Considerations on biologicals for patients with allergic disease in times of the COVID-19 pandemic: An EAACI statement

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Abstract

The outbreak of the SARS-CoV-2-induced coronavirus disease 2019 (COVID-19) pandemic re-shaped doctor-patient interaction and challenged capacities of healthcare systems. It created many issues around the optimal and safest way to treat complex patients with severe allergic disease. A significant number of the patients are on treatment with biologicals, and clinicians face the challenge to provide optimal care during the pandemic. Uncertainty of the potential risks for these patients is related to the fact that the exact sequence of immunological events during SARS-CoV-2 is not known. Severe COVID-19 patients may experience a "cytokine storm" and associated organ damage characterized by an exaggerated release of pro-inflammatory type 1 and type 3 cytokines. These inflammatory responses are potentially counteracted by anti-inflammatory cytokines and type 2 responses. This expert-based EAACI statement aims to provide guidance on the application of biologicals targeting type 2 inflammation in patients with allergic disease. Currently, there is very little evidence for an enhanced risk of patients with allergic diseases to develop severe COVID-19. Studies focusing on severe allergic phenotypes are lacking. At present, noninfected patients on biologicals for the treatment of asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, or chronic spontaneous urticaria should continue their biologicals targeting type 2 inflammation via self-application. In case of an active SARS-CoV-2 infection, biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established and treatment with biologicals should be re-initiated. Maintenance of add-on therapy and a constant assessment of disease control, apart from acute management, are demanded.

1 | INTRODUCTION

The outbreak leading to the pandemic of SARS-CoV-2-induced coronavirus disease 2019 (COVID-19) has pushed healthcare systems to the limits of their capacity across the globe. This infection can cause severe respiratory illness and multi-organ failure with clinical presentations greatly resembling SARS-CoV-1 and MERS-CoV, resulting in intensive care unit (ICU) admission and high mortality. We discuss immunological and clinical considerations for patients on biologic agents (biologicals) targeting the type 2 inflammatory response due to difficult-to-treat allergic diseases in the context of COVID-19.

2 | IMMUNOLOGICAL FEATURES OF SARS-COV-2 INFECTION IN THE CONTEXT OF TYPE 2 INFLAMMATION

Both innate and adaptive immune responses participate in antiviral immunity. The interactions between SARS-CoV-2 and both arms of the immune system have been poorly clarified until now, particularly in the view of asymptomatic individuals, patients with mild disease, and those who fully recover. Natural killer cells are involved in control of the acute phase of the viral infection, whereas CD8+ T cells are the key player in the following steps. Antibody-secreting cells and T follicular helper cells are instrumental in the production of specific antiviral IgA, IgM, and IgG antibodies early on. Antibody-dependent macrophage activation as well as lymphocyte and macrophage pyroptosis (an excessive form of inflammatory cell apoptosis) might occur and contribute to more severe tissue damage, as described in SARS-CoV infection. Among mediators, type I interferons (type I IFN) play a central role. In other coronavirus infections such as severe acute respiratory syndrome (SARS), type I IFN is critical for the initiation of immune response and virus clearance. Delayed production of type I IFN and an insufficient cytotoxic response is associated with a more severe clinical disease. Observations from SARS or Middle East respiratory syndrome (MERS) and, more recently, COVID-19 patients suggest an overshooting immune response in severe cases with widespread
lung damage and disease aggravation around 7-14 days after onset. Those severe COVID-19 patients may also experience a picture of a so-called cytokine storm and associated organ damage, particularly acute respiratory distress syndrome, acute kidney and liver failure, myocarditis, and disseminated vascular coagulation. These manifestations are characterized by an exaggerated release of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α (Figure 1). Consequently, these highly increased pro-inflammatory cytokines are believed to be potential targets for biological therapy. These type 1- and type 3-driven inflammatory responses are counteracted by anti-inflammatory cytokines, such as IL-10 and TGF-β, as well as potentially type 2 responses. Moreover, eosinophils have been reported to play a role in virus response. Lower eosinophil counts were reported in association with severe cases, while an elevated eosinophil count was associated with a better prognosis, although no functional relationship has been established so far and this finding may be an epiphenomenon. Thus, probably all shades of cytokine responses (type 1 and type 3, type 2, and regulatory cytokines) are required in the healing of SARS-CoV-2 infection. An appropriate induction and downregulation of individual response batteries is necessary to achieve an efficient viral clearance, an avoidance of excessive inflammatory reaction, and irreversible tissue damage (Figure 2).

