



Position statement of the Brazilian Association of Allergy and Immunology on the management of allergen-specific immunotherapy (AIT) in patients vaccinated against COVID-19

Posicionamento da Associação Brasileira de Alergia e Imunologia sobre o manejo da imunoterapia específica com alérgenos (ITA) em pacientes vacinados contra COVID-19

Fernando Monteiro Aarestrup¹, Anna Caroline Nóbrega Machado Arruda¹, Clóvis Eduardo Santos Galvão¹, Gil Bardini Alves¹, Geórgia Véras de Araújo Gueiros Lira¹, Ernesto Akio Taketomi¹, Marcos Reis Gonçalves¹, Mariana Graça Couto Miziara¹, Sidney Soutaban Maranhão Casado¹, Simone Valladão Curi¹, Veridiana Aun Rufino Pereira¹, Elaine Gagete¹

ABSTRACT

The COVID-19 pandemic represents a serious challenge for all medical specialties. Allergen-specific immunotherapy (AIT) is considered the only therapeutic procedure capable of modifying the natural history of allergic diseases and characterizes the state of the art in the field of allergy and immunology. This therapeutic strategy of immunomodulation is able to promote remission and control of allergic diseases for prolonged periods, even after cessation. There are few data regarding use of AIT in patients vaccinated against COVID-19 and, to date, there is no official position statement published by international allergy and clinical immunology societies. This document aims to establish practical recommendations for the management of AIT in patients who have received the COVID-19 vaccine. The immunological mechanisms involved in immunoprophylaxis with vaccines and the mechanism of action of AIT have been compared to provide a solid basis for establishing precise recommendations.

Keywords: Allergen immunotherapy, immunologic desensitization, COVID-19.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the existence of a pandemic caused by SARS-CoV-2, a new type of human coronavirus. Since then, health professionals and scientists have

RESUMO

A pandemia de COVID-19 representa um grande desafio para todas as especialidades médicas. A imunoterapia com alérgenos (ITA) é considerada o único procedimento terapêutico capaz de modificar a história natural das doenças alérgicas, e caracteriza o estado da arte na área de Alergia e Imunologia. Esta estratégia terapêutica de imunomodulação é capaz de promover a remissão e controle das doenças alérgicas por períodos prolongados, mesmo após o seu término. Existem poucos dados em relação ao emprego da ITA em pacientes vacinados contra COVID-19, e até o momento não há um posicionamento oficial das sociedades internacionais da área de Alergia e Imunologia Clínica. Este documento tem como objetivo estabelecer recomendações práticas para o manejo da ITA em pacientes que receberam a vacina contra COVID-19. Os fenômenos imunológicos envolvidos na imunoprofilaxia vacinal e no mecanismo de ação da ITA foram comparados, proporcionando o estabelecimento de recomendações precisas.

Descritores: Imunoterapia com alérgenos, dessensibilização imunológica, COVID-19.

been searching for ways to control the spread of this new disease, called COVID-19, through the development of new drugs and immunoprophylactic vaccin strategies.¹⁻³

1. Scientific Department of Immunotherapy - Brazilian Association of Allergy and Immunology - ASBAI.

According to the WHO, the current epidemiological data on the disease are alarming, with more than 100 million confirmed cases and approximately two million deaths worldwide. To date, there are no effective specific therapies to combat SARS-CoV-2 infection. Fortunately, for the first time in the history of medicine, therapeutic vaccine strategies against a disease were developed in less than a year, allowing the beginning of immunization.⁴⁻⁵

This document aims to establish practical recommendations on how to proceed with the management of allergen-specific immunotherapy (AIT) in patients vaccinated against COVID-19.

Vaccines against COVID-19

Several methodologies⁴⁻⁵ have been used to develop immunizers against COVID-19. The following information briefly describes the different types of technological platforms used.

Viral inactivation

This classical technology consists of viral replication in cell culture and subsequent virus inactivation by chemical or physical agents. Adjuvants can be added to these vaccines to increase immunogenicity. Examples of specific immunoprophylactic vaccines based on inactivated viruses are the vaccines against influenza (caused by the influenza virus), hepatitis A, and poliomyelitis.

