

REVIEW ARTICLE

Update on pathomechanisms and treatments in allergic rhinitis

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Abstract

Allergic rhinitis (AR) is a global health problem with increasing prevalence and association with an enormous medical and socioeconomic burden. New recognition of immune cells such as type 2 innate lymphocytes (ILC2s), T helper (Th2) 2 cells, follicular helper T cells, follicular regulatory T cells, regulatory T cells, B cells, dendritic cells, and epithelial cells in AR pathogenesis has been updated in this review paper. An in-depth understanding of the mechanisms underlying AR will aid the identification of biomarkers associated with disease and ultimately provide valuable parameters critical to guide personalized targeted therapy. As the only etiological treatment option for AR, allergen-specific immunotherapy (AIT) has attracted increasing attention, with evidence for effectiveness of AIT recently demonstrated in several randomized controlled trials and long-term real-life studies. The exploration of biologics as therapeutic options has only involved anti-IgE and anti-type 2 inflammatory agents; however, the cost-effectiveness of these agents remains to be elucidated precisely. In the midst of the currently on-going COVID-19 pandemic, a global life-threatening disease, although some studies have indicated that AR is not a risk factor for severity and mortality of COVID-19, this needs to be confirmed in multi-centre, real-life studies of AR patients from different parts of the world.

KEYWORDS

allergic rhinitis, COVID-19, immune cells, immunotherapy, mechanisms

1 | INTRODUCTION

During the past few years, there has been a global outbreak of allergic diseases, including allergic rhinitis (AR), which are associated with a considerable medical and socioeconomic burden.¹ Nevertheless, recently noticeable progress has been made to further understand different subsets of immune cells (Figure 1) such as type 2 innate lymphocytes (ILC2s), T helper 2 cells (Th2), T follicular helper cell (Tfh), follicular regulatory T cells (Tfr), regulatory T (Treg) cells, B cell, B regulatory (Breg) cell, dendritic cells (DCs), and epithelial cell in AR. This review discusses the role of these immune cells in AR, as well as mechanism-oriented therapies; especially allergen-specific immunotherapy (AIT), and biologics. Indeed, with the ongoing coronavirus

disease 2019 (COVID-19) pandemic, a global life-threatening disease, several challenges are associated with patient management in clinical practice.² Thus, this review also provides an updated AR patient management protocol in the context of COVID-19.

2 | PATHOMECHANISMS IN AR

2.1 | New cognition of ILC2s in AR

ILC2s is a novel population of lineage-negative cells that initiates type 2 allergic inflammation, with the activation of ILC2s usually being dependent on epithelial cell-derived cytokines.^{3,4} Myeloid

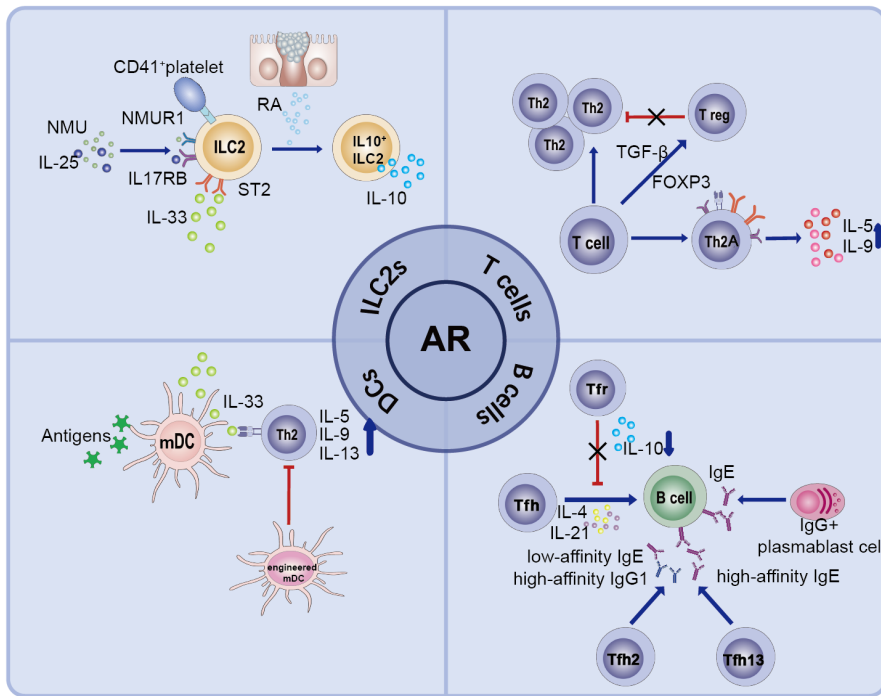


FIGURE 1 Regulation of immune cells in allergic rhinitis (AR). ILC2s, group 2 innate lymphoid cells; mDC, myeloid dendritic cell; NMU, neuromedin U; NMUR1, neuromedin U receptor; RA, retinoic acid; IL-17Rb, IL-25 receptor; ST2, IL-33 receptor

