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Perspective

Coronavirus disease 2019 and allergen immunotherapy

Theoretical benefits invite to adjustments in practice recommendations

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Introduction

During the coronarvirus disease 2019 (COVID-19) pandemic that the world is currently facing, many professional groups have made specialty-specific recommendations. Thus, several workgroups[1-3] have published suggestions on how to manage allergen immunotherapy (AIT), which are timely and adequate for the present situation. However, none of these recommendations review the immune effects of AIT in light of the immunologic changes caused by COVID-19 and more specifically severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Taking a closer look at what is currently known in this field, one could conclude there might be a theoretical advantage for patients with allergy to receive sublingual or subcutaneous AIT. With this in mind, several suggestions made by AIT workgroups could be formulated differently.

In this perspective article, we take a brief look at what is currently known about immunologic responses to COVID-19; then we review the findings on immunologic changes caused by AIT and discuss their possible benefit or disadvantage for patients receiving AIT. Finally, we propose alternative approaches to 3 practical suggestions on adjustments in AIT administration made by the previously mentioned workgroups.

Severe Acute Respiratory Syndrome Coronavirus 2 and the Immune Response

The body's response to the COVID-19 infection characterizes itself by a timing imbalance.[4] In the first phase, immune suppression by the virus occurs, especially of the innate immune system, whereas during the second phase, in the critically ill patient, overstimulation occurs.

First Phase

All previous coronaviruses indicate mechanisms to evade the initial response of the innate immune system. Their proteins interfere with the production and downstream effect of interferon (IFN), especially types I and III.[5] Consequently, chemokine production and influx of innate immune cells (monocytes, neutrophils, and natural killer cells) are reduced. Blood samples have been taken to study the initial immune response after a moderate infection with SARS-CoV-2, confirming the ablated response of monocytes and natural killer cells.[6]

Advanced Phase

In the second phase, Some patients develop an overactivation of their immune system, presenting with a high level of interleukin (IL) 6, probably produced by the innate immune cells (especially macrophages), leading to the frequently lethal cytokine storm.[7]

Immune Changes Caused by Allergen Immunotherapy

Highly expert groups in the immune changes secondary to AIT have taught us that immune effects can be documented from the first week of AIT onward.[8,9] After low-grade natural allergen exposure, dendritic cells (DCs) from individuals with allergy, in the absence of interferon gamma, drive immature T_H0 lymphocytes toward T_H2 and T_H2A cells. However, after exposure to allergen in high doses, as in AIT, innate immune cells (DCs and group 2 innate lymphoid cells) change their production of cytokines from type 2 (IL-5 and IL-13) to IL-2, IL-12, and IL-27. These changes shift immature T_H0 cells to T_H1 or regulatory B and T cells.

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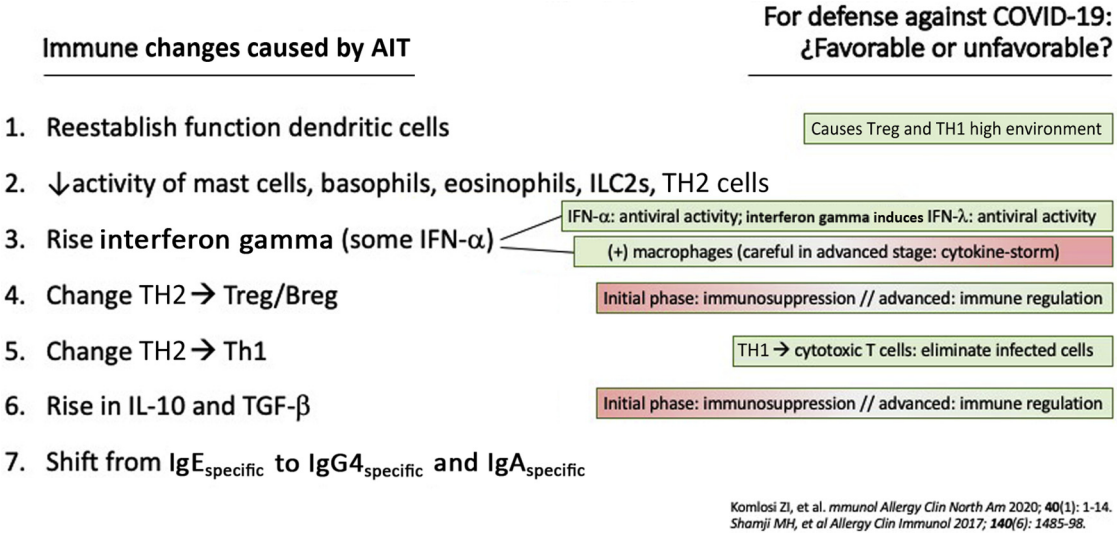

