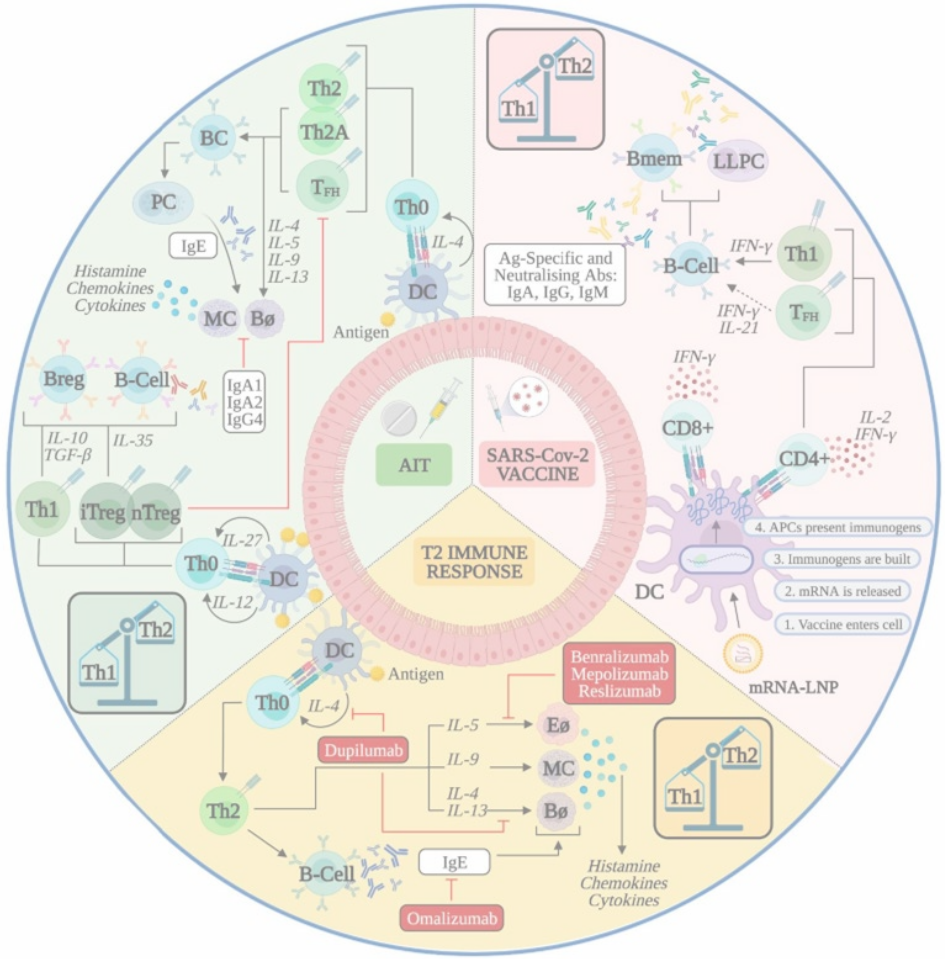
# ¿HAY INTERFERENCIA ENTRE LA INMUNOTERAPIA DE ALÉRGENOS (AIT) Y LAS INMUNIZACIONES?





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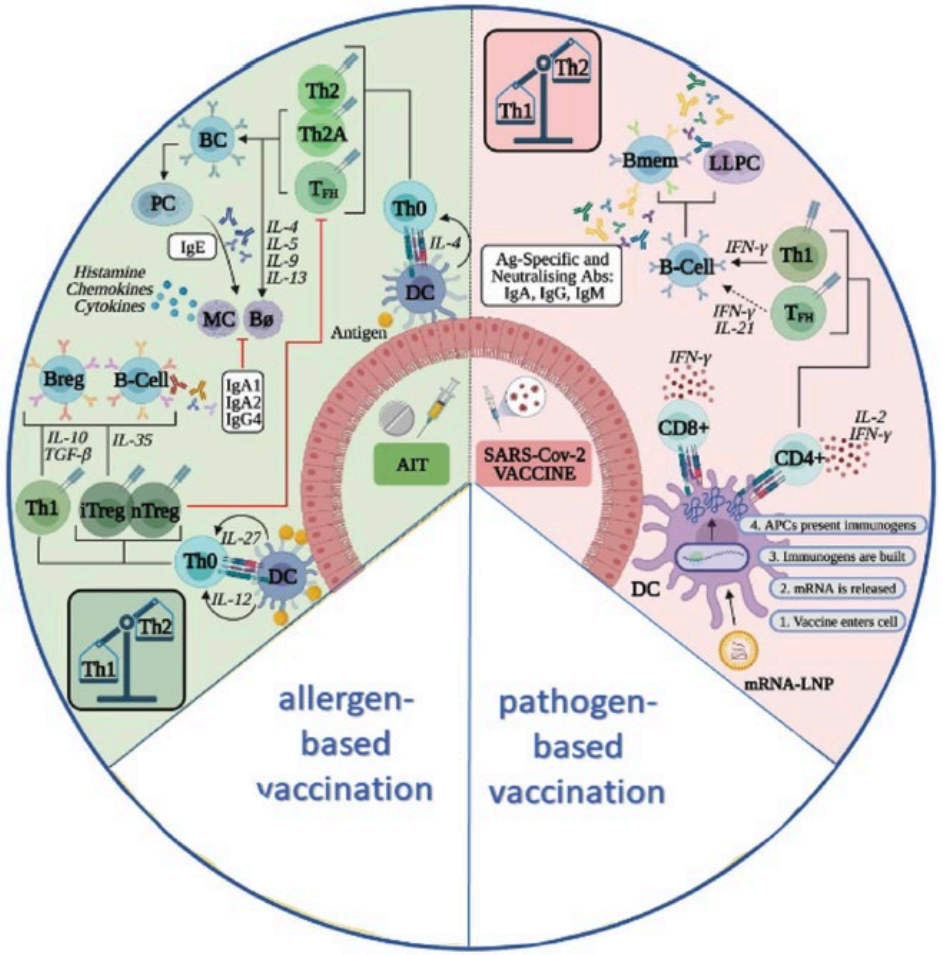
**Grupo de Investigación en Vacunas GENVIP**

# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

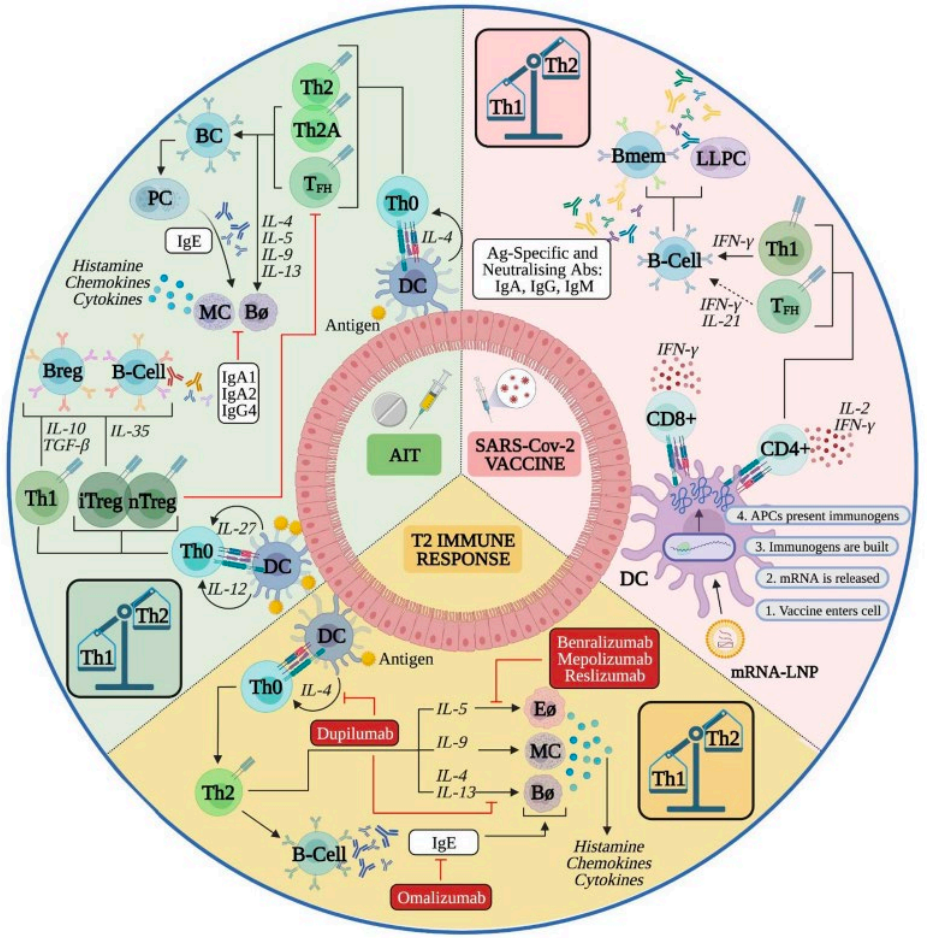



¿Existe algún tipo de interferencia entre la Inmunoterapia de Alérgenos (AIT) y las Inmunizaciones?


@gomez_rial5

# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

¿Existe algún tipo de interferencia entre la Inmunoterapia de Alérgenos (AIT), los tratamientos inmunomoduladores Th2, las Inmunizaciones?

# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

*Masieri et al. World Allergy Organization Journal* (2021) 14:100601
http://doi.org/10.1016/j.waojou.2021.100601

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

## Allergen Immunotherapy management during vaccinations: An international survey

Simonetta Masieri, MD[a], Claus Bachert, MD, PhD[b,c,d], Pedro Ojeda, MD, MPH[e], Chang-Keun Kim[f], Carlo Cavaliere[g] and Giorgio Ciprandi[h]*, the Study Group on AIT & Vaccinations[†]

### ABSTRACT

Vaccination against viral and bacterial pathogens represents a challenging issue in allergic subjects, mainly concerning patients undergoing allergen immunotherapy (AIT). For this reason, an international survey has been performed involving a panel of experts who responded to a series of questions, also concerning the COVID-19 impact on allergen immunotherapy and vaccinations. The results showed that co-administration of vaccines and AIT requires caution, mainly during the pandemic era. Moreover, the choice of AIT product should be oriented considering also the safety profile.