3 | SARS-COV-2 INFECTION AND ALLERGIC DISEASE

In line with a paucity of mechanistic data on COVID-19 in the context of type 2 inflammation, knowledge on the disease course in patients treated with biologicals targeting type 2 inflammation due to severe asthma or other atopic diseases, such as CSU, AD, and CRSwNP, is scarce to absent. To our knowledge by April 12, 2020, only 6 studies presented disease characteristics of SARS-CoV-2 infection on patients with allergy or atopic diseases as a comorbidity (Table 1; Supplementary Material). While in a study including...
1591 patients infected with SARS-CoV-2 and admitted to ICUs of Lombardy, Italy, asthma was not referred to as a specific comorbidity and grouped under “others.” Allergic disease seemed to have no influence on presented symptoms and the course of the disease. None of these patients were on biologicals to treat their pre-existing allergic disease. In a recent report from the COVID-19-Associated Hospitalization Surveillance Network based on data from 14 US states from March 1, 2020, to March 30, 2020, 17% of hospitalized COVID-19 patients had asthma as a comorbidity. The highest percentage was in the 18- to 49-year-old patient group with 27.3% asthmatics. No information on severity of the disease and therapy has been provided. This supports the importance of a prospective assessment of atopic diseases in the context of COVID-19.

4 | BIOLOGICAL THERAPIES TARGETING TYPE 2 INFLAMMATION: KEY ISSUES

In the past years, new biological therapies for severe asthma, atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP),
and chronic spontaneous urticaria (CSU) have been developed targeting different aspects of the type 2 immune response.\textsuperscript{16–24} Anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) are approved for severe asthma with peripheral eosinophilia, uncontrolled under high-intensity treatment. Benralizumab, a monoclonal antibody that binds to the $\alpha$ subunit of IL-5 receptor (IL-5R$\alpha$),\textsuperscript{25} was also recently approved for uncontrolled eosinophilic severe asthma. Dupilumab, a monoclonal antibody directed against the $\alpha$ subunit of the IL-4 receptor (IL-4R$\alpha$) acting as a dual antagonist of both IL-4 and IL-13, was approved for uncontrolled severe type 2 asthma, moderate-to-severe AD, and CRSwNP. Omalizumab, a humanized monoclonal anti-IgE antibody, has also been approved for IgE-mediated persistent allergic asthma and CSU.

The spread of the disease prompted allergists and immunologists to reduce their service to the acceptable minimum and important guidance of patients receiving biological therapies is limited, so insecurity on how to manage their disease in case of an infection may occur. To date, the role of type 2 cytokines in the pathogenesis and severity of COVID-19 is not well established, and therefore, guidance of patients on biologicals targeting pathways of the allergic response during this pandemic is scarce. Main questions in this context area are as follows: (a) To what extent is there an increased

<table>
<thead>
<tr>
<th>Biological</th>
<th>Target structure</th>
<th>Application interval</th>
<th>Infection rate (%)/Biological/placebo (Total n/group)</th>
<th>References</th>
<th>Indication</th>
</tr>
</thead>
</table>
| Benralizumab | IL-5R alpha | Q4W | n = 1926  
Viral URTI\textsuperscript{a}  
24.1/0 (14/11) | 1 47 | Severe uncontrolled eosinophilic asthma |
| | | Q8W | n = 61  
Viral upper respiratory tract infections  
12.5/13.8 (32/29) | 1 47 | Severe uncontrolled eosinophilic asthma |
| | | | | | |
| Dupilumab | IL-4R alpha | Various (QW, Q2W, Q4W, Q8W), placebo | n = 422,  
URTI (5.7-8.3/7.3), Influenza (0-5.7/1.2), HSV1 (1.8-6.0/3.7), Viral infections (0-1.2/3.7) | 2 | Atopic dermatitis |
| | | Combined (200 mg/300 mg Q2W), placebo | n = 1897, viral upper respiratory tract infections (18.2/19.6), upper respiratory tract infections (11.6/13.6), influenza (5.9/8.0) | 3 | Moderate-to-severe uncontrolled asthma |
| | | 300 mg Q2W, placebo | n = 210,  
Viral URTI (9/18), Influenza (3/6) | 4 | Severe steroid-dependent asthma |
| | | Adolescence. 200/300 mg Q2W, 300 mg Q4W, placebo | n = 250,  
URTI (7.2-12.2/17.6), HSV infections (1.2-4.8/3.5) | 5 | Atopic dermatitis |
| | | 300 mg Q2W, placebo | n = 276  
URTI (5.4-6.7/12.7) | 6 | Chronic rhinosinusitis with nasal polyps |
| | | 300 mg QW/Q2W, placebo | n = 1379  
URTI (3-5/2), HSV (0-3/1), HSV1 (2-4/2), HSV2 (1/1)  
VZV (herpes zoster) (0-1/1), | 7 | Atopic dermatitis |
| | | 300 mg QW/Q2W, placebo | n = 740  
URTI (10-14/10) Influenza (3-4/5)  
HSV (2-3/1), VZV (herpes zoster) (<1-1/2), HSV1 (4-5/3) | 8 | Atopic dermatitis |
| | | 300 mg Q2W,  
real-life, open label | n = 241  
URTI (1.2)  
HSV (<1%) | 9 | Atopic dermatitis |
| | | 300 mg Q2W | n = 1491  
viral URTI (2.5) Influenza (2.1)  
HSV1 (4.3) | 10 | Atopic dermatitis |