Non-replicating viral vectors

This new technology uses genetically modified viruses with total absence of pathogenic potential. In the corresponding vaccine against COVID-19, for example, the viruses only carry the gene that encodes the spike protein (protein S) of SARS-CoV-2. Therefore, only protein S can be produced, and works as a vaccine vector in the human cell. From that moment on, the immune system begins to develop a specific response against SARS-CoV-2.

Vaccines based on messenger RNA (mRNA)

This innovative production platform has been studied for a long time, but it is the first time it is being used in medical practice. In this case, it consists of the administration of synthetic mRNA encoding the SARS-CoV-2 S protein, triggering the production of this protein by human cells. This mRNA molecule

contains exclusively specific genetic information and has no potential to modify the human genome or cause COVID-19. The process takes place exclusively in the cytoplasm, and there is no interaction between the viral mRNA and the DNA of the human cell at any time. This platform for the development of mRNA-based vaccines enables immunizer production on a large scale and in a short period of time, besides allowing future changes in case of viral mutations that generate new SARS-CoV-2 variants.

Table 1 shows the general characteristics of the main vaccines being used worldwide.

Fundamentals of the immunological mechanism of immunoprophylactic vaccines and AIT

The development of vaccines with the purpose of stimulating protective responses against infectious agents revolutionized the history of mankind. The basic mechanism of the vaccines relies mainly in the development of antigen-specific immunological memory. Both the cellular immune response mediated by T cells and the humoral immune response coordinated by B cells participate in this process. Vaccine development strategies using inactivated or attenuated whole microorganisms, specific infectious agent molecules, and more recently, those incorporating mRNA technologies, represent the most important measure to prevent infectious diseases in terms of public health.^{4,5}

The different COVID-19 vaccine production platforms induce a cellular immune response with the development of specific T cell clones capable of recognizing SARS-CoV-2, developing an effector response via cytokine production, whose main objective is to prevent viral replication. The vaccine stimulus also acts by promoting the clonal proliferation of specific B cells, leading to IgG production; SARS-CoV-2. Inactivated virus vaccines stimulate the immune system concomitantly through several molecules. In contrast, new technologies and vaccine production using viral vectors induce the immune response via the virus S protein. Although there are different technological platforms, the basic mechanism of the protective immune response is the same, regardless of the type of vaccine administered.^{4,5,7}

Fundamentally, immunoprophylaxis is characterized by immunological memory that provides rapid and effective responses to specific antigens. Several

mechanisms of antigenic recognition and effector immune responses are used to inhibit the proliferation of infectious agents.

AIT has been used for over a century as a therapeutic strategy to modify the specific immune response to certain allergens. Currently, much is known about the cells and cytokines involved in the mechanism of action of AIT, which is based on immunomodulation, inducing specific peripheral immune tolerance. Several cell types participate in this process, involving both innate and adaptive immune responses. Innate lymphoid cells (ILCs), T cells, and B cells coordinate this process by a cytokine network that orchestrates the response through effector cells such as mast cells, eosinophils, and basophils. The main participants in the mechanism of AIT immunomodulation are regulatory T cells (Treg), regulatory B cells (Breg), and immunosuppressive

cytokines, such as transformed cell growth factor beta (TGF- β) and interleukin 10 (IL-10). AIT immunomodulation acts on type 2 inflammatory response by reducing allergen-specific CD4+ TH2 cells in the circulation, as well as decreasing the activity of type 2 innate lymphoid cells (ILC-2). Treg and Breg cells induce peripheral tolerance to allergens, mainly through the synthesis of TGF- β and IL-10. Additionally, AIT modifies the Th2 to Th1 cytokine production profile. Thus, there is a decreased production of IL-4, IL-5, and IL-13 in response to the presence of specific allergens, reducing the type 2 inflammatory response that classically occurs in atopic patients. As a result of this immunomodulation process, AIT decreases IgE production and increases the production of allergen-specific IgG4. All these immunological phenomena characterize desensitization, increasing allergen tolerance.^{6-8,12-15}