✓ 95% creen que no hay interferencias entre AIT y vacunas

| Question | Answers |
|---|---|
| Do you have experience of your patients being vaccinated for infectious diseases during AIT? | **Yes 95%** |
| How many patients did follow? | **Mean 206 (range 2 >3000)** |
| Do you believe, in your experience, that there could be a negative interference between vaccinations and AIT? | **No 95%** |
| Do you change the AIT schedules during concomitant vaccinations? | **No 58%** |
| Do you stop the AIT before vaccination and restart it later? | **No 77%** |
| If your patients haven't stopped AIT, even accidentally, have there been any issues? | **No 100%** |
| Did you observe adverse reactions to AIT during vaccinations? | **No 98%** |
| If yes, what adverse reactions to AIT did you observe? | **Usually local reactions, rarely systemic reactions, very rarely anaphylaxis (only one doctor)** |
| Did you observe adverse reactions to vaccinations during AIT? | **No 87%** |
| If yes, what adverse reactions to vaccinations did you observe? | **Mild local reaction alone** |
| When AIT patients have to be vaccinated, do you behave the same way with SLIT or SCIT? | **No 57%** |
| Do you consider vaccination for COVID-19 similar to that for other infectious diseases? | **Yes 70%** |
| Do you provide patients who have to be vaccinated for COVID-19 the same indications that you would give them for the other vaccinations? | **Yes 84%** |
| During this COVID-19 pandemic and under vaccination for this virus, do you prescribe products considering their safety profiles (no documented severe reactions, no anaphylaxis)? | **Yes 75%** |

**Table 1.** Questionnaire concerning the management of allergen immunotherapy (AIT) during vaccinations

@gomez_rial5

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- ✓ 95% creen que no hay interferencias entre AIT y vacunas
- ✓ 58% mantiene el calendario de AIT durante la vacunación
- ✓ 77% no detiene la AIT antes de la vacunación

| Question | Answers |
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- ✓ 95% creen que no hay interferencias entre AIT y vacunas
- ✓ 58% mantiene el calendario de AIT durante la vacunación
- ✓ 77% no detiene la AIT antes de la vacunación
- ✓ 98% no observa ningún tipo de reacción adversa a la AIT
- ✓ 87% no observa ningún tipo de reacción adversa a la vacuna

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- ✓ 57% se comporta de un modo diferente entre SLIT (sublingual) y SCIT (subcutánea)

| Question | Answers |
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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

ORIGINAL ARTICLES | Eur Ann Allergy Clin Immunol | Vol 47, N 1, 10-14, 2015

D. Ullrich[1], K. Ullrich[1], S. Mussler[2], S. Thum-Oltmer[2]

## Vaccination during concurrent subcutaneous immunotherapy: safety of simultaneous application

***Summary***

***Background.*** *During subcutaneous immunotherapy (SCIT), injections should be separated from vaccinations against infectious diseases by at least 1 week, because it is assumed that adverse reactions can result from the additional activation of the immune system.* ***Material and Methods.*** *Data of a total of 875 individuals receiving SCIT and/or vaccination in one ENT-practice were included and analyzed retrospectively. 444 individuals had received vaccination against infectious diseases, 336 allergic patients received only SCIT. Moreover, 79 allergic patients had received vaccination and SCIT injections simultaneously on one day in different locations, while 16 patients inadvertently received SCIT injections within up to 4 days after vaccination. Some of the patients were observed for consecutive years receiving several vaccinations parallel to SCIT. Systemic reactions (SRs) during SCIT were classified according to the WAO (World Allergy Organization) grading.* ***Results.*** *Patients exclusively receiving vaccinations did not report any drug-related SR. One SR third grade and two SRs second grade occurred in 3 asthmatic patients exclusively receiving SCIT. The patients simultaneously receiving vaccination and SCIT did not have any SR. This was also the case for the subjects consecutively receiving parallel SCIT and vaccination for up to 5 years.* ***Conclusion.*** *The international guidelines for allergen-specific immunotherapy (SIT) recommend an intermission of at least one week between SCIT and the administration of vaccines. However, these findings demonstrate the possibility to shorten or abolish this interval without increasing the risk of SRs.*

***Table 2*** *- Number of patients receiving SCIT and vaccination simultaneously (n = 95).*

| Number of patients receiving simultaneously | Vaccination with | | | | |
|---|---|---|---|---|---|
| SCIT with | Influenza | Pneumococcus | TBE | Hepatitis | Tetanus |
| mite | 25 | 3 | - | - | - |
| early blooming trees | 56 | - | - | 3 | 1 |
| grasses | 43 | 2 | 2 | - | - |
| cat | 2 | 1 | - | 1 | - |
| lepidoglyphus | 1 | - | - | - | - |
| wasp | 2 | - | - | - | - |
| bee | 1 | - | - | - | - |
| dog | 1 | - | - | - | - |

Patients receiving at least 2 SCIT preparations and 1 vaccine occur multiple. Patients receiving one SCIT preparation and at least 2 different vaccines occur multiple. Patients receiving 1 SCIT preparation and the same vaccine more than once occur once only. (TBE = tick borne encephalitis)

***Table 3*** *- Number of patients receiving "SCIT" or "SCIT and vaccination simultaneously" at least once between 2007 and 2012 with systemic reactions (SRs) according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (5).*

| | SCIT (n = 336) | SCIT + vaccination simultaneously (n = 95) |
|---|---|---|
| Patients with SR* grade 1 (n) | - | - |
| Patients with SR* grade 2 (n) | 2 | - |
| Patients with SR* grade 3 (n) | 1 | - |
| Patients with SR* grade 4 (n) | - | - |

***Table 4*** *- Number of adults and children receiving inadvertent vaccination and SCIT within a time frame of at maximum 4 days (n = 16). There were no systemic reactions in any patient.*

| | Adults | Children |
|---|---|---|
| Influenza | 4 | 6 |
| Tetanus / diphtheria | 1 | 1 |
| Pneumococcus | 1 | - |
| Measles / mumps / rubella | - | 3 |

- ✓ Recomendación de <u>espaciar 7 días AIT y vacunas</u>
- ✓ Se puede <u>acortar o eliminar este intervalo sin aumentar el riesgo de reacciones sistémicas</u>

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

Received: 4 April 2020 | Revised: 17 April 2020 | Accepted: 20 April 2020
DOI: 10.1111/all.14336

EAACI POSITION PAPER

Allergy WILEY

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

Ludger Klimek[1] | Marek Jutel[2] | Cezmi Akdis[3] | Jean Bousquet[4,5,6,7] | Mübeccel Akdis[3] | Claus Bachert[8] | Ioana Agache[9] | Ignacio Ansotegui[10] | Anna Bedbrook[7] | Sinthia Bosnic-Anticevich[11] | G. Walter Canonica[12,13] | Tomas Chivato[14] | Alvaro A. Cruz[15,16] | Wiencyslawa Czarlewski[17] | Stefano Del Giacco[18] | Hui Du[19] | Joao A. Fonseca[20,21,22,23] | Yadong Gao[24] | Tari Haahtela[25] | Karin Hoffmann-Sommergruber[26] | Juan-Carlos Ivancevich[27] | Nikolai Khaltaev[28] | Edward F. Knol[29] | Piotr Kuna[30] | Desiree Larenas-Linnemann[31] | Erik Melén[32] | Joaquim Mullol[33,34] | Robert Naclerio[35] | Ken Ohta[36] | Yoshitaka Okamoto[37] | Liam O'Mahony[38] | Gabrielle L. Onorato[7] | Nikos G. Papadopoulos[39] | Ruby Pawankar[40] | Oliver Pfaar[41] | Boleslaw Samolinski[42] | Jurgen Schwarze[43] | Sanna Toppila-Salmi[25] | Mohamed H. Shamji[44] | Maria Teresa Ventura[45] | Arunas Valiulis[46,47] | Arzu Yorgancioglu[48] | Paolo Matricardi[49] | Torsten Zuberbier[50,51] | the ARIA-MASK study group

## 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.

## 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).

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

Position paper

Allergologie select, Vol. 5/2021 (251-259)

## COVID-19 vaccination and allergen immunotherapy (AIT)


ISSN 2512-8957
DOI 10.5414/ALX02245E
e-pub: August 27, 2021

A position paper of the German Society for Applied Allergology (AeDA) and the German Society for Allergology and Clinical Immunology (DGAKI)

Ludger Klimek[1], Oliver Pfaar[2], Eckard Hamelmann[3], Jörg Kleine-Tebbe[4], Christian Taube[5], Martin Wagenmann[6], Thomas Werfel[7], Randolf Brehler[8], Natalija Novak[9], Norbert Mülleneisen[10], Sven Becker[11], and Margitta Worm[12]

**Abstract.** Background: Vaccinations against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) are intended to induce an immune response to protect against infection/disease. Allergen immunotherapy (AIT) is thought to induce a (different) immune response, e.g., to induce tolerance to allergens. In this position paper we clarify how to use AIT in temporal relation to COVID-19 vaccination. Four SARS-CoV-2 vaccines are currently approved in the EU, and their possible immunological interactions with AIT are described together with practical recommendations for use. Materials and methods: Based on the internationally published literature, this position paper provides specific recommendations for the use of AIT in temporal relation to a SARS-CoV-2 vaccination. Results: AIT is used in 1) allergic rhinitis, 2) allergic bronchial asthma, 3) insect venom allergy, 4) food allergy (peanut). Conclusion: For the continuation of an ongoing AIT, we recommend an interval of 1 week before and after vaccination for subcutaneous immunotherapy (SCIT). For sublingual immunotherapy (SLIT) and oral immunotherapy (OIT), we recommend taking them up to the day before vaccination and a break of 2 – 7 days after vaccination. Initiation of a new SCIT, SLIT, or OIT should be delayed until 1 week after the day of the second vaccination. For SCIT, we generally recommend an interval of ~ 1 week to COVID-19 vaccination.