(Continues)
risk of allergic patients on biologicals targeting type 2 inflammation to being infected or developing severe disease upon SARS-CoV-2 infection and (b) the degree of side effects that arise from potential immunosuppressive biologicals against the benefits of controlling the diseases such as severe asthma, AD, CRSwNP, or CSU.

### 5 | BLOCKING TYPE 2 INFLAMMATION AND VIRAL INFECTIONS

The low number of reports of patients on biologicals targeting type 2 disease is encouraging since type 2 diseases may predispose patients to viral infections due to compromised barriers.

Consequently, epidemiologic evidence closely links virus infections to both development and exacerbation of allergic diseases. The infection and persistence of respiratory viruses is attributed to impaired innate immune responses and a predisposition to mount strong type 2 immune responses. In line with this argumentation, some of these drugs provided evidence for a reduction of viral infections in asthmatics such as anti-IgE treatment with omalizumab. It may cause anti-inflammatory and immunomodulatory effects by restoring the capacity of human plasmacytoid dendritic cells (pDCs) to produce IFN-α, increasing antiviral activity, and reducing viral-induced asthma exacerbations.

<table>
<thead>
<tr>
<th>Biological</th>
<th>Target structure</th>
<th>Application interval</th>
<th>Infection rate (%) Biological/placebo (Total n/group)</th>
<th>References</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>Human IL-5</td>
<td>75 mg IV Q4W, 100 mg SC Q4W</td>
<td>n = 576 Influenza 5/3 (191/191), 3/3 (194/191) Viral URTI 1/1 (191/191) 0/1 (194/191) HSV1 &lt;1/0 (191/191) HSV2 &lt;1/0 (191/191)</td>
<td>11 48</td>
<td>Severe, eosinophilic asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg SC Q4W</td>
<td>n = 135 Influenza 4/2 (69/66) Viral URTI 1/2 (69/66) Herpes zoster 0/2 (69/66)</td>
<td>12 49</td>
<td>Severe, eosinophilic, steroid-dependent asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg Q4W</td>
<td>n = 551 Influenza 3/1, (273/278) HSV1 &lt;1/0. (273/278) Herpes zoster &lt;1/1, (273/278)</td>
<td>13 50</td>
<td>Severe, eosinophilic asthma</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Q2W or Q4W</td>
<td>n = 3.3/3.4 (243/84) Influenza 9/9 (1028/730) Viral URTI 3/5 (1028/730)</td>
<td>14</td>
<td>Severe allergic asthma</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Human IL-5</td>
<td>3.0 mg/kg (iv)/every 4 weeks</td>
<td>n = 1000 Influenza 3/1 (1000/1000) Viral URTI 1/1 (1000/1000)</td>
<td>15</td>
<td>Severe, eosinophilic asthma</td>
</tr>
</tbody>
</table>

Abbreviation: CRSwNP: chronic rhinosinusitis with nasal polyps

*a* Any rhinovirus infection
TABLE 3  Recommendations of national societies and international societies on the management of patients with severe allergic disease

