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Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement

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Abstract

The current COVID-19 pandemic influences many aspects of personal and social interaction, including patient contacts with health care providers and the manner in which allergy care is provided and maintained. Allergen-specific immunotherapy (AIT) is one of the most important treatment options for IgE-mediated allergies and is based on inducing an appropriate immune response in the allergic patient. This manuscript outlines the EAACI recommendations regarding AIT during the COVID-19 pandemic and aims at supporting allergists and all physicians performing AIT in their current daily practice with clear recommendations on how to perform treatment during the pandemic and in SARS-CoV-2 infected patients.

KEYWORDS
allergy treatment, clinical immunotherapy, immunotherapy vaccines and mechanisms

1 | INTRODUCTION

The current COVID-19 pandemic influences many areas of social life, medical treatments and the way allergy diagnosis and treatment is performed. Allergen-specific immunotherapy (AIT) is one of the most important treatment options for IgE-mediated allergies and is based on immunological effects on the diseased patient. This manuscript outlines the EAACI recommendations regarding AIT during the COVID-19 pandemic and aims at supporting allergists and all physicians performing AIT in their current daily practice with clear recommendations on how to perform treatment during the pandemic and in SARS-CoV-2 infected patients.

1.1 | Coronavirus disease 2019 (COVID-19)

On March 11, 2020, the World Health Organization (WHO) declared a pandemic of an infectious disease recently referred to as "coronavirus disease 2019" (COVID-19). Currently, COVID-19 is spreading rapidly across the globe. COVID-19 is caused by a novel strain of human coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named by the International Committee on Taxonomy of Viruses (ICTV). SARS-CoV-2 was first detected in a cluster of patients with pneumonia in December 2019 in Wuhan, China.[1,2] SARS-CoV-2 is a Betacoronavirus of the subgenus Sarbecovirus and the subfamily Orthocoronavirinae. It can be isolated from human samples obtained from respiratory secretions, nasal and pharyngeal smears and isolated on cell cultures.[1,2] SARS-CoV-2 is the 7th member of the coronavirus family able to infect humans. It differs from the Middle East respiratory syndrome coronavirus (MERS-CoV), the severe acute respiratory syndrome coronavirus (SARS-CoV), and viruses responsible for the common cold (229E, OC43, NL63, and HKU1).[3] Coronaviruses are zoonotic: they can be transmitted between animals and humans.

COVID-19 presents with many different clinical manifestations, ranging from asymptomatic cases to mild and severe disease, with or without pneumonia.[4]

Common signs of COVID-19 are respiratory problems, fever, cough, shortness of breath, and difficulties in breathing. Other signs of viral airway infection may include nasal symptoms and sore throat. In more severe cases, infection with COVID-19 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death.[4-8] In the published scientific literature on COVID-19, higher age, chronic respiratory diseases, diabetes mellitus, coronary artery disease, and immunodeficiency of different origins are listed as risk factors for severe illness, hospitalization, and death.[4-6,8]

As COVID-19 is caused by a newly identified viral strain, there are no therapeutics proved to be effective in clinical trials or vaccines, so far, and there is presumed to be no pre-existing immunity in the population.[9] In most instances, coronaviruses are believed to be transmitted through large respiratory droplets from person to person, through inhalation or deposition on mucosal surfaces. Other routes implicated in the transmission of coronaviruses include contact with contaminated fomites and inhalation of aerosols produced during aerosol-generating procedures, such as sneezing or coughing. The SARS-CoV-2 virus has been detected in respiratory, fecal, and blood specimens.[10] The highest risk of healthcare-associated transmission occurs in the absence of standard precautions, when primary infection prevention and control measures for respiratory infections are not in place, and when handling patients whose COVID-19 diagnosis is yet to be confirmed. Since airborne transmission is possible, we recommend a cautious approach because of possible transmission through aerosols.[11,12]

More disease background information is available online from the European Centre for Disease Prevention and Control (ECDC),[13] WHO,[14] and the ECDC's Rapid Risk Assessment.[9]

1.2 | Allergen-specific immunotherapy (AIT)

AIT is the only disease-modifying therapy that confers a long-term clinical benefit for allergic airway diseases such as in allergic bronchial asthma or allergic rhinoconjunctivitis and other allergic conditions.[15] Since its[16]emergence over one hundred years ago (1911), AIT is an established and internationally recognized procedure for the causal treatment of immediate-type allergic reactions (type I allergy) and associated diseases.