dendritic cells (mDCs) from the nasal mucosa of AR patients can secrete IL-33 to activate ILC2s via the IL-33/ST2 pathway.⁵ In the peripheral blood and airway mucosa of *Alternaria*-challenged mice, CD41⁺platelets have been shown to spontaneously attach to ILC2s, and CD41⁺ILC2s exhibit significantly higher proliferation and increased type 2 cytokine production in response to IL-33 than CD41⁻ILC2s.⁶ However, how long it takes for platelets to fully potentiate ILC2s in the peripheral blood remains unknown. More recently, neuropeptides have been reported to be involved in ILC2 activation at mucosa sites.⁷ Rare neuroendocrine cells such as tuft cells and pulmonary neuroendocrine cells (PNECs) from the airway epithelial layer can secrete peptides and sense hypoxia, as well as environmental stimuli.^{8–10} ILC2s selectively express the neuromedin U receptor 1 (NMUR1), and the combined expression of NMU and IL-25, but not NMU alone, strongly promotes murine ILC2s activation induced by the house dust mite (HDM) in a cell-intrinsic manner.^{11,12} Following OVA inhalation, murine lung PNECs release calcitonin gene-related peptide (CGRP), which can further enhance IL-5 production from ILC2s in the presence of both IL-25 and IL-33.¹³ The sympathetic, parasympathetic, and sensory fibers located near the nasal mucosa have been shown to be able to synthesize neuropeptides.¹⁴ In terms of neuropeptide expression levels, we discovered that substance P (SP), vasoactive intestinal peptide (VIP), and CGRP were significantly higher in the nasal secretions of allergic rhino-conjunctivitis patients, but not in their tears.¹⁵ Herein, it is worthy to investigate the regulatory role of neuropeptides in ILC2s activation in AR patients. AR appears to be associated with a high risk of depression and anxiety,^{16,17} and understanding the interactions between psychological factors and neuro-immune regulation may help us further understand the activation of ILC2s in the nasal mucosa.

To date, understanding of the heterogeneity and ILC2 plasticity has gradually increased in allergic diseases. The induction of IL-10⁺ILC2s from ILC2s in inflamed tissues of chronic rhinosinusitis with nasal polyps (CRSwNP), through retinoic acid (RA) stimulation in vitro, has been shown to functionally suppress the proliferation of Th2 cells and ILC2s via IL-10.¹⁸ Interestingly, when exposed to antigens, blood IL-10⁺KLRG1⁺ILC2s of non-allergic, but not allergic individuals, can produce IL-10.⁷ Due to the decreased presence of IL-10⁺ILC2s in AR patients,⁷ it seems that this deficit in the number and function of IL-10⁺ILC2s leads to downstream intolerance to allergens. Further understanding the heterogeneity of ILC2s based on “omics” data may provide therapeutic targets as well as predictive biomarkers for different therapies.

2.2 | T cell subsets in AR

Recently, the heterogeneity of Th2 cells has been investigated in association with allergic airway diseases.¹⁹ A subpopulation of memory T cells, termed pathogenic Th2 (Th2A) cells, has been discovered in AR individuals.^{20–22} Requiring local epithelial cell-derived cytokine stimulation, Th2A cells produced more IL-5 and IL-9 than conventional Th2 cells, partially due to higher expression levels of epithelial cell-derived cytokine receptors.^{23,24} When evaluating the link between Th2A cells and the pathological process of AR, Th2A cells were mainly found in the peripheral blood of AR patients during the symptomatic stage,²⁵ suggesting that the pathogenicity of Th2 cells is also related to clinical symptoms. Therefore, restricting the number of Th2A cells might prevent the progression of symptoms in AR patients.

Distinct from Th2 and Th2A cells, Tfh cells secrete IL-4 and IL-21, which are essential for B-cell class switching to IgE.^{26–29} As a surrogate of germinal center (GC) Tfh cells,^{30,31} circulating Tfh (cTfh) cell numbers are increased in grass pollen (GP)–allergic patients upon GP stimulation.³² In response to HDM stimulation, a significant increase in the number of IL-4⁺cTfh2 cells, but not CXCR5⁺Th2, cTfh17 or cTfh1 cells, is related to HDM-specific IgE production in AR patients.³³ Furthermore, IL-13-secreting Tfh cells are responsible for the high-affinity IgE generated in *Alternaria*-sensitized mice, while Tfh2 cells lead to production of low-affinity IgE and high-affinity IgG1.³⁴

Tfr cells represent a specialized subpopulation of Tfh cells with signatures from Treg and are present in B cell follicles. Accumulating evidence has highlighted a heterogeneity of Tfr cells in humans and mice,^{35–37} of which Tfr (CD4⁺CXCR5⁺CD45RA^{low}Foxp3⁺) cells with IL-10-deficient secretion have been shown to be inadequate in suppressing memory B cells in AR patients.^{38,39}

Restoring Treg function in AR is one of the therapeutic targets, which is mainly dependent on the regulation of FOXP3 and inhibitory cytokines such as IL-10 and transforming growth factor- β (TGF- β). Notch2-expressing lentivirus transfection can directly promote Treg cell differentiation from CD4⁺T cells in a dose-dependent manner by upregulating FOXP3 expression in the nasal mucosa of AR patients⁴⁰; which was also confirmed in AR mouse models.⁴¹ Alternatively, the conversion of mature TGF- β by CD83/OVA-carrying exosome exposure facilitates the generation of antigen-specific Tregs from CD4⁺T cells in mice.⁴² In recent studies, miR-146a knocking down peripheral blood mononuclear cells induced a significant reduction in the proportion of Tregs and the expression of FOXP3 and TGF- β , suggesting that miR-146a may enhance Treg differentiation and function in AR patients.⁴³

2.3 | B cell in AR

B cells participate in AR pathogenesis through the production of allergen-specific IgE. A circulating B-cell population with a high expression level of CD23, that can switch into memory B cells, might be involved in the disease pathogenesis.³⁹ In the nasal mucosa of AR patients, specific IgE is secreted by IgG⁺ plasmablast cells or activated IgD⁺ naïve B cells undergoing sequential or direct class switch recombination.^{44,45} However, the equivalent mechanisms taking place in the nasal mucosa of local allergic rhinitis (LAR) patients, another subset of AR, remain unclear. Recently, it has been reported that *Dermatophagoides pteronyssinus* (*Der p*) challenge in the nasal mucosa of LAR patients leads to induction