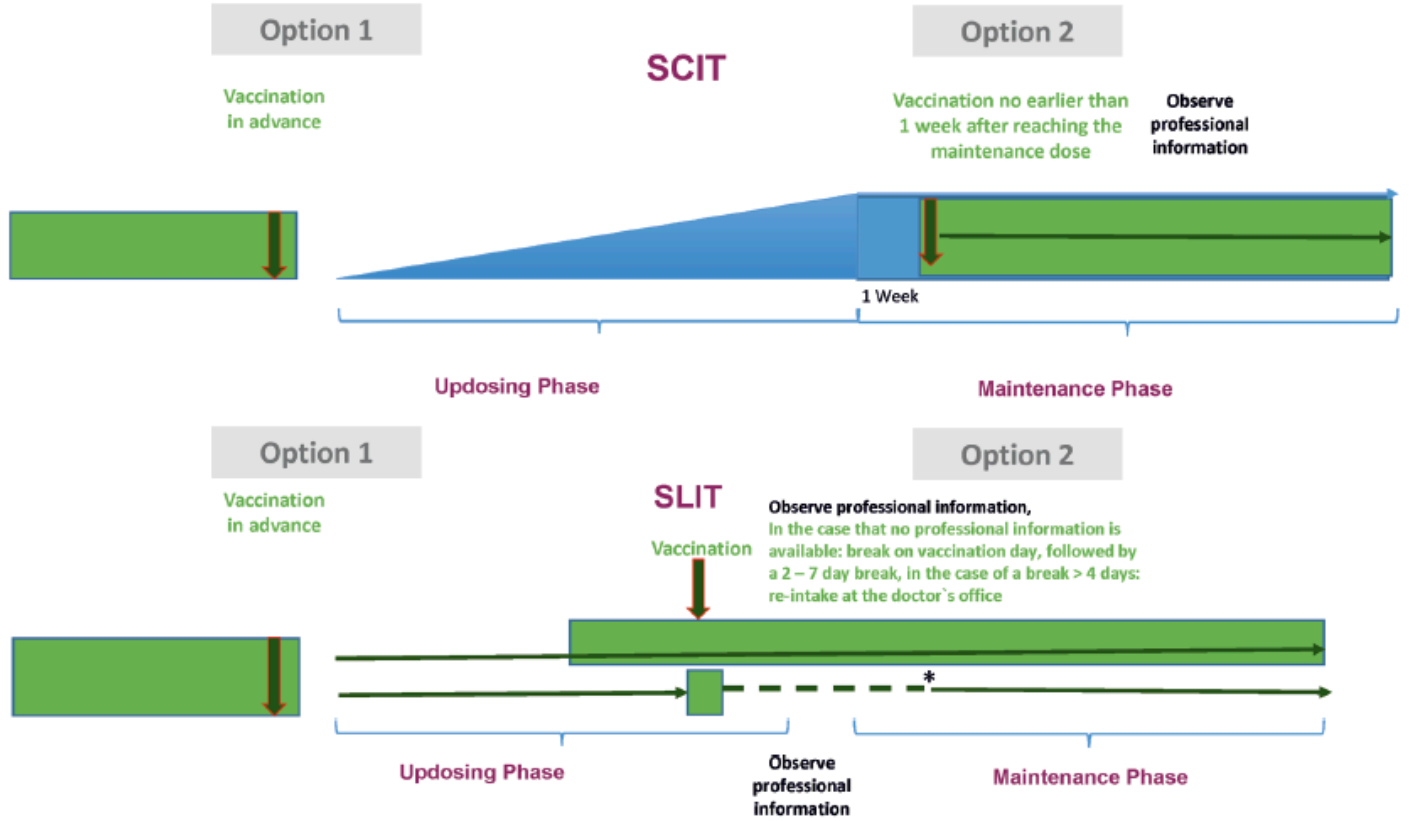


Figure 1. Recommendations for subcutaneous immunotherapy (SCIT) and sublingual immunotherapy SLIT. During the phases marked in green, vaccination can be carried out; during the phases marked in blue, there should be no vaccination.

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

*Allergologie select, Vol. 7/2023 (84-89)*

Review

## Vaccination against infectious agents and allergen-specific immunotherapy: A critical analysis


ISSN 2512-8957

Margitta Worm[1] and Oliver Pfaar[2]

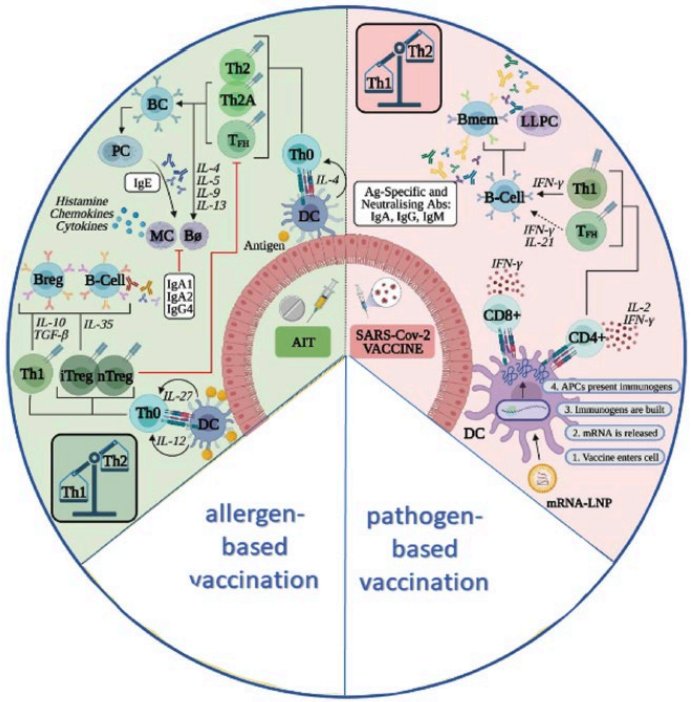


Figure 1. Immune mechanisms during AIT and vaccination against pathogens, modified from Jutel et al. [19].

## Conclusion

Both AIT and vaccination against pathogens modulate the systemic T- and B-cell-dependent acquired immune response. Both treatments are antigen-specific therapies; therefore, direct interactions are not expected, but so-called bystander effects may occur. This refers, for example, to effects of cytokines that are specifically released during an AIT and that may influence other cells of the immune system or the effector cells of the allergic immune response.

So far, there are very few data on possible interactions of AIT and VIA; however, national but also European and other international guidelines recommend not to apply AIT and pathogen-based vaccination at the same time, but to do so in a time-delayed manner with an appropriate therapy interval. Since both therapies usually do not have to be acutely implemented directly, an appropriate management with the patient is usually uncomplicated and very easy to plan. From a medical point of view, the main reason for the time intervals is the better ability to assess a causal relationship in the event of the occurrence of an adverse reaction.

## Interference of allergen- and pathogen-based vaccination

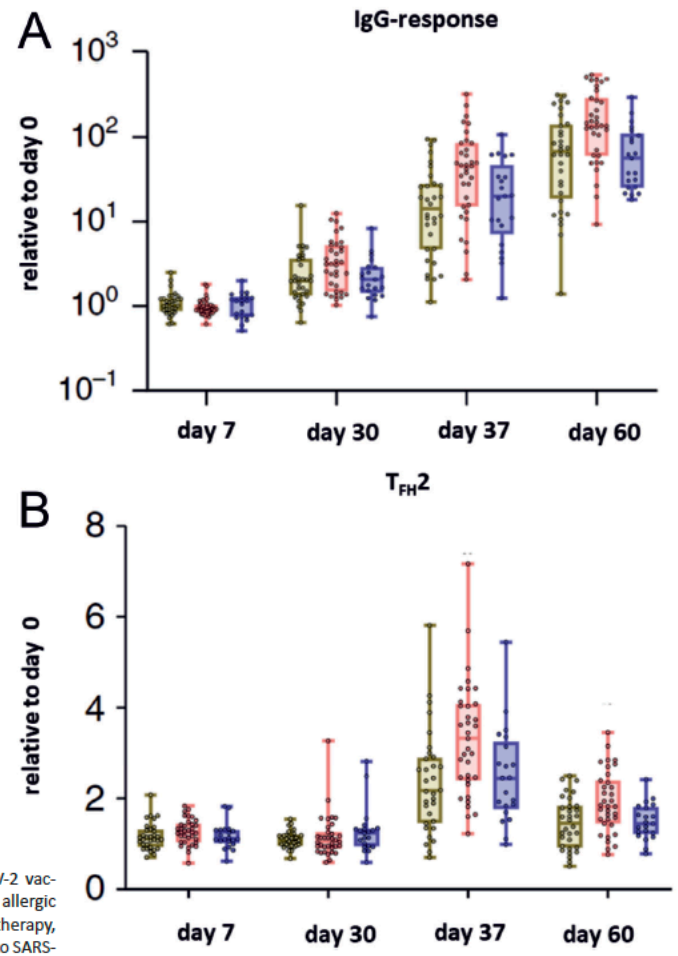


Figure 2. A: Antibody responses to SARS-CoV-2 vaccine (WIBP-CorV, Sinopharm) in patients with allergic rhinitis receiving an allergen-specific immunotherapy, modified from Yao et al. [12]. B: TFH2 response to SARS-CoV-2 vaccine in patients with allergic rhinitis receiving allergen immunotherapy, modified from Yao et al. [12].

