOULD BIOLOGICS FOR SEVERE ASTHMA BE USED DIFFERENTLY IN THE COVID-19 ERA?

Management of patients with severe asthma during the COVID-19 pandemic may be a challenge, particularly of those on therapy with biologics. In the event they get infected with SARS-CoV-2 and develop COVID-19, the Allergist/Immunologist must be consulted on whether the treatment should be maintained or withdrawn while infection is active, and must be part of the decision on whether biological therapies available, which target the type 2 immune response, would be safe in the context of COVID-19.

Based on the information available, we are providing the current knowledge regarding the management of severe asthma patients with biologics during the COVID-19 pandemic.

Biological therapy drugs are indicated for patients with severe asthma who are not controlled adequately with other treatments.¹⁰ Currently available biologics licensed as add-on treatment for patients with severe asthma are omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab. These biologics target type 2 inflammatory pathways and are effective at reducing exacerbations, maintaining control over asthma symptoms, and reducing systemic steroid use.^{11,12}

Even though biologics are generally considered safe, especially in adults, data obtained from clinical trials on long-term use are limited to one- or two-year follow up safety registration studies.¹³⁻¹⁵ Thus, the safety profiles of these biologics in the face of the COVID-19 pandemic cannot yet be conclusively assessed, and two critical balanced questions should be considered: 1.) Is there an increased risk or not of patients using biologics to become infected with SARS-CoV-2, and 2.) Once asthmatic patients using biologics become infected, would the COVID-19 become more severe because of using biologics, or would the biological therapy help to decrease the risk of infection and severity?

For the current approved classes of biologics, the three anti-IL5/IL5r have their major effect targeting eosinophils producing either reduction or depletion of tissue and peripheral blood eosinophils. Thus, the primary question could be raised whether eosinophils or their products (primarily through T2 mechanisms) have any role in modifying susceptibility, severity, immunity, or resistance to viral infections. The primary unknown question is whether eosinophils could be mechanistically important in COVID-19 infection. There may be some evidence of herpes zoster infection occurring with anti-IL5 therapy in patients with eosinophilic severe asthma¹⁶ (also, with anti-IL4/IL13 in patients with severe atopic dermatitis),¹⁷ but COVID-19 appears to work through different biologic pathways.

The other two biologics (anti-IgE and anti-IL4/IL13) have their primary effects by inhibiting T2 immunity. The question is whether reduction of T2 mechanisms is beneficial or harmful in COVID-19 susceptibility or progression perhaps through effects on angiotensin-converting enzyme 2 (ACE2) and on transmembrane protease serine 2 enzyme (TMPRSS2). Additionally, there is some early evidence that ICS therapy is associated with reduction in ACE2 and TMPRSS2 gene expression from sputum.¹⁸ These data may imply that other drugs that inhibit immune function such as anti-IL-6 may be therapeutic targets for COVID-19 infection.¹⁹

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody (mAb) that selectively binds to human immunoglobulin E (IgE).²⁰ In clinical studies in allergic asthma treated

with omalizumab, the incidence of infections such as pharyngitis was low ($\geq 1/1000$ to $< 1/100$). In omalizumab studies including patients with chronic spontaneous urticaria, infections such as nasopharyngitis, sinusitis, and viral upper respiratory tract infections were frequent ($\geq 1/100$ to $< 1/10$).²⁰ However, most of the adverse events (AE) were mild to moderate in severity.²¹

Related to the viral infections, IgE plays a central effector role in the pathophysiology of inflammatory diseases of the airways.²⁰ The PROSE study evaluated whether treatment with omalizumab to reduce IgE would shorten the frequency and duration of rhinovirus illnesses in children with allergic asthma. The authors showed that treatment with omalizumab was able to reduce the duration of rhinovirus infections, viral shedding, and risk of rhinovirus illnesses.²² This has been further studied in *ex vivo* models which show a beneficial effect of omalizumab on viral clearance and interferon levels.