Table 1

Main types of immunizers used against COVID-19

Vaccine	Manufacturer	Technology/Platform	Administration
CoronaVac	Sinovac Research and Development Co., Ltd ⁵	Inactivated virus	1st dose: day 0 2nd dose: 28 days after
AD26. COV2.S	Janssen Pharmaceutical	Viral vector (non-replicating)	Single dose or 1st dose: day 0 2nd dose: 56 days after
Covaxin	Bharat Biotech International Limited	Inactivated virus	1st dose: day 0 2nd dose: 14 days after
Covishield	AstraZeneca + University of Oxford ⁵	Viral vector (non-replicating)	1st dose: day 0 2nd dose: 3 months after
Sputnik V	Russian Research Institute of Epidemiology and Microbiology, Gamaleya ^{4,5}	Viral vector (non-replicating)	1st dose: day 0 2nd dose: 21 days after
BNT1 62	Pfizer/BioNTech + Fosun Pharma ^{4,5}	Messenger RNA (mRNA)	1st dose: day 0 2nd dose: 21 days after
mRNA-1273	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Messenger RNA (mRNA)	1st dose: day 0 2nd dose: 28 days after

In conclusion, AIT is an allergen-specific response immunomodulation strategy, not presenting direct similarities with the vaccine immunoprophylaxis used in the prevention of infectious diseases.

COVID-19 immunization and AIT administration

The American Academy of Allergy, Asthma, and Immunology (AAAAI), the European Academy of Allergy, Asthma, and Clinical Immunology (EAACI), and the Brazilian Association of Allergy and Immunology (ASBAI) recommend not interrupting AIT during the COVID-19 pandemic, enabling adequate control of respiratory allergic diseases, such as rhinitis and asthma. Therapeutic regimen adaptations and biosafety measures during the application have been suggested to reduce the possibility of SARS-CoV-2 transmission to patients using specific aeroallergen or hymenoptera venom AIT.⁶⁻¹²

The Brazilian National Health Surveillance Agency (ANVISA) recently approved the use of two immunizers against COVID-19 in the country, and has included them in the National Immunization Plan (PNI). This new scenario requires a position on AIT management in patients undergoing COVID-19 immunization. The continuous evaluation process of new immunizers by ANVISA will soon offer several types of vaccines to the Brazilian population.

Classically, government health agencies and medical societies that address the subject of vaccine immunoprophylaxis recommend a two-week interval between the doses of some vaccines.^{6,13} This recommendation relates to the possibility of two different immunizers administered within a short interval of time leading to reduced vaccine immune response. There are few data on the use of AIT in patients vaccinated against COVID-19 and, to date, there is no official position of international societies in the field of allergy and clinical immunology. It should be considered that the allergic desensitization that characterizes AIT is not intended to induce the response against a new antigen; the mechanism of action of AIT is based on the regulation of the existing allergen-specific immune response, inducing immunological tolerance. Conceptually, the administration of AIT, either subcutaneously (SCIT) or sublingually (SLIT), does not interfere in vaccine response induction, since their mechanisms of action are different from the mechanisms involved in infectious disease immunoprophylaxis (Table 2).^{6-8,12-15} However, further studies are needed to better evaluate this issue.

SCIT, although presenting high safety standards, may cause reactions at the site of administration and systemic adverse effects, such as runny nose and nasal itching, which may be confused with reaction symptoms caused by COVID-19 immunizers and

Table 2

Characteristics of the basic immunological mechanism of action of COVID-19 and AIT vaccines

Immunological mechanism	COVID-19 vaccine	AIT
Cellular immunity	Proliferation of antigen-specific T lymphocytes	Suppression of Th2 cells, induction of allergen-specific Tregs and Th1
Humoral immunity	Production of specific IgGs and proliferation of antigen-specific B lymphocytes	Decreased allergen-specific IgEs, increased specific IgG4, and Breg cell induction
Immune memory and tolerance	Development of antigen-specific immunological memory and protective immunity	Desensitization through specific allergen tolerance induction

with COVID-19 signs and symptoms. As with the administration of the immunizers, an interval of at least two weeks is recommended between SCIT and COVID-19 vaccine. This position is valid both for the use of specific AIT for aeroallergens and for Hymenoptera venom. As for SLIT, due to the small occurrence of adverse effects, it is recommended not to suspend or postpone the treatment because of the COVID-19 immunization.