<table>
<thead>
<tr>
<th>National Society/International Society</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>ETFAD51</td>
<td>To continue all immune-modulating treatments, including immunosuppressive therapy, since exacerbations of underlying diseases can have a large negative impact on patients’ immunity. “Targeted treatment selectively interfering with type 2 inflammation, such as dupilumab, is not considered to increase the risk for viral infections and might thus be preferred compared to conventional systemic immunosuppressive treatments, such as cyclosporine, in a situation such as the COVID-19 pandemic. However, this theoretical advantage is not supported by robust clinical data.”</td>
</tr>
<tr>
<td>AAAAI <a href="http://www.aaaai.org">www.aaaai.org</a> based on Ref. 39</td>
<td>There is no evidence, which 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 biologic agents during the COVID-19 pandemic in patients for whom such agents are clearly indicated and have been effective.</td>
</tr>
<tr>
<td>ACAAI <a href="http://www.college.acaai.org">www.college.acaai.org</a> April 8, 2020</td>
<td>For patients with severe asthma currently on a biologic therapy, there is no information at this time that these treatments should be stopped. These severe asthma patients are at an increased risk to COVID-19 infection, and optimal control of their chronic condition is of utmost importance.</td>
</tr>
<tr>
<td>AAD (Guidance March 20, 2020, <a href="http://www.aad.org">www.aad.org</a>)</td>
<td>Patient should not stop biologics without consulting their physician! 1. Noninfected and no symptoms → physicians should continue to weigh the risk vs. benefits of the use of biologic medication on a case-by-case basis based on a. the original indication b. the severity of the original indication, c. the patient’s age (&gt; 60 y) d. comorbidities related to higher risk of mortality in case of COVID-19 2. Patients on biologic therapy positive for COVID-19: recommend to discontinue or postpone the biologic therapy until the patient recovers from COVID-19. Patients being considered for biologic therapy initiation: risk vs. benefits a. Low-risk patients → case-by-case basis. b. High-risk population → recommendation that physicians consider deferring initiation of biologic therapy.</td>
</tr>
<tr>
<td>BSACI <a href="http://www.bsaci.org">www.bsaci.org</a> April 5, 2020</td>
<td>• Defer commencement of omalizumab in new patients until COVID-19 restrictions are lifted. • Administer home omalizumab therapy earlier than the fourth dose specified in the product information, by administering training at the second dose and transitioning to home therapy for the third dose. While home therapy is not licensed where there is a history of anaphylaxis of any cause, in cases where there is a clear trigger and no association with omalizumab doses, home therapy could be used. In this case, consider provision of a written anaphylaxis action plan and adrenaline autoinjectors, if not already done.</td>
</tr>
<tr>
<td>DGAKI <a href="http://www.dgaki.de">www.dgaki.de</a> April 8, 2020</td>
<td>• Unavailability with biologics may lead to many patients requiring treatment with systemic steroids and potentially negative impact on immune responses directed against SARS-CoV-2 • Stopping treatment with biologics may lead to worsening of the underlying disease, which may therefore provide negative influence on the course of acquired COVID-19 disease. According to WHO, patients with chronic lung disease (eg, such as asthma) may be prone to more severe disease. a. viral asthma exacerbations occur less frequently and with lower severity under treatment with biologics b. those immune processes targeted by biologics most probably do not affect virus defense • Based on current knowledge, we therefore recommend to maintain treatment based on a joint agreement between treating physician and patient.</td>
</tr>
<tr>
<td>WAO worldallergy.org April 8, 2020</td>
<td>For patients: “There is currently no evidence that inhaled corticosteroids (nasal or bronchial), antihistamines or biologic medications have any effect on the risk of contracting COVID-19. If you stop or modify your treatment, you run the risk that your allergic disease, particularly your asthma control, could become worse, causing you to need rescue medical treatment or be admitted to the hospital.” <a href="https://www.worldallergy.org/UserFiles/file/Allergic_patients_during_COVID-19.pdf">https://www.worldallergy.org/UserFiles/file/Allergic_patients_during_COVID-19.pdf</a></td>
</tr>
<tr>
<td>PAS52</td>
<td>• It is recommended to continue biologic therapy with anti-IgE or anti-IL-5 in patients with severe asthma. • It is acceptable to start and then continue biologic therapy with anti-IgE or anti-IL-5 antibodies in patients with severe bronchial asthma in accordance with the current Biological Treatment Programme of the National Health Fund. • Continuation and, in specific cases, initiation of biologic therapy with anti-IgE antibodies (omalizumab) in patients with severe chronic urticaria are acceptable.</td>
</tr>
</tbody>
</table>

It has been reported that type 2 response and Treg response can antagonize these effects and may be beneficial. In this context, the inhibition of type 2 response in severe and critical COVID-19 cases may cause an aggravation of the disease. Therefore, such biologics should be discontinued in very severe disease. Due to their long in vivo half-life in the range of a few weeks, it remains unclear to which extent such an action would impact the acute management and what the risk of losing disease control and comorbidity later on could be. Recent systematic reviews on approved biologics in severe asthma showed that biologics targeting IL-5-signaling pathway (mepolizumab, reslizumab, and benralizumab) slightly increase drug-related adverse events.
For anti-IgE (omalizumab) and anti-IL-4Rα (dupilumab) treatments, rate ratios were rather small. Benralizumab and omalizumab showed an increase in AEs with low-to-moderate certainty in severe allergic asthma. There was an increased rate of dupilumab-related AEs (low certainty) in severe asthma. Data from clinical trials demonstrated good safety profiles of biologicals with regard to viral infections of the upper respiratory tract (Table 2).