Recently, Heymann et al., investigated whether the administration of omalizumab could diminish the asthmatic response in patients inoculated with rhinovirus 16, in a randomized, double-blind, placebo controlled trial. The results showed that blocking IgE with omalizumab had its strongest effect in reducing lower respiratory tract symptoms and improving lung function during the first four days of the infection.²³

There are no data regarding the incidence nor severity of patients with COVID-19 receiving omalizumab. Physicians and other healthcare professionals should use their best clinical judgment when evaluating patients and making treatment decisions. Alternatives to hospital visits exist like self-injection at home, although this option is not available or licensed in every country; very recently, the U.S. Food and Drug Administration (FDA) has approved omalizumab for short-term home administration during the COVID-19 pandemic.²⁴

Mepolizumab is a mAb directed against interleukin-5 (IL5). Mepolizumab has a long-term safety profile and no increase AE rate over the study period or when compared to previous placebo-controlled trials; the most common AEs were respiratory tract infections (67%), headaches (29%), worsening of asthma (27%), bronchitis (21%), and injection-site reactions (12%).^{13,25}

Systemic allergic/hypersensitive reactions were recorded in 2% of patients, and 1% of patients experienced a nonallergic systemic reaction. On-treatment opportunistic infections (7%) were also reported, none of which were parasitic infections.^{13,25}

Severe eosinopenia (approximately 20-40 eosinophils/cubic millilitre in peripheral blood) has been reported in early studies among patients with COVID-19 from China, and the magnitude of eosinopenia was related to a worse prognosis.²⁶ It was believed that low eosinophil counts in peripheral blood would be related to the infection with the SARS-CoV-2 virus itself, and not necessarily an indicator that treatments which reduce eosinophil counts in patients with asthma would be associated with more severe COVID-19 disease. Interestingly, more recent studies from China and from Italy do not further report eosinopenia in patients with severe COVID-19.^{3,27,28} Of note, in a small phase 2 trial, patients with PDGFRA-negative hypereosinophilic syndrome, presenting with mean eosinophil counts of over 2300/mm³ at baseline, had a marked decrease in both peripheral blood and tissue eosinophils 12 weeks after receiving benralizumab.²⁹

Although the relationship of eosinophil counts and COVID-19 is uncertain, attention is warranted to monitor eosinophil counts among patients with asthma, chronic rhinosinusitis with nasal polyps, and hypereosinophilic syndrome who are using biological therapies which lead to decrease in eosinophil counts, and the clinical course of COVID-19 if they get infected with the SARS-CoV-2 virus.

GSK stated that they cannot make recommendations on whether interrupting therapy with mepolizumab would impact the risk of infection with SARS-CoV-2. In patients treated with mepolizumab 100 mg subcutaneous (SC), no specific data are currently available on the risk of infection with SARS-CoV-2 or the severity of illness in patients infected with this virus. Physicians should use their best clinical judgement based on their knowledge of individual patient needs, disease impairment and the risks vs the benefits of treatment.³⁰ Self-injection of mepolizumab permits its administration at home thus decreasing chances of viral exposure in the clinic.

Reslizumab is a mAb against IL5, so it has the same mechanism of action as mepolizumab. In an open label extension of a placebo controlled Phase III trial, the most frequently reported AEs in both reslizumab-experienced and reslizumab-naïve patients were asthma worsening (28% vs. 46%), nasopharyngitis (14% vs. 14%), upper respiratory tract infection (10% vs. 9%), sinusitis (8% vs. 6%), headache (7% vs. 11%), and local administration-related AEs (1%).¹⁴ The intravenous administration of this drug must be performed in the clinic or hospital.

Benralizumab is a humanized afucosylated mAb against IL5 alpha receptor (IL5Ra) that induces eosinophil apoptosis through the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC) involving natural killer cells, which further induces peripheral blood eosinophil depletion. The most common AEs were viral upper respiratory tract infections (14-16%) and worsening asthma (7-10%). The most common serious adverse events (SAEs) were worsening asthma (3-4%), pneumonia (<1%-1%), and pneumonia caused by bacterial infection (0-1%). No cases of helminth infection were reported, and rates of hypersensitivity AEs were similar across the study groups.^{15,31,32}

AstraZeneca reports that currently there are no available data regarding the risk of infection with the SARS-CoV-2 in patients being treated with benralizumab, nor regarding severity or progression of the disease. In the absence of any data indicating a potential harm, it would be reasonable to continue the administration of biologics during the COVID-19 pandemic in patients for whom such therapies are clearly indicated and have been associated with efficacy.³³ Self-injection is available which permits its administration at home, decreasing in-clinic exposure.