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

## ESPECIFICIDAD
Capaz de reconocer diferencias de tan solo 1 aa en la secuencia de 1 proteína

## DIVERSIDAD
Repertorio de linfocitos reconoce al menos mil millones antígenos diferentes

## MEMORIA
Capacidad para recordar el encuentro con un patógeno y responder mejor la siguiente vez

## AUTOLIMITACIÓN
Capacidad para regular la respuesta y detenerla cuando la amenaza ha terminado

Inmunología: Biología y Patología del Sistema inmunitario. Regueiro JR et al ISBN: 9788491104209

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

J ALLERGY CLIN IMMUNOL
VOLUME 140, NUMBER 6

Mechanisms of allergic diseases

**Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers**

Mohamed H. Shamji, PhD, FAAAI, and Stephen R. Durham, MD, FRCP *London, United Kingdom*

## Mecanismo de generación de respuesta inmune a la AIT

AIT, allergen specific immunotherapy

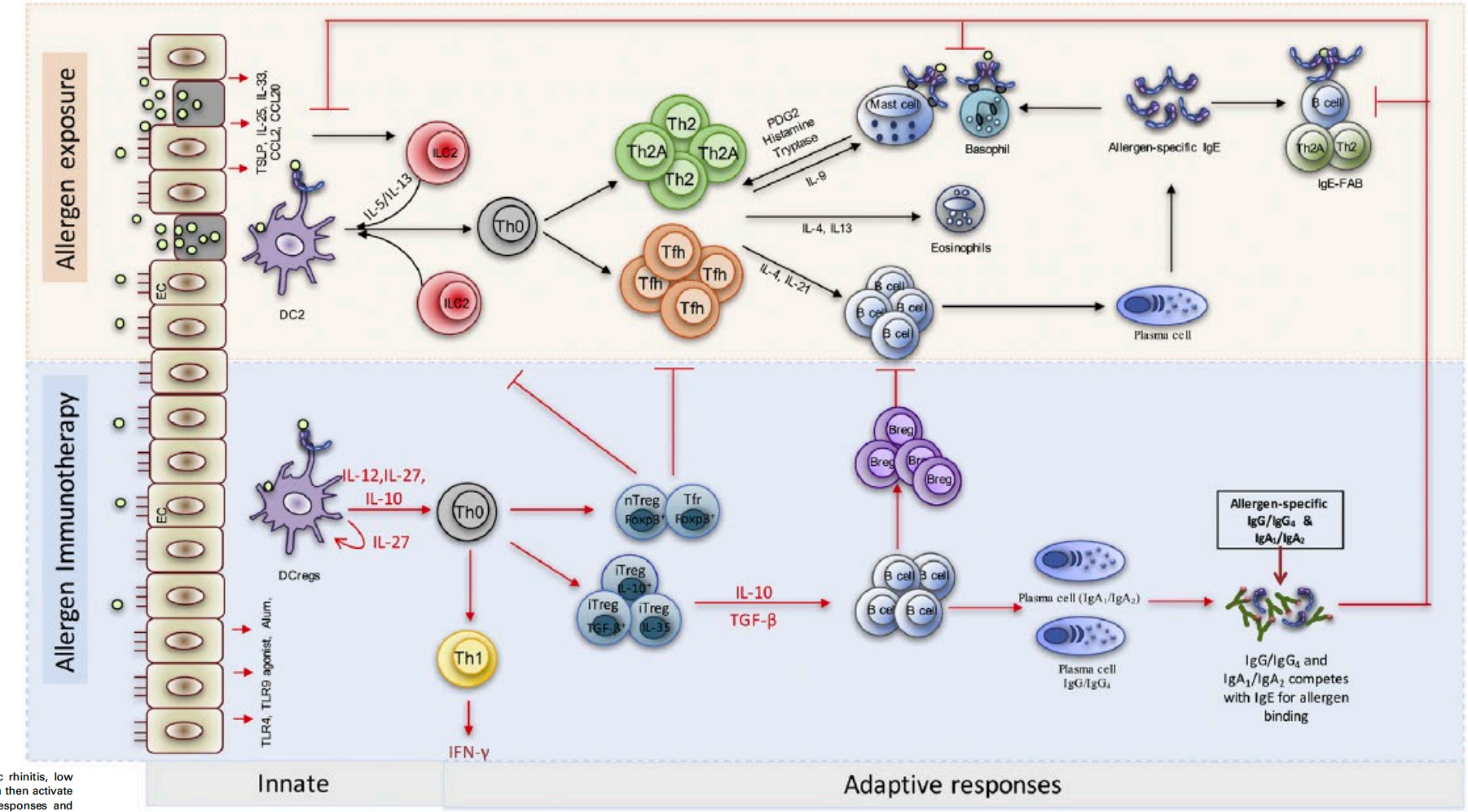


**FIG 2.** Mechanisms of AIT. During the initial sensitization phase in patients with allergic rhinitis, low allergen exposure at the nasal mucosal surface results in activation of epithelial cells, which then activate DCs. DCs uptake and present antigens to naive T cells to induce allergic $T_H2$ *(Th2A)* responses and IgE-facilitated antigen presentation. Subsequent allergen re-exposure leads to mast cell and basophil degranulation, causing classic early-phase reactions. Subsequent infiltration of other leukocytes leads to late-phase allergic inflammation. High-dose allergen exposure by immunotherapy restores DC function, which produces IL-12, IL-27, and IL-10 and promotes immune deviation from a $T_H2$ to $T_H1$ response and induction of Treg and Breg cells (including other B-cell subsets) that produce IgA, IgG, and $IgG_4$ blocking antibodies. Suppressive activities of Treg cells, Breg cells, and IgG-blocking activity is indicated by *red arrows*. *EC*, Epithelial cells; *TLR*, Toll-like receptor.

# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

NATURE REVIEWS | IMMUNOLOGY VOLUME 21 | FEBRUARY 2021 | 83

## A guide to vaccinology: from basic principles to new developments

Andrew J. Pollard[1,2] ✉ and Else M. Bijker[1,2]

## Mecanismo de generación de respuesta inmune a una vacuna

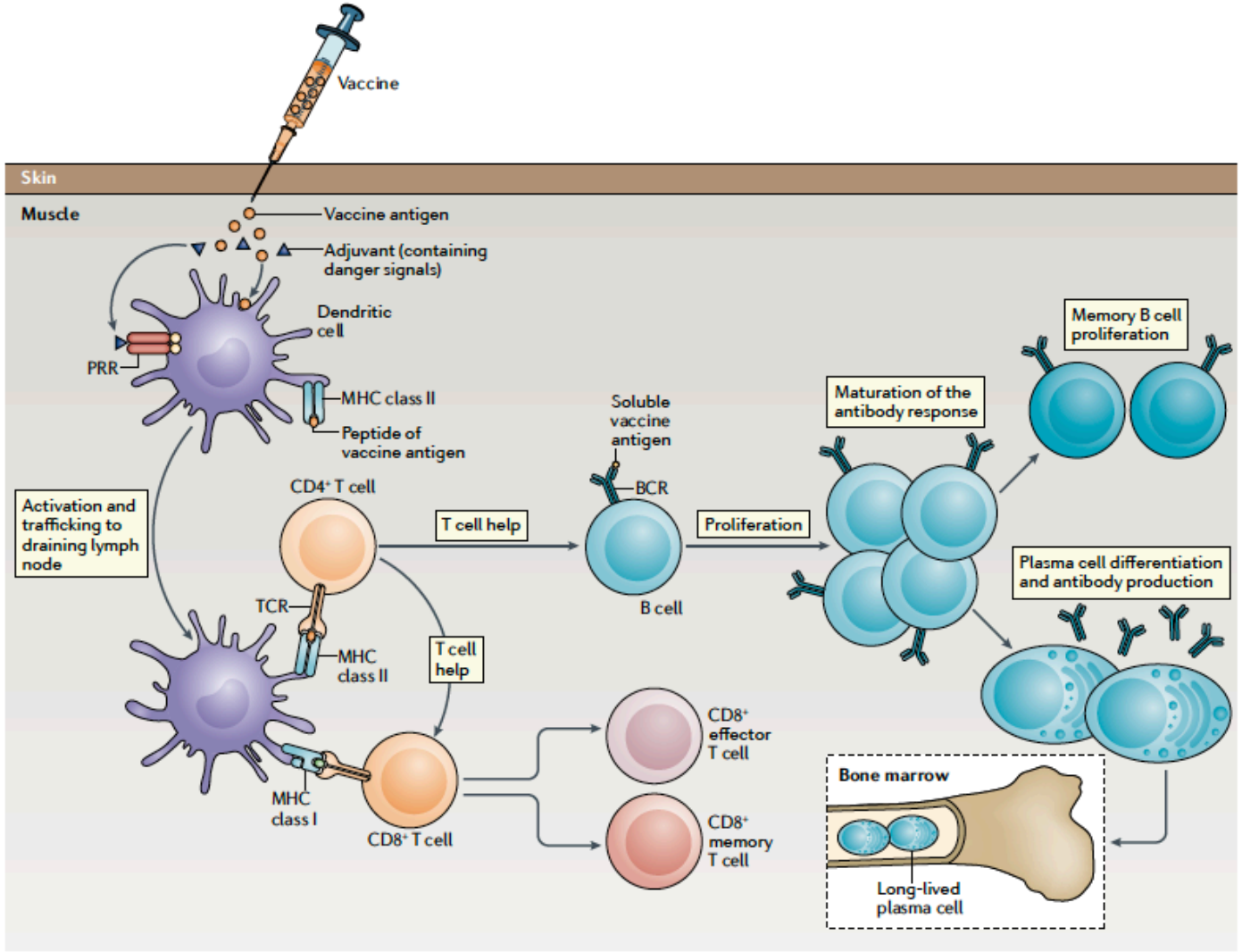


Fig. 3 | **The generation of an immune response to a vaccine.** The immune response following immunization with a conventional protein antigen. The vaccine is injected into muscle and the protein antigen is taken up by dendritic cells, which are activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant, and then trafficked to the draining lymph node. Here, the presentation of peptides of the vaccine protein antigen by MHC molecules on the dendritic cell activates T cells through their T cell receptor (TCR). In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the T cells drive B cell development in the lymph node. Here, the T cell-dependent B cell development results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes. The production of short-lived plasma cells, which actively secrete antibodies specific for the vaccine protein, produces a rapid rise in serum antibody levels over the next 2 weeks. Memory B cells are also produced, which mediate immune memory. Long-lived plasma cells that can continue to produce antibodies for decades travel to reside in bone marrow niches. $CD8^+$ memory T cells can proliferate rapidly when they encounter a pathogen, and $CD8^+$ effector T cells are important for the elimination of infected cells.