**6 | PRACTICAL AND CLINICAL RECOMMENDATIONS**

**6.1 | Recommendations from national societies**

Time restrictions did not allow for official guidelines to be published so far. However, several societies issued statements on the use of biologicals during the COVID-19 pandemic (Table 3). A consensus-based ad hoc expert panel of allergy/immunology specialists from the United States and Canada recommends continuing administration of biologicals in patients with proven efficacy and converting the patient to a prefilled syringe for potential home administration if this is available or otherwise in-office application can occur with a plan to transition to home administration. Initiation of biologic therapy for AD should be weighed very carefully, but it remains a viable option as this is administered at home. In a recent communication, the European Task Force on Atopic Dermatitis (ETFAD) suggested that targeted treatment selectively interfering with type 2 inflammation, such as dupilumab, is not considered to increase the risk for viral infections and might thus be preferred compared to immunosuppressive treatments such as cyclosporine in a situation such as the COVID-19 pandemic, although stressing that this theoretical advantage is not supported by robust clinical data.

The key recommendation for an accurate management of noninfected patients on biologicals targeting type 2 inflammation because of an underlying severe allergic disease is the continuation of their drug regimen with close follow-up. During the COVID-19 pandemic, social distancing is encouraged for everybody and home application of the biologicals should be practiced if doable since an exacerbation of their disease requiring hospitalization would expose them to an increased risk of acquiring a SARS-CoV-2 infection. If that is not possible, it should be ensured that the application takes place in a safe environment (Figure 3).

All patients with a SARS-CoV-2 infection, irrespective of the severity of the infection, should withhold the application of biologicals until recovered.

If patients display mild clinical manifestations that allow home isolation, telemedical follow-up by the physician in charge should take place to ensure proper management, and background controller treatment (topical steroids or other controller medications as recommended by current guidelines) should be continued, as described for asthma, AD, CRSwNP, and CSU. Surgical interventions for CRSwNP should be delayed in any case possible.

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**FIGURE 3** Clinical algorithm on the use of biologicals for the treatment of allergic diseases in the context of COVID-19. Noninfected patients on biologicals for the treatment of asthma, AD, CRSwNP, or CSU should continue their biologicals targeting type 2 inflammation via self-application. In case of an active SARS-CoV-2 infection and moderate-to-severe COVID-19, biological treatment needs to be stopped until clinical recovery and SARS-CoV-2 negativity is established. Thereafter, treatment with biologicals can be re-initiated (AE) in severe eosinophilic asthma. For anti-IgE (omalizumab) and anti-IL-4Rα (dupilumab) treatments, rate ratios were rather small. Benralizumab and omalizumab showed an increase in AEs with low-to-moderate certainty in severe allergic asthma. There was an increased rate of dupilumab-related AEs (low certainty) in severe asthma. Data from clinical trials demonstrated good safety profiles of biologicals with regard to viral infections of the upper respiratory tract (Table 2).
In case of hospital admission for moderate, severe, or critical SARS-CoV-2 infection, management of the allergic disease should be in accordance with current guidelines by involving the respective subspecialties. In particular, for asthma inhalation therapy use preferably metered dose inhalations with chambers that are not to be shared and pulmonary function tests should be performed only if highly necessary (Figure 3).

Once resolution/recovery of the disease is established (eg, via a negative SARS-CoV-2 test) but no shorter than 2 weeks postonset of the disease/positive testing, the re-administration of the biological should be re-initiated (Figure 3).

7 | CONCLUSIONS

In conclusion, current evidence does not suggest a higher risk for severe COVID-19 in allergic individuals but data that allow estimating the risk of severe allergic phenotypes in case of SARS-CoV-2 infection are missing. Treatment of patients on biologicals targeting type 2 inflammation in allergic disease should be maintained in noninfected individuals. In case of an infection, withholding the treatment is recommended until recovery. Additional data on those patients with more severe phenotypes will provide more insight to define more precisely the risk profile of individuals with allergic disease who are of elevated risk. The collection of such data is imperative for future data-informed adaptations of these guidelines.

CONFLICT OF INTEREST

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REFERENCES


SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.