AIT induces an immune tolerance responses against the allergen in sensitized patients.[17]

Systematic reviews and meta-analyses have confirmed that AIT is effective in reducing symptoms together with rescue medication in patients with allergic asthma [18] and allergic rhinoconjunctivitis.[19]

This applies to both subcutaneous immunotherapy (SCIT)[20,21] and sublingual immunotherapy (SLIT), liquid drops or tablets placed under the tongue.[22]

The reduced risk of developing asthma in patients with allergic rhinitis is another advantage of AIT. This is still under debate but was demonstrated to be effective at least in the short term.[23,24] AIT is also effective in patients with IgE-mediated food allergy [23-26] and insect venom allergy.[27] Moreover, analyses by the European Academy of Allergy and Clinical Immunology (EAACI) demonstrated the cost-effectiveness of this disease-modifying therapy option.[28-30]

1.3 | AIT and viral infections

Even though it is well established that allergic airway diseases are associated with an increased risk of infection, little is known about the potential influence of viral infections on AIT.[31]

In a prospective and comparative clinical study, Ahmetaji et al. found no significant difference in the efficacy or in the improvement of symptoms of allergic asthma patients under subcutaneous allergen-specific immunotherapy with or without symptomatic influenza, nor in the standard chemical and hematology parameters and different cytokines during a one-year follow-up.[32] These preliminary data suggest that SCIT in influenza-infected patients is safe and well-tolerated.

Lemoli et al. evaluated the safety and clinical effectiveness of sublingual grass tablet immunotherapy in a group of HIV-positive patients with allergic rhinitis under antiretroviral HIV therapy. HIV infection has been regarded to be a relative contraindication for AIT. Highly active antiretroviral treatment has improved the immune function and life expectancy in HIV-infected patients whose respiratory allergic incidence is similar to that of the general population.[33] Clinical efficacy data showed a significant improvement in SLIT-treated patients compared to controls but no considerable alteration of peripheral T CD4 lymphocyte cell counts and HIV viral load in either group. These data show that SLIT therapy in viro-immunological controlled HIV-positive patients is efficacious, safe, and well-tolerated.

Cytomegalovirus (CMV) was shown to enhance the allergenic potential of otherwise poorly allergenic environmental protein antigens in a mouse model of airway co-exposure to CMV and ovalbumin (OVA).[34] In contrast, immune reactions to virus-like-particles (Vlp) may enforce the immune responses in AIT and may even be used as AIT adjuvants for inhalational and food (peanut) allergen in the near future.[35,36]

With the limited experimental data available so far, it seems that patients with allergic rhinitis did not develop additional distinct symptoms and more severe courses than other patients.[4] Allergic children showed a mild course, similar to other children.[4]

2 | IMMUNE MECHANISMS IN AIT AND COVID-19—DIFFERENCES AND SIMILARITIES

AIT aims to induce allergen-specific immune tolerance in allergy patients by using multiple mechanisms including T cells, B cells, innately lymphoid cells (ILC), and effector cells, such as eosinophils, mast cells, and basophils. One of the main changes is the development of a T and B regulatory cell response and their suppressive cytokines such as IL-10 and TGF-β and surface molecules such as CTLA-4 and PD1, all of which form a suppressive milieu.[29,37] This immune regulatory response is taking place in targeted antigen-/allergen-specific T and B cells but does not affect the whole immune system and does not cause any systemic immune deficiency. T-cell responses in severe COVID-19 are represented with lymphopenia that is mainly affecting memory T lymphocytes. Both CD4 and CD8 T cells decrease; however, this change is more pronounced in CD8 + T cells. Cytotoxic T lymphocytes and NK cells in patients infected with SARS-CoV-2 are essential for an appropriate anti-viral response.[38] A recent study suggests that patients show functional exhaustion of cytotoxic T lymphocytes associated with SARS-CoV-2 infection. The total number of NK and CD8 + T cells was markedly decreased in patients with SARS-CoV-2 infection.[38] This may cause a disruption of anti-viral immunity and may play a role in the pathogenesis and severity of COVID-19.