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# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

EAACI POSITION PAPER

Allergy WILEY

Received: 5 October 2021 | Revised: 5 January 2022 | Accepted: 12 January 2022

## COVID-19 vaccination in patients receiving allergen immunotherapy (AIT) or biologicals—EAACI recommendations

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**Recommendation 1:** COVID-19 vaccines should be administered at the interval of 7 days from the subcutaneous allergy vaccines to unequivocally assign potential side effect of each one. Likewise, sublingual daily dose should be stopped 3 days before COVID-19 vaccine administration and restarted 7 days after.

**Recommendation 2:** A 7-day interval between administration of a biological targeting the T2 immune response and COVID-19 vaccine is recommended to unequivocally assign potential side effects of each other.

**Recommendation 3:** A 7-day interval between administration of biological targeting the non-Type 2 immune response and COVID-19 vaccination is recommended to unequivocally assign potential side effect of each other.

**Abstract**

Immune modulation is a key therapeutic approach for allergic diseases, asthma and autoimmunity. It can be achieved in an antigen-specific manner via allergen immunotherapy (AIT) or in an endotype-driven approach using biologicals that target the major pathways of the type 2 (T2) immune response: immunoglobulin (Ig)E, interleukin (IL)-5 and IL-4/IL-13 or non-type 2 response: anti-cytokine antibodies and B-cell depletion via anti-CD20. Coronavirus disease 2019 (COVID-19) vaccination provides an excellent opportunity to tackle the global pandemics and is currently being applied in an accelerated rhythm worldwide. The vaccine exerts its effects through immune modulation, induces and amplifies the response against the severe acute respiratory syndrome coronavirus (SARS-CoV-2). Thus, as there may be a discernible interference between these treatment modalities, recommendations on how they should be applied in sequence are expected.

The European Academy of Allergy and Clinical Immunology (EAACI) assembled an expert panel under its Research and Outreach Committee (ROC). This expert panel evaluated the evidence and have formulated recommendations on the administration of COVID-19 vaccine in patients with allergic diseases and asthma receiving AIT or biologicals. The panel also formulated recommendations for COVID-19 vaccine in association with biologicals targeting the type 1 or type 3 immune response. In formulating recommendations, the panel evaluated the mechanisms of COVID-19 infection, of COVID-19 vaccine, of AIT and of biologicals and considered the data published for other anti-infectious vaccines administered concurrently with AIT or biologicals.

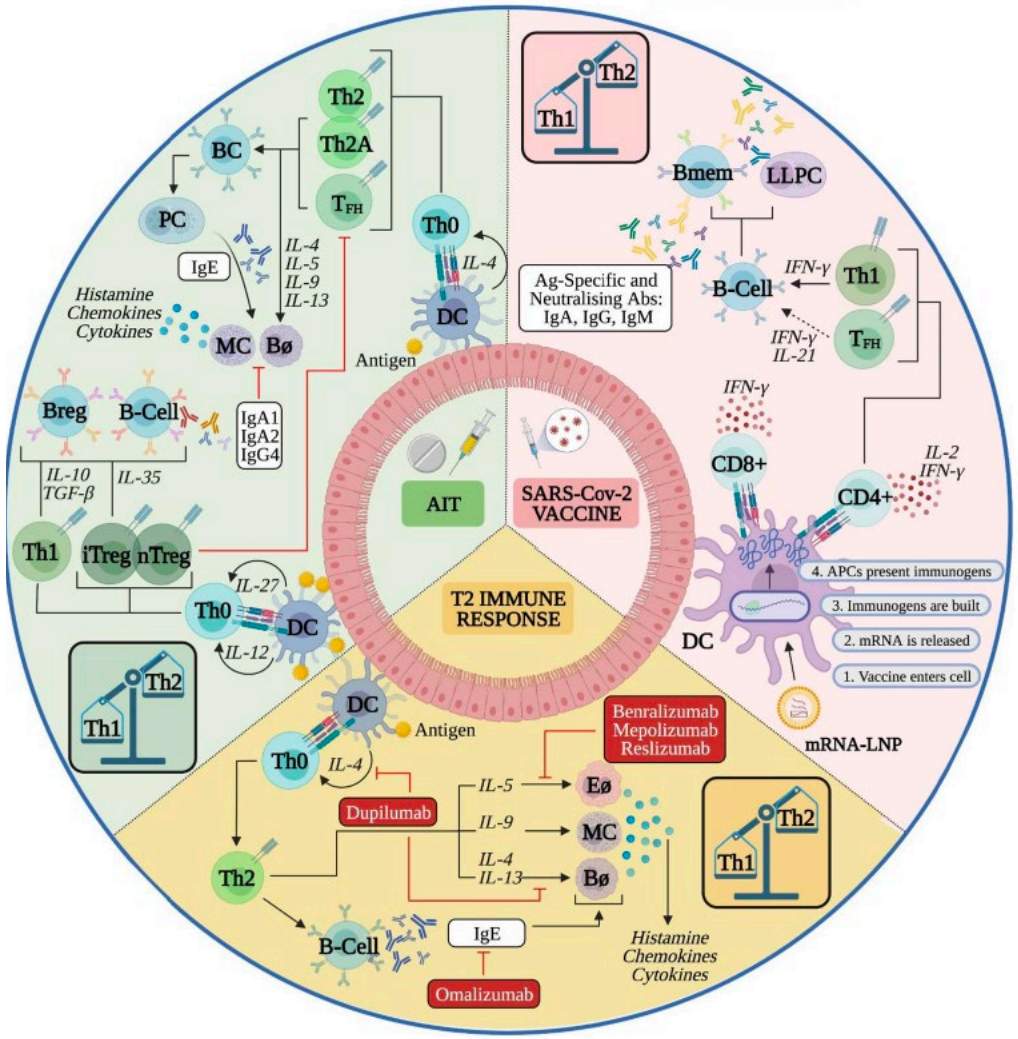


FIGURE 2 Immune modulatory responses of COVID-19 vaccination, allergen immunotherapy and Biologicals T2 responses

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## COVID-19 vaccination in patients receiving allergen immunotherapy (AIT) or biologicals—EAACI recommendations

| | AIT | Biologicals targeting T2 inflammation | COVID-19 | COVID-19 vaccine |
|---|---|---|---|---|
| Immunological changes | ▪ No impact on the whole immune system; no systemic immune deficiency<br>▪ response targets allergen-specific T and B | ▪ No impact on the whole immune system (only on specific blocked pathways); no systemic immune deficiency reported<br>▪ Response targets specific T2 pathways: IgE (Omalizumab), IL-4Rα (Dupilumab), IL-5 (Mepolizumab, Reslizumab), IL-5Rα (Benralizumab), Alarmins (anti-TSLP or anti-IL33 under development) | ▪ does not significantly increase the severity of allergic disease<br>▪ the disruption of T1 and innate antiviral immunity plays a role in the pathogenesis and severity of COVID-19 | ▪ The formation of LLPCs and Bmem<br>▪ Induced a dose-dependent SARS-CoV-2-specific Ab response<br>▪ Germinal Center-derived B-cell response induced by SARS-CoV-2 mRNA vaccines |
| T-cell responses | ▪ decreases allergen-specific T2 responses (Th2 cells and ILC2) in circulation and in the affected organs such mucosal tissues<br>▪ induction of allergen-specific Treg<br>▪ together with Breg cells T regs create a tolerogenic milieu: by the release of IL-10, TGF-βand by direct cell contact-mediated bymolecules like CTLA-4 and PD-1<br>▪ switch between T2 and T1 | ▪ Decreases expansion and activation of memory Th2 responses (Omalizumab and Dupilumab) and effector responses by directly or indirectly blocking specific effector cytokines (all of them).<br>▪ Induction of Treg cells (showed in vitro for Omalizumab) | ▪ CD4 and CD8 T cells decrease (lymphopenia in severe cases)<br>▪ inhibition of IFN-γ signalling results in reduced antiviral response and ongoing pro-inflammatory response<br>▪ excessive inflammation and worsening of the disease<br>▪ decreased number of Treg cells<br>▪ progressive increase in (Tfh) in non-severe COVID-19<br>▪ in severe disease a systemic severe inflammatory response occurs with a CRS—T1 and 3-driven<br>▪ these inflammatory responses are potentially counteracted by anti-inflammatory cytokines, such as IL-10 and TGF-β, and potentially by T2 responses which facilitate recovery | ▪ Tfh cells are crucial regulators of GC and affinity-matured Ab responses<br>▪ Other CD4 T-cell subsets might serve different important functions, including facilitating optimal CD8 T-cell responses<br>▪ SARS-CoV-2 mRNA-LNP vaccines favour the functional polarization of total CD4 T cells towards Th1, while Tfh cells are characterized by the production of both Th1 (IFN-γ) and Th2 (IL-4) cytokines |
| $CD8^+$ T cells | ▪ No major change | ▪ Inhibition of tissue and mucosal infiltration of CD8 +T cells and Tc2 in particular. | ▪ total number of NK and CD8+ T cells markedly decreased in severe COVID (functional exhaustion of Tc) | ▪ No indication that the induction of $CD8^+$ T cells is required for successful protection against SARS-CoV-2 via vaccination |
| Th1—Th2 response | | ▪ Specific blocking of Th2 responses. | | ▪ Th1- and Th2-biased Tfh cells are both relevant in shaping a neutralizing response to SARS-CoV-2<br>▪ mRNA-LNP vaccines skewed Tfh cells towards a Th1 phenotype when using full-length S D furin as immunogen, or towards a mixed Th1/Th2 phenotype when RBD was the immunogen<br>▪ rRBD-AddaVax induced Th2-biased $T_{FH}$ cells |

TABLE 1 Immunological characteristics of AIT and COVID-19. Ab—antibody; B—B lymphocyte; Breg—regulatory B cell; COVID-19—coronavirus disease 2019; CRS—cytokine release syndrome; CTLA-4—cytotoxic T-lymphocyte-associated protein 4; GC—germinal centre; Ig—immunoglobulin; IL / ILR—interleukin / interleukin receptor; ILC—innate lymphoid cell; INF-γ—interferon γ; LLPC— long-lived high-affinity plasma cell; LNP—lipid nanoparticle; mRNA—messenger RNA; NK—natural killer cell; PD-1—programmed cell death protein 1; RBD—receptor-binding domain; rRBD-AddaVax—recombinant RBD protein adjuvanted with squalene-based oil-in-water nano-emulsion (AddaVax); S—spike; SARS-CoV—severe acute respiratory syndrome coronavirus; T—T lymphocyte; T1 / 2 / 3—type 1 / 2 / 3 immune response; Tc1/2—cytotoxic lymphocyte type 1 or 2; $T_{FH}$—follicle T helper cell; TGF-β—transforming growth factor β; Th1/2—T helper cell type 1 or 2; Treg—regulatory T cells; TSLP—thymic stromal lymphopoietin

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### 5 | CONCLUSIONS

EAACI recommendations are based on the mechanistic evaluation as well as clinical experience and evidence involving other anti-infective vaccines.