Dupilumab is a humanized mAb directed against the alpha-chain of the IL4 receptor (IL4Ra), which is shared for both IL4 and IL13; hence, this drug is able to inhibit the signalling of both ILs. The most frequently observed adverse drug reactions in dupilumab treatment for asthma were upper respiratory tract infection (14%), injection site erythema (13%), and headache (10%).³⁴ SAEs were reported in up to 8% of patients. The most frequent SAE was pneumonia.³⁵

Sanofi Genzyme stated that there are no clinical data indicating that treatment with dupilumab could increase the risk of COVID-19 infection, and they emphasized the following: “regarding drug uses which are not included in the approved product label, the safety and efficacy of such uses have not been assessed and thus are not approved. Regarding the prescription of the product referenced in the enclosed materials for a use that is different from those listed in the approved product label, physicians should make that decision based on their own medical judgment and discretion”. Sanofi Genzyme also included data from pivotal asthma and nasal polypoidosis studies in the report and emphasized that the reported rate of respiratory tract infections had similar frequencies.³⁶

WHAT ARE THE RESPIRATORY ORGANIZATION RECOMMENDATIONS FOR SEVERE ASTHMA IN LIGHT OF COVID-19?

The *Global Initiative for Asthma (GINA)* suggests that people with asthma should continue to use their inhaled asthma control medications including ICS during the COVID-19 epidemic. Biological therapies should be used in severe asthma patients who qualify for them, in order to limit the need for OCS as much as possible.³⁷

The *American Academy of Allergy, Asthma & Immunology (AAAAI)* states that there is no evidence that suggests immune response to COVID-19 will be impaired in asthma patients treated with anti-IL5 (anti-IL5Ra), anti-IL4/IL13, or anti-IgE medications. In the absence of any data indicating a potential for harm, it would be reasonable to continue administration of biological therapies in patients for whom such therapies are clearly indicated and have been associated with efficacy. AAAAI emphasizes leveraging home administration for biologics as appropriate, to mitigate the risk of missing one or several doses. Nevertheless, some patients may require a face-to-face interaction for biologic administration.³⁸

The *American College of Allergy, Asthma and Immunology (ACAAI)* recommends that patients with asthma remain on their medication, as none of these medications, including inhaled corticosteroids

and biologics, have been shown to increase the risk of getting COVID-19. There is no information at this time that biologics (for severe asthma) should be stopped. These severe asthma patients can have an increased risk of COVID-19 infection, and optimal control of their chronic condition is of utmost importance.³⁹

The *European Respiratory Society (ERS)* and *European Lung Foundation (ELF)* provided their recommendation on anti IL5s; however, no information was given on other products including dupilumab or omalizumab. Subsequent suggestions were given as answers to frequently asked questions, and no official guidance on severe asthma management (in light of COVID-19) was released so far. Those suggestions were: “to not cease or modify any asthma medication administration due to any concerns about COVID-19; there is a risk that doing so could hinder your asthma control; anti-IL5 should not increase the risk of getting COVID-19, and continuing its intake could theoretically reduce the risk of an asthma attack in case you were to contract the virus”.⁴⁰

Several national societies, such as the *British Thoracic Society (BTS)* and the *Italian Society of Allergy, Asthma & Clinical Immunology (SIAAIC)*, recommend continuing the biologic treatment, and they highlight the need for transition efforts (from the clinic to home care). Centers must organize themselves to promote a home-based administration of biologics, and patients should be advised to continue their treatments.^{41,42}

CAN WE USE BIOLOGICS IN PATIENTS WITH ASTHMA UNDER TREATMENT FOR COVID-19?

Worldwide, there has been considerable public, social, and political attention paid to unproven treatments against COVID-19. These have centered on the use of hydroxychloroquine, chloroquine, azithromycin, and zinc supplements. At present no randomized controlled trials have demonstrated efficacy and no evidence-based medicine (EBM) recommendations exist.⁴³ Nonetheless these interventions would have no theoretical interference on biologics for patients with severe asthma.

Other randomized controlled trials (RCTs) involving antivirals (namely remdesivir, lopinavir,

and ritonavir), convalescent immune or recovery plasma/sera, and developing humanized monoclonal antibodies against SARS-CoV2 infection (including tocilizumab, an IL6 receptor antagonist) are all under study^{43,44} and potentially would be also compatible with biologics in severe asthma.