Special situations

- In specific cases, applications of AIT subcutaneously (SCIT), may be performed with the interval of at least 48 hours before and after the application of the COVID-19 vaccine. This suggestion takes into consideration the risks of loss of control of the allergic disease due to the impairment of the desensitization process, however, the risks and benefits must be evaluated.
- In patients with a previous history of SLIT reactions, a 48-hour interval before and after the COVID-19 vaccine may be recommended. This suggestion takes into consideration the possibility, however infrequent, of the occurrence of adverse effects of SLIT, which may be confused with those of the application of the COVID-19 vaccines.

References

1. World Health Organization. WHO's COVID-19 response [Internet]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#>.
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. Available from: <https://covid19.who.int/>
3. Aarestrup FM. Imunopatologia da COVID-19 e suas implicações clínicas. *Arq Asma Alerg Imunol*. 2020;4(2):172-80.
4. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. *Front Immunol*. 2020;14,(11):585354.
5. Izda V, Jeffries MA, Sawalha AH. COVID-19: A review of therapeutic strategies and vaccine candidates. *Clin Immunol*. 2021;222:108634.
6. American Academy of Allergy, Asthma and Immunology [Internet]. [cited 2021 Feb 8]. Available from: <https://www.aaaai.org/ask-the-expert/scit>.
7. Klimek L, Jutel M, Akdis C, Bousquet J, Akdis M, Bachert C, et al. ARIA-MASK Study Group: Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement. *Allergy*. 2020;75(7):1546-54.
8. Dell'Edera A, Borghesan F, Favero E, Rattazzi M, Scarpa R, Tartaglia L, et al. Venom immunotherapy during COVID-19 pandemic: Experience from a University Allergy Center in Northern Italy. *World Allergy Organ J*. 2020;13(12):100489.
9. Compalati E, Erlewyn-Lajeunesse M, Runa Ali F, Ojeda Fernández P, Garcia Nuñez I, Frati F, et al. Allergen Immunotherapy in the Era of SARS-CoV-2. *J Investig Allergol Clin Immunol*. 2020;30(6):459-61.
10. Machado AS, Falcão ACAM, Serpa FS, Sano F, Rizzo JA, Elabras Filho J, et al. Recomendações da Associação Brasileira de Alergia e Imunologia para pacientes com Asma durante a COVID-19. *Arq Asma Alerg Imunol*. 2020;4(1):133-4.
11. Rosario Filho NA, Magalhães Rios JL, Morandi JLB, Tebyricá JN, Lira GVGA, Antila MA, et al. Imunoterapia específica em época de pandemia de COVID-19. *Arq Asma Alerg Imunol*. 2020;4(2):238.
12. Klimek L, Pfaar O, Worm M, Bergmann KC, Bieber T, Buhl R, et al. Allergen immunotherapy in the current COVID-19 pandemic: A position paper of AeDA, ARIA, EAACI, DGAKI and GPA: Position paper of the German ARIA Group in cooperation with the Austrian ARIA Group, the Swiss ARIA Group, German Society for Applied Allergology (AEDA), German Society for Allergology and Clinical Immunology (DGAKI), Society for Pediatric Allergology (GPA) in cooperation with AG Clinical Immunology, Allergology and Environmental Medicine of the DGHNO-KHC and the European Academy of Allergy and Clinical Immunology (EAACI). *Allergol Select*. 2020 May 28;4:44-52.
13. Sociedade Brasileira de Imunizações [Internet]. [cited 2021 Feb 8]. Available from: <https://sbim.org.br>.
14. Kleine-Tebbe J, Klimek L, Hamelmann E, Pfaar O, Taube C, Wagenmann, et al. Severe allergic reactions to the COVID-19 vaccine – statement and practical consequences. *Allergol Select*. 2021;5:26-8.
15. Taketomi EA, Miranda JS, Cunha-Júnior JC, Silva DAO. Allergen-specific immunotherapy follow-up by measuring allergen-specific IgG as an objective parameter. In: Metodiev K (ed.). *Immunotherapy*. Rijeka: InTech, 2017. p. 381-401. Available from: <http://dx.doi.org/10.5772/66711>.

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Corresponding author:
Fernando Monteiro Aarestrup
E-mail: fmaarestrup@hotmail.com