Figure 1. Immune changes secondary to AIT and their interaction with COVID-19, which are at some points binominal. AIT reestablishes the function of DCs, enhancing their production of interferon. In addition, instead of producing type 2 cytokines, DCs start releasing type 1 cytokines, thus favoring the development of T_H1 cells and regulatory T cells. This process favors patients who are facing viral infections because T_H1 cells drive the activation of cytotoxic T cells, which are important for the adaptive elimination of the virus. In COVID-19, regulatory T cells and cytokines (IL-10 and tumor growth factor beta) could reduce the cytokine storm, although in the beginning of an infection their inhibitory action might not be beneficial. The first line of defense against viruses is interferon (eg, type I [α and β] and type III [$\gamma\lambda$]). AIT induces interferon production, mainly interferon gamma; however, interferon alfa is also produced by DCs after AIT. This production is beneficial at first contact with the virus; however, even though interferon gamma stimulates macrophages, this may not be advantageous in critically ill patients. AIT, allergen immunotherapy; COVID-19, coronavirus disease 2019; DC, dendritic cells; ILC2s, group 2 innate lymphoid cells; T_H1, T helper type 1 cells. (Reproduced from Shamji MH and Durham SR. *J Allergy Clin Immunol.* 2017;140(6):1485-1498; and Komlósi ZI et al. *Immunol Allergy Clin North Am.* 2020;40(1):1-14.)

The regulatory T and B cells are among the first regulatory cells that can be detected, secreting IL-10 and tumor growth factor beta. These cytokines have an immune-regulating function, decreasing the activity of mast cells, skin eosinophils, and group 2 innate lymphoid cells, resulting in a reduction in the late-phase skin reaction after a month. They also produce the class switch in B cells from specific immunoglobulin (Ig) E to IgG_4 and IgA.[8] DC function is restored, enhancing interferon gamma production. Weeks later, T_H1 cells become active, producing interferon gamma and enhancing the cellular immune response by stimulating cytotoxic T cells. The most recently documented effects are still much broader, involving a marked reduction in T_H2A cells and an increase in T and B memory cells, follicular helper cells, and other cytokines, such as IL-35. Some manufacturers provide AIT with adjuvants, which further reinforces some of these mechanisms, especially the shift toward T_H1.

Allergen Immunotherapy and Severe Acute Respiratory Syndrome Coronavirus 2

Currently, no immunologic or clinical evidence is available on how AIT and SARS-CoV-2 interact. Their interaction is not straightforward (Fig 1). Stimulating the production of interferon alpha, the shift toward T_H1 and improving immune regulation could possibly be beneficial, but all depends on the timing of the interaction and on the presence of other costimulating molecules.[10] However, in general, real-life evidence indicates that allergy augments and AIT reduces the frequency of respiratory tract infections.[11] The first cause of frequent respiratory infections in childhood is respiratory allergy. Thus, improving the control of allergic diseases should be beneficial during a pandemic. In addition, AIT adjuvants could be of value at the moment of first contact with a virus, enhancing the innate immune response by trained immunity.[12]

A Slightly Different Angle on Allergen Immunotherapy–Related Practical Issues

The following suggestions should always be weighed in light of the local situation in the clinic or hospital where AIT is administered because the risk of SARS-CoV-2 transmission varies widely among places and will vary in time in the months to come.

To Space or Not to Space AIT Administrations

AIT might provide a possible advantage to patients during the COVID-19 pandemic. Thus, we argue that the prime focus should be on continuing AIT paying special attention to efficacy and safety, interpreting safety as the maximum effort to reduce the risk of transmission. However, if we follow the suggestion of spacing AIT administrations as much as safety (ie, no adverse events secondary to AIT) allows, we are giving up on efficacy because efficacy is linked to the monthly dosage.[13] We argue in favor of starting AIT, preferably sublingual immunotherapy, or, in clinics where social distancing can be practiced, subcutaneous immunotherapy can be an option.

Maximum Reduction of Transmission Risk

The workgroups have given several suggestions. We would like to add some that were not present in all documents.

- Strict hand sanitizing as soon as patients come into the office.
- Obligatory face masks.
- Separate AIT administration time from patient-consulting time.
- Start early, when there is little movement on the streets and in the clinics.
- Prescreening before coming to the clinic for suspicious symptoms during the past 2 weeks.
- If positive, online physician interview.
- Preshot screening: peak flow yes, but at home.

- 30-minute wait time in the car after shot.
- Consider allowable for low-risk patients with controlled allergies.

Conclusion

It will probably still take several months at least until SARS-CoV-2 is over, and many individuals will likely get infected. We must enhance as best as possible our own and our patients' innate immunity to prevent the virus from advancing. AIT might play a role in such preventive measures.

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