IN SUMMARY...

There is no evidence suggesting that the immune response to SARS-CoV-2 should be impaired in asthma patients treated with biological therapies. In the absence of data that would indicate any potential harm, the advice is to continue the administration of biological therapies during the COVID-19 pandemic in patients for whom such therapies are clearly indicated and have been effective.

As in the placebo controlled trials with omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab in asthmatic patients, no risk of increased infection susceptibility, or immunosuppressive effect was reported to date and, in the case of omalizumab, there is a possible anti-infectious effect; hence, we do not need to discontinue these treatments during the current pandemic.

Stopping biologics may lead to higher risk of asthma exacerbations, increased OCS use, and higher probability of emergency room access and hospitalization that themselves represent risk factors for SARS-CoV-2 exposure/infection. Thus, when balancing costs and benefits, discontinuing biologic treatment is currently not recommended for patients with severe asthma with no COVID-19.

COVID-19 has a mortality risk which is particularly high in the elderly and obese, especially those with underlying cardiovascular, respiratory and metabolic co-morbidities.^{45,46} It also seems to have greater adverse effects in particular populations, related to race, low socioeconomic status, co-morbidities, or differences in susceptibility.⁴ Therefore, we should be able to precisely evaluate and guarantee that patients with asthma must maintain their control treatment, including biological therapies, considering their ages, co-morbid diseases, and specific circumstances, namely socioeconomic status.

Until we collect more information and evidence, for the patients with severe asthma plus co-

morbidities infected by SARS-CoV-2, the decision of maintaining or postponing biological therapy until the patient recovers should be a case-by-case based decision supported by a multidisciplinary team.

A registry of cases of COVID-19 in patients with severe asthma, including those treated with biologics, will help to address a clinical challenge where we have more questions than answers.

List of Abbreviations

AAAAI: American Academy of Allergy, Asthma and Immunology; ACAAI: American College of Allergy, Asthma and Immunology; ACE2: Angiotensin-converting enzyme 2; ADCC: Antibody-Dependent Cell-mediated Cytotoxicity; AEs: Adverse events; BTS: British Thoracic Society; DNA: Deoxyribonucleic acid; ERS: European Respiratory Society; ELF: European Lung Foundation; FDA: Food and Drug Administration; IgE: Immunoglobulin E; IL4: Interleukin 4; IL5: Interleukin 5; IL5Ra: Interleukin 5 alfa receptor; IL5r: Interleukin 5 receptor; IL6: Interleukin 6; IL13: Interleukin 13; ICS: inhaled corticosteroids; ICU: Intensive Care Unit; COVID-19: Coronavirus Disease 2019; EBM: Evidence Based Medicine; GINA: Global Initiative for Asthma; GSK: Glaxo Smith Kline; mAb: Monoclonal antibody; NHLBI: National Heart, Lung, and Blood Institute; OCS: Oral corticosteroids; PDGFRA: Platelet-Derived Growth Factor Receptor A; PROSE study: Preventative Omalizumab or Step-up therapy for fall Exacerbations study; RCTs: Randomized Controlled Trials; SAEs: Serious Adverse Events; SARP: Severe Asthma Research Programme; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SC: Subcutaneous; SIAAIC: Italian Society of Allergy, Asthma and Clinical Immunology; T2: Type 2 inflammation; TMPRSS2: Transmembrane Protease Serine 2 Enzyme; USA: United States of America

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this article.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent

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Author Contributions

Mário Morais-Almeida and Rita Aguiar conceived and wrote the first draft of the manuscript and participated in all steps until the final version with equal contribution. Bryan Martin, Ignacio Ansotegui, Motohiro Ebisawa, L. Karla Arruda, Marco Caminati, Giorgio Walter Canonica, Tara Carr, Geoffrey Chupp, Jonathan Corren, Ignacio Dávila, Hae-Sim Park, Nicola A. Hanania, Lanny Rosenwasser, Mario Sanchez-Borges, J. Christian Virchow, and Anahí Yáñez provided critical contributions to the manuscript. Eugene R. Bleeker provided critical contributions to and supervision of the manuscript. All authors critically reviewed and approved the final version of the submitted manuscript.

Declaration of Competing Interest

The authors do not report any competing interests related to this article.

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