AIT significantly decreases allergen-specific Th2 cells in circulation and reduces the general type2 response by decreasing Th2 cells and type 2 ILCs.[39-41] COVID-19 does not significantly increase in severity in allergic patients, with conditions such as rhinitis, urticaria, and atopic dermatitis.[4,42] It has not been demonstrated if there is a switch between TH1 and TH2 cells in COVID-19, but there are developing data that disease severity is linked to a systemic Th1 response and inflammasome activation together with a cytokine storm. Similar to SARS and MERS, a cytokine storm is a common feature of severe COVID-19 cases and a major reason for acute respiratory distress syndrome (ARDS) and multi organ failure. Several levels of evidence suggest that the rapid COVID-19 mortality might be due to a virus-activated "cytokine storm syndrome".[43] In a study of 41 hospitalized severe COVID-19 patients, high levels of proinflammatory cytokines were observed including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα.[44]

AIT changes the cellular composition and inflammatory mediators in the affected organs, for example in the nose in allergic rhinitis.[17] Eosinophils and their inflammatory mediators decrease in allergic rhinitis in the nose during AIT. In COVID-19, systemic eosinopenia was observed in 52.9% of the patients. Decreased blood eosinophil counts correlate positively with lymphocyte counts in severe ($r = 0.486$, $P < .001$) and nonsevere ($r = 0.469$, $P < .001$) patients after hospital admission.[4] The reasons and mechanisms of systemic eosinopenia remain to be investigated.

In AIT, reduced eosinophil counts and regulation of specific TH2 response is only seen after several years of continuous therapy. This supports that AIT is not going to interfere with viral infections. AIT has a clear desensitization effect on effector cells. This effect is antigen specific and acts early during the course of AIT. Mast cells are not considered to be relevant in viral infection response.

Allergen-specific antibody levels change in the course of AIT with decreased specific IgE in the long run and a relatively rapid increase in specific IgG1 and IgG4.[29,45] In COVID-19, like many viral infections, SARS-CoV-2-specific IgM increases in the acute phase followed by specific IgG.[46-48]

Overall, the COVID-19 immunological mechanisms seem to be similar to SARS and MERS and also to severe influenza infections. An appropriate anti-viral immune response should develop with cytotoxic T cells and IgM and IgG antibodies, whereas a very strong uncontrolled immune response as in a cytokine storm becomes detrimental (Table 1).

3 | PREVENTING ALLERGY FACILITIES AND CONTROL MEASURES IN AIT

We recommend using the infection prevention and control measures in any patient undergoing AIT according to ECDC and WHO. This implies that the recommended infection prevention and control measures of

TABLE 1 Immunological characteristics of AIT and COVID-19

Immunological changes	AIT	COVID-19
T-cell responses	Suppression of TH2 cells, induction of Treg and TH1 cells	Lymphopenia in severe cases
CD8 + T cells	There is no major change	Severe lymphopenia is observed in CD8 + T cells
TH1-TH2 responses	AIT decreases allergen-specific Th2 responses in circulation and in the affected organs such as in the nose	Severe disease shows a systemic severe inflammatory response with a cytokine storm
Eosinophils	Decrease in their numbers and mediators in the nose	Systemic decrease in their numbers in more than half of the patients.
Specific antibody levels	Allergen-specific IgE decreases in the late course, with an early increase in specific IgG4	In the acute phase, virus-specific IgM increases followed by virus-specific IgG during convalescence.

individual regions or countries should be followed, including those this document, as well as the procedures for reporting and for the transfer of persons under investigation and of probable/confirmed COVID-19 cases.

Those feeling ill with typical respiratory symptoms should be encouraged to contact healthcare services by telephone or E-Health/telemedicine/online to seek medical advice [13,49](triage). This will reduce the number of people with symptoms of COVID-19 that have contact with the Allergy center healthcare personnel.[13,49]

Allergy services and primary care staff, including physicians, nursing, and administrative staff with patient contact, should be aware of the following: (a) the current COVID-19 epidemiologic situation in their country and globally; (b) known risk factors for infections; (c) clinical symptoms and signs of COVID-19; (d) recommended infection prevention and control measures in their region or country, including those in this document; and (e) procedures for reporting and for the transfer of persons under investigation and of probable/confirmed cases.

Appropriate personal protective equipment (PPE) should be available onsite for all personnel at the point-of-care to provide standard, contact, and droplet protection.

In each Allergy facility, a dedicated member of staff (e.g., head doctor/nurse) should lead the COVID-19 preparedness and implement relevant infrastructure and control measure policies.

Signs should be posted at all entrance doors listing the main symptoms compatible with COVID-19 (fever, cough, and shortness of breath) and informing visitors with any of these symptoms not to enter the Allergy Unit. Everyone within the Allergy clinic and all those entering the practice should adopt appropriate hand hygiene measures, using soap and water, or an alcohol-based handrub.