The current assessment does not suggest any relevant interference compromising neither the safety nor the efficacy of AIT, biologicals or COVID-19 vaccines.

Further evidence from disease registries and other real-world data bases must be accumulated in order to refine current recommendations.

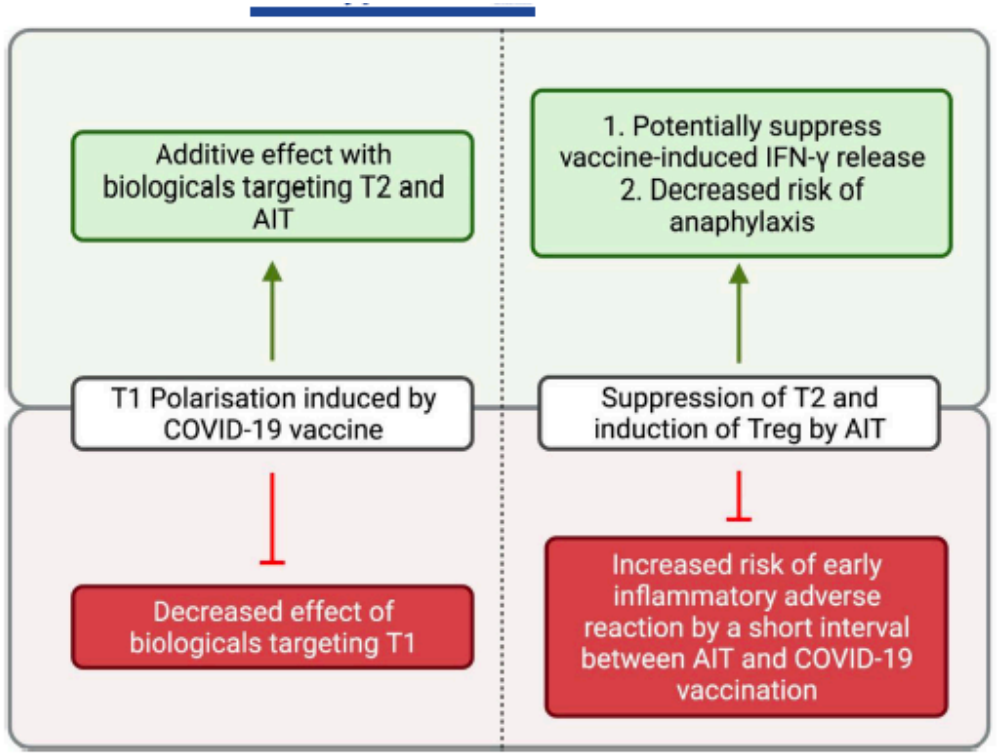


FIGURE 3 Potential impact of the COVID-19 vaccination on the efficacy and safety of AIT and biological treatment and vice versa

TABLE 3 Summary of studies on patients under treatment with allergen immunotherapy (AIT) / biologicals receiving anti-infectious vaccines

| Treatment | Vaccine | Underlying disease | Patients number | Conclusion |
|---|---|---|---|---|
| AIT (*Garner-Spitzer, 2018*) [101] | Booster of tick-borne encephalitis | Allergic rhinoconjunctivitis and asthma | 119 (49 allergic, 21 allergic on AIT and 49 non-allergic) | No effect of AIT on antibody response |
| Omalizumab (*Criado PR, 2019*) [119] | Yellow fever | chronic spontaneous urticaria (CSU) | 28 | No cases of mild yellow fever |
| Omalizumab (*Turner P, 2020*) [122] | Live-attenuated influenza | Moderate- severe asthma | 478 | Well tolerated |
| Dupilumab (*Blauvelt A, 2019*)[129] | -Tdap (tetanus toxoid, reduced diphteriua toxoid, acellular pertussis vaccine)<br>- meningococcal polysaccharide vaccine | Atopic dermatitis | 87 treated by dupilumab / 91 with placebo | Satisfactory and equal IgG response with or without dupilumab 4 weeks after injection |

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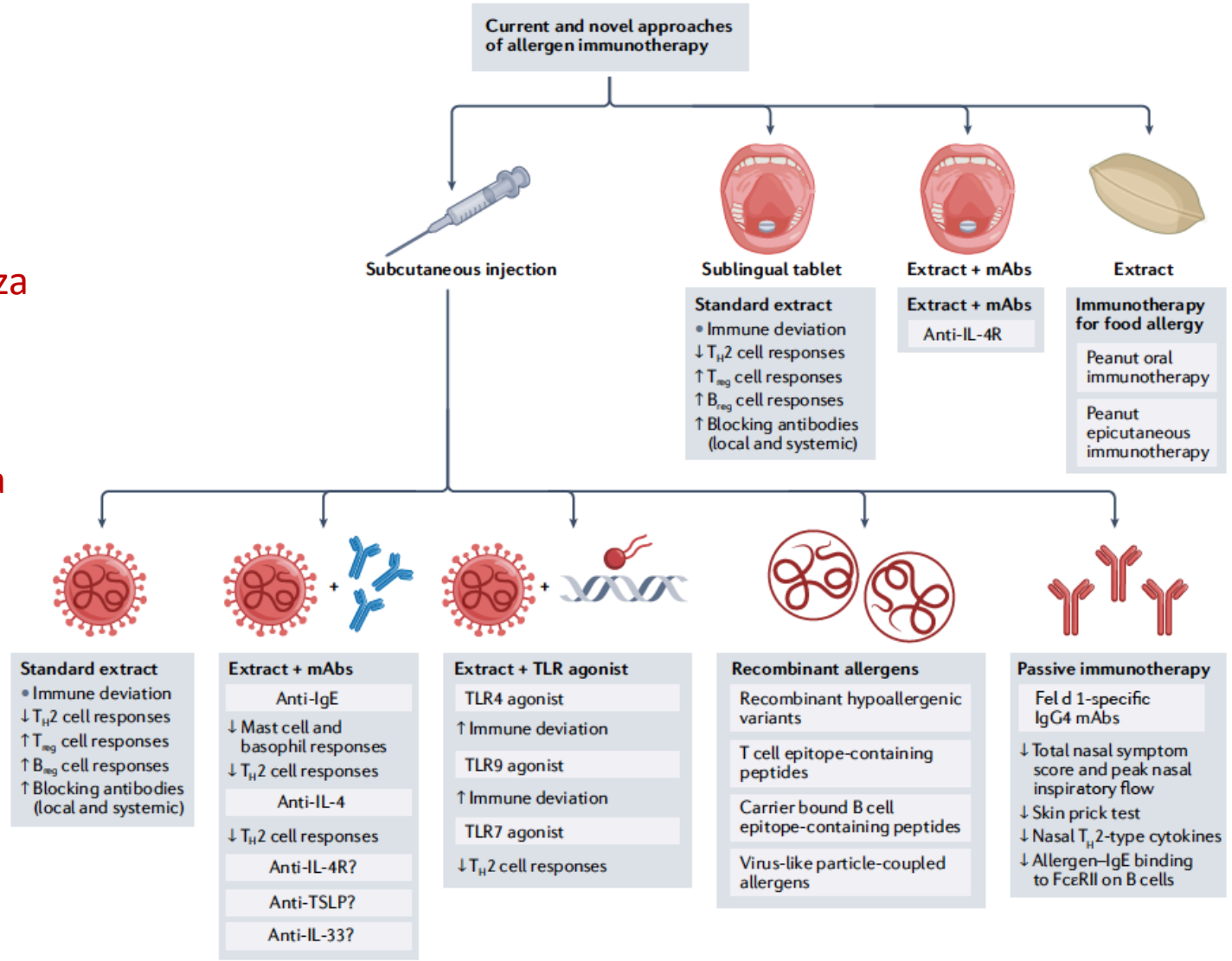
# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

NATURE REVIEWS | IMMUNOLOGY VOLUME 23 | MAY 2023 | 317

## Allergen immunotherapy: past, present and future

*Stephen R. Durham and Mohamed H. Shamji*

- ✓ El campo de la Inmunoterapia en alérgenos avanza
- ✓ Nuevas herramientas AIT
- ✓ Conocimiento mecanismos de base inmunológica



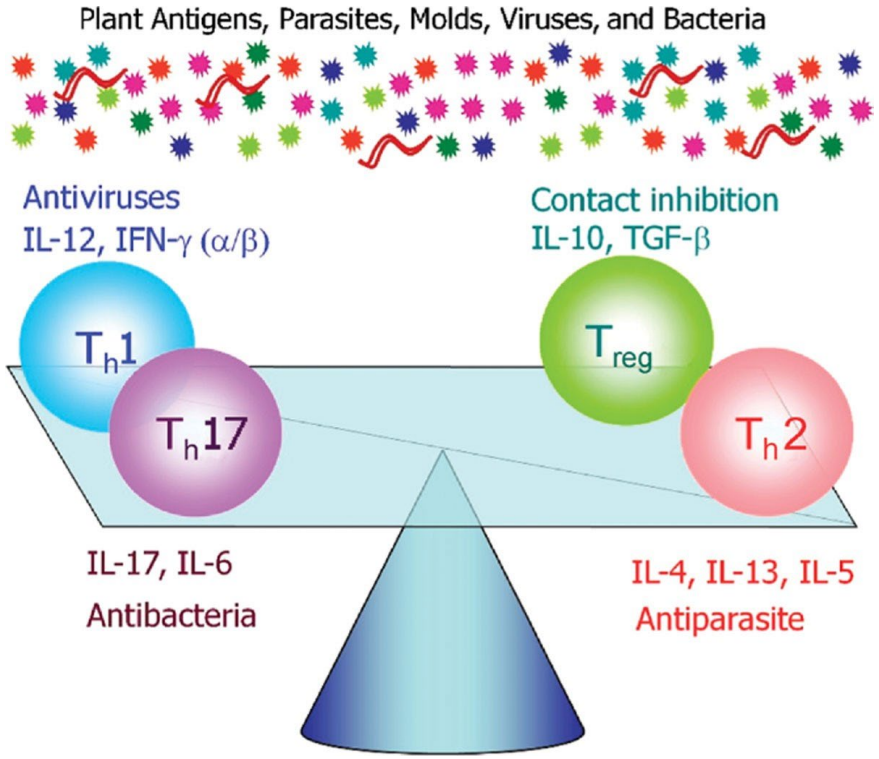
# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