Based on a case-by-case risk assessment, the use of PPE for AIT should be considered. With the current knowledge on the transmission of COVID-19, in which respiratory droplets seem to play a significant role (although airborne transmission cannot be ruled out at this stage), and taking into consideration the possible shortage of PPE in healthcare settings due to the increasing number of COVID-19 patients, the suggested set of PPE for droplet, contact, and airborne transmission (gloves, goggles, gown, and FFP2/FFP3 respirator) can be adapted for the clinical assessment of suspected COVID-19 cases. If available, a surgical mask should be provided for patients with respiratory symptoms (e.g., cough).[50]

Healthcare workers performing aerosol-generating procedures (AGP), such as swabbing,[50] should wear the suggested PPE set for the prevention of droplet, contact, and airborne transmission (gloves, goggles, gown, and FFP2/FFP3 respirator).[51]

To maximize the use of PPE if there is an insufficient supply, staff should be assigned to carry out procedures, or a procedure, in designated areas.[52]

4 | MANAGING AIT DURING THE COVID-19 PANDEMIC

AIT is a treatment that requires recurrent doctor/nurse/patient contact over a more extended period, for example, 3 years.

In SCIT, injections are administered with daily, weekly (up dosing phase), or monthly (continuation phase) intervals.

In SLIT, the initiation is given in allergy clinics or in a doctor´s office, while continuation is performed by patients themselves with regular control visits.

Each SCIT or SLIT product needs approval by the competent authority. It must contain information on how to use the AIT product for patients, allergologists, and nurses. For most products authorized in Europe, instructions for use recommend that patients experiencing an acute respiratory tract infection should temporarily discontinue AIT treatment until the infection is resolved. We recommend taking similar action in COVID-19. Confirmed cases should discontinue AIT, both SCIT and SLIT, independent of disease severity, until the symptoms have completely resolved and/or an adequate quarantine has been performed. The possibility of expanding injection intervals in the continuation phase may be beneficial. In patients having recovered from COVID-19 or who are found to have a sufficient SARS-CoV-2 antibody response after (asymptomatic) disease,[14] AIT can be started or continued as planned.

AIT can also be started or continued as usual in patients without clinical symptoms and signs of COVID-19 or other infections and without a history of exposure to SARS-CoV-2 or contact to COVID-19 confirmed individuals within the past 14 days.

SLIT offers the possibility of administration at home, thus avoiding the need to travel to or stay in an allergy clinic or doctor's office, which would be associated with a risk of infection.

5 | RECOMMENDATIONS IN NONINFECTED INDIVIDUALS DURING COVID-19 PANDEMICS OR RECOVERED PATIENTS AFTER COVID-19 INFECTION

Interrupting subcutaneous immunotherapy is not advised. **Especially in potentially life-threatening allergies, such as venom allergy, SCIT should be continued regularly. The possibility of expanding injection intervals in the continuation phase should be checked and may be beneficial.**

Interrupting sublingual immunotherapy is not advised. Supply the patient with sufficient medication for a minimum of a 14-day quarantine.

Sublingual immunotherapy can be taken at home. The intake of SLIT by the patient at home or any place is advantageous in avoiding contact to potentially infected persons.

Both subcutaneous and sublingual immunotherapy can be continued in the current COVID-19 pandemic, in any asymptomatic patient without suspicion of SARS-CoV-2 infection and/or contact with SARS-CoV-2 positive individuals, in any patient with a negative test result (RT-PCR) or in any patient after an adequate quarantine or with detection of serum IgG to SARS-CoV-2 without virus-specific IgM.

Preparedness of your Allergy clinic is imperative when coping with COVID-19. Follow WHO guidelines and advise staff accordingly.

These recommendations are conditional since there is a paucity of data and they should be revised regularly with incoming new information on COVID-19.

6 | RECOMMENDATIONS IN COVID-19 DIAGNOSED CASES OR SUSPECTED FOR SARS-COV-2 INFECTION

Interrupting subcutaneous immunotherapy is advised.

Interrupting sublingual immunotherapy is advised.

Both subcutaneous and sublingual immunotherapy should be discontinued in symptomatic patients with exposure to or contact with SARS-CoV-2-positive individuals, or patients with positive test results (RT-PCR).

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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APPENDIX 1

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