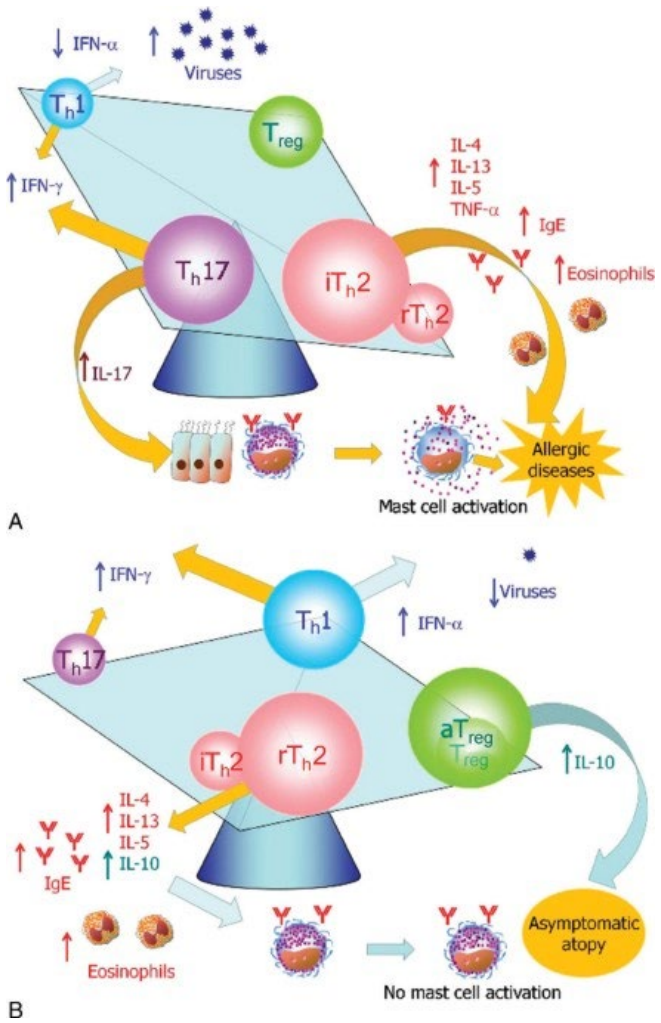
WAO Journal • January 2008

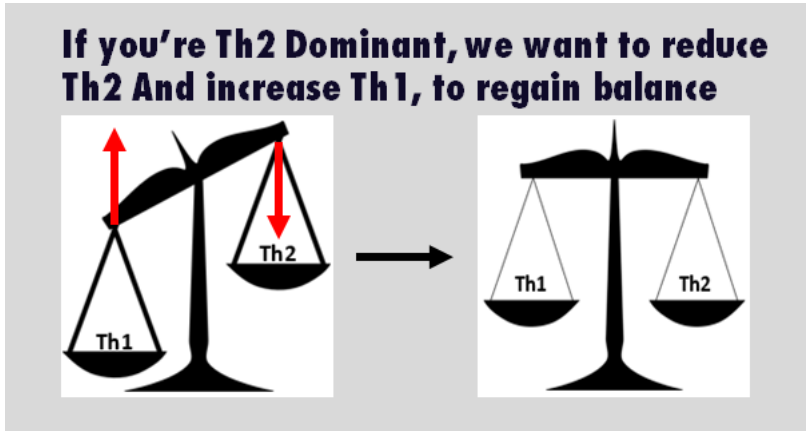
REVIEW ARTICLE

## Role of Regulatory and Proinflammatory T-Cell Populations in Allergic Diseases

*Kanami Orihara, PhD,* Susumu Nakae, PhD,*† Ruby Pawankar, MD, PhD,‡ and Hirohisa Saito, MD, PhD*†*

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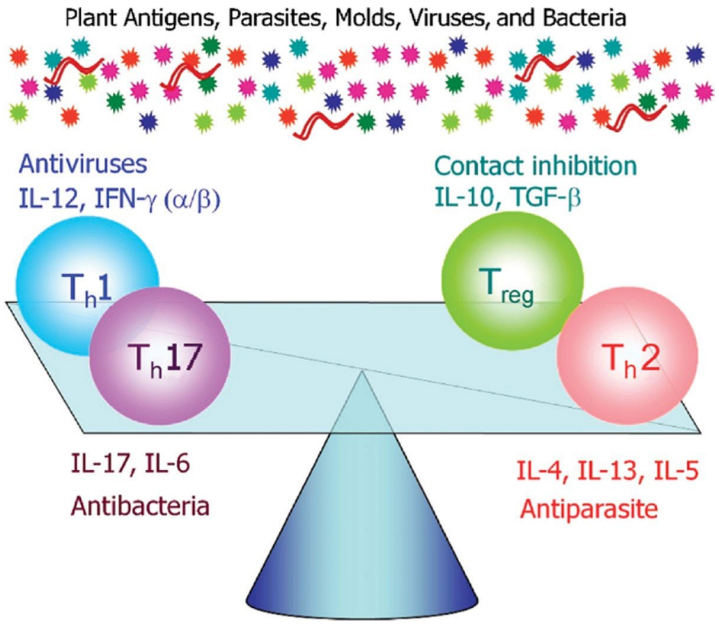


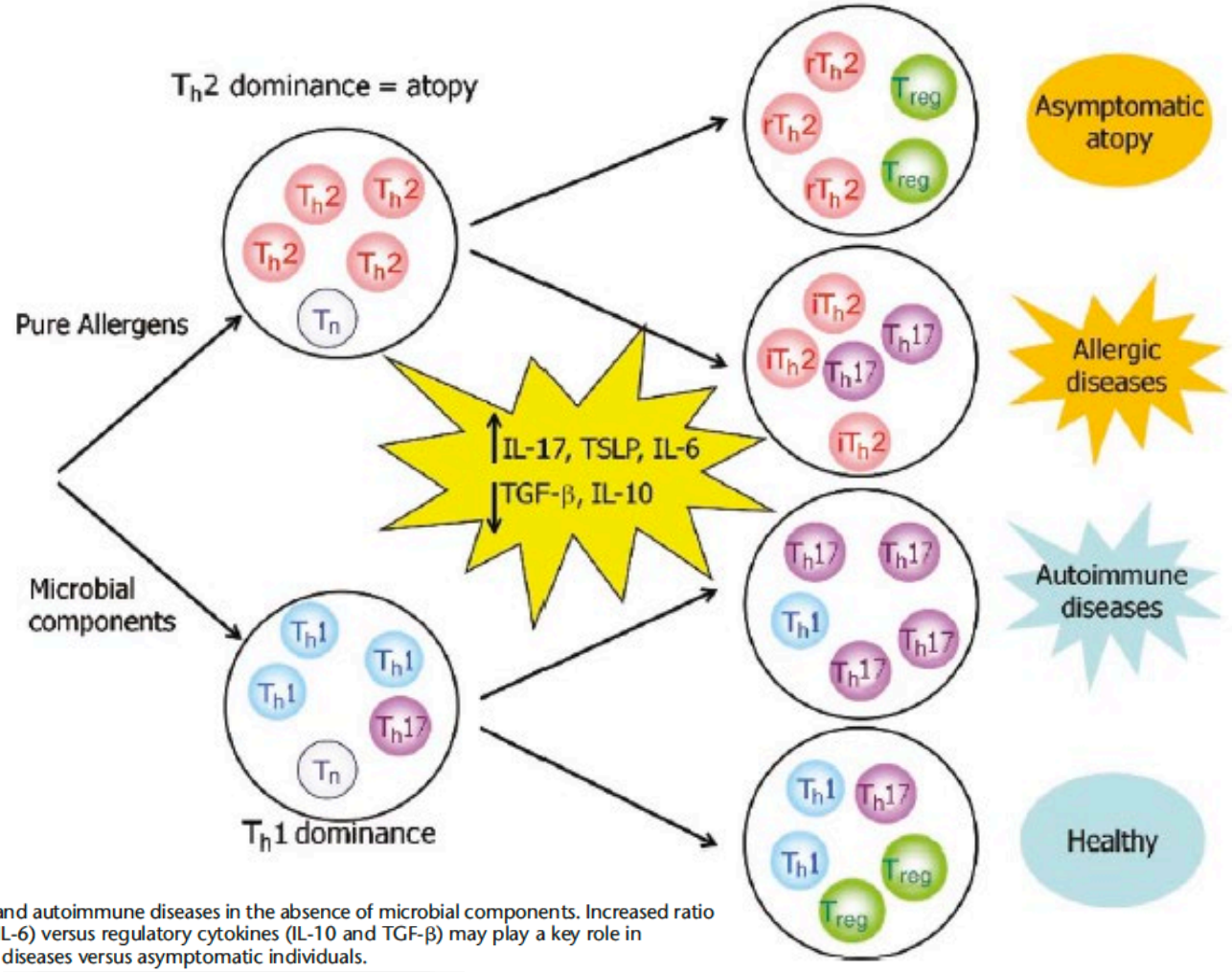


**FIGURE 4.** A model for development of allergic and autoimmune diseases in the absence of microbial components. Increased ratio of proinflammatory cytokines (IL-17, TSLP, and IL-6) versus regulatory cytokines (IL-10 and TGF-β) may play a key role in determining inflammatory allergic/autoimmune diseases versus asymptomatic individuals.

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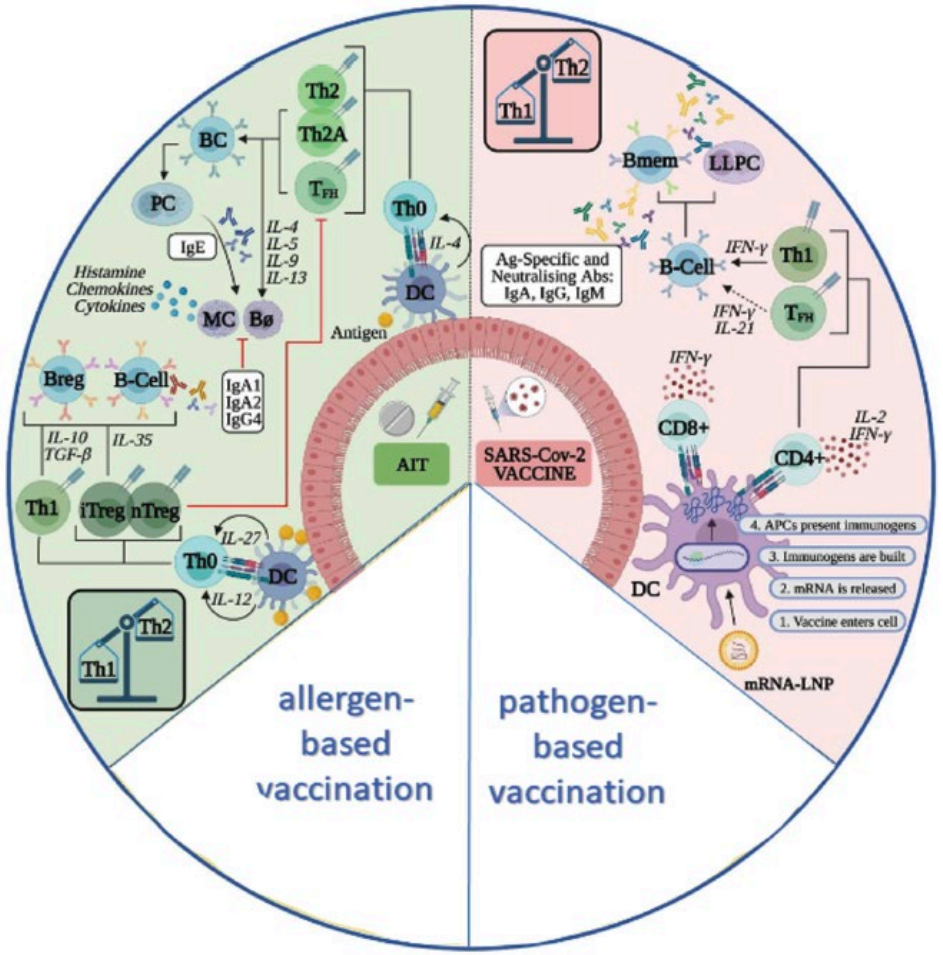
# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?



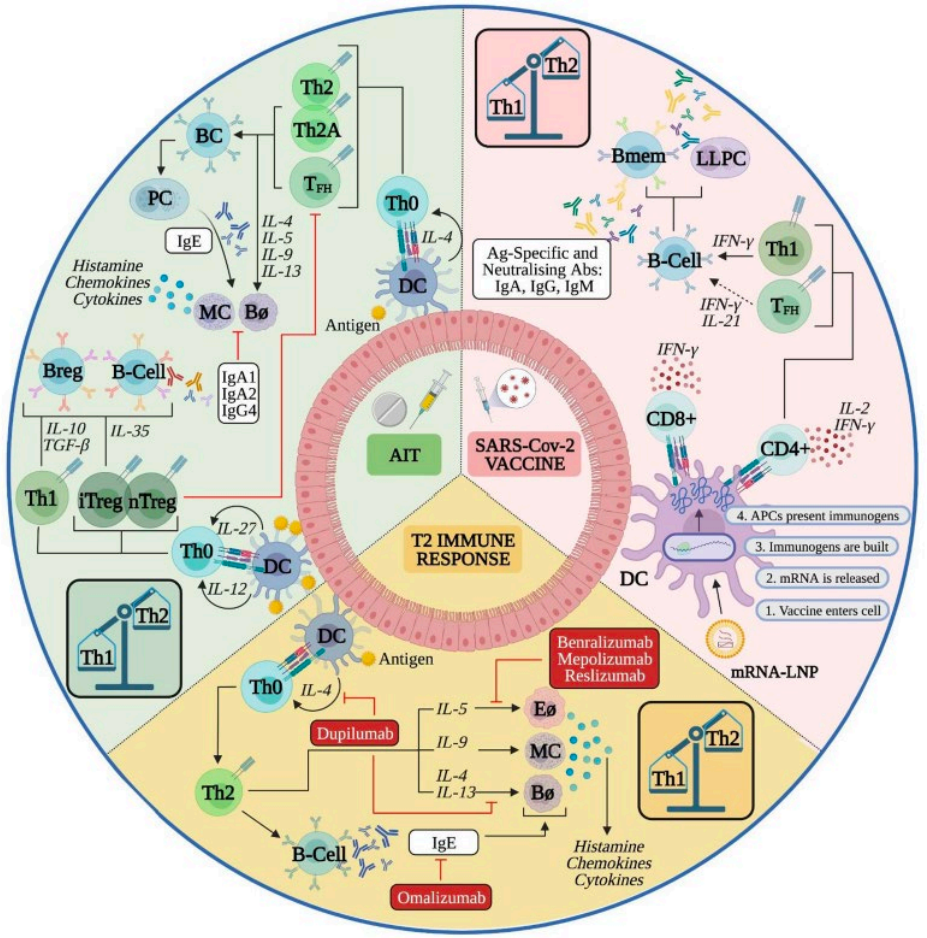

¿Existe algún tipo de interferencia entre la Inmunoterapia de Alérgenos (AIT) y las Inmunizaciones?

**NO**

# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?

¿Existe algún tipo de interferencia entre la Inmunoterapia de Alérgenos (AIT), los tratamientos inmunomoduladores Th2, las Inmunizaciones?

**NO**

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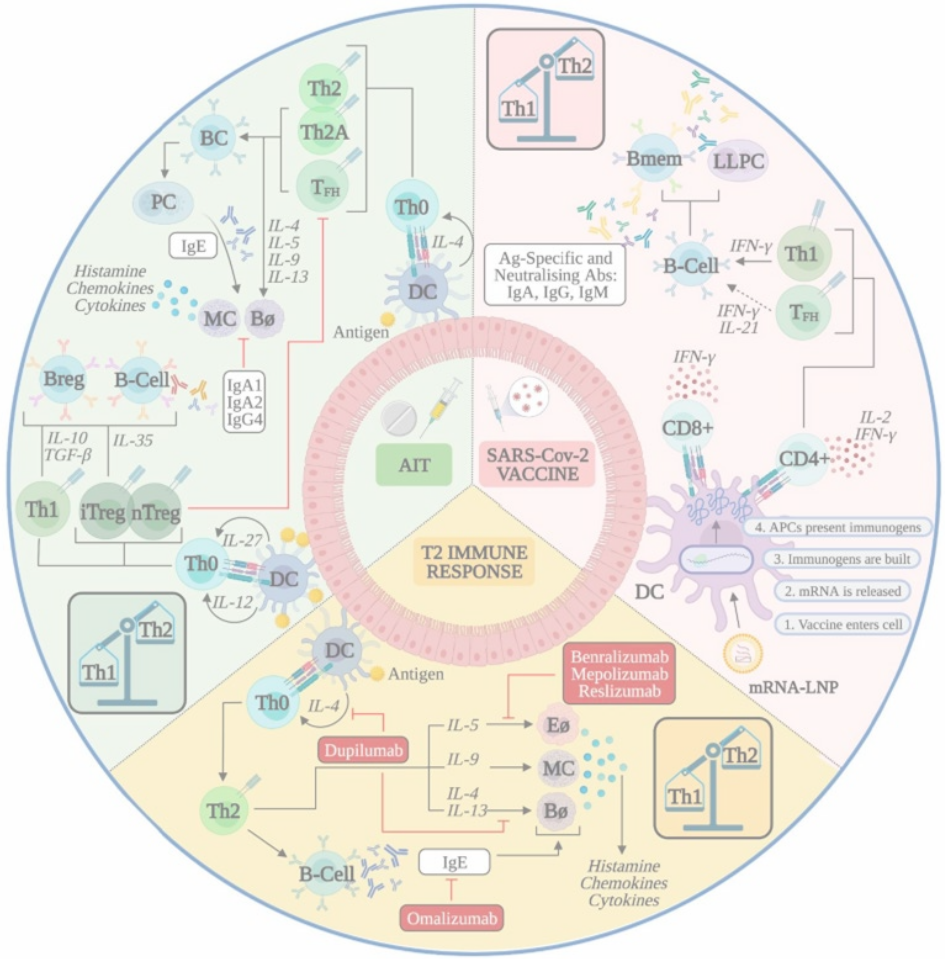
# ¿Hay interferencia entre la inmunoterapia de alergenos y las inmunizaciones?


- La falta de información puede producir retrasos en la administración de las inmunizaciones o la AIT
- Se trata de mecanismos inmunológicos independientes donde la administración simultánea no produce interferencias ni mayor riesgo de efectos secundarios
- Recomendación: espaciar 7 días AIT/Inmunización. Simplemente, para en caso de producirse efectos secundarios, saber en respuesta a que ha sido

# ¿HAY INTERFERENCIA ENTRE LA INMUNOTERAPIA DE ALÉRGENOS (AIT) Y LAS INMUNIZACIONES?





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**Grupo de Investigación en Vacunas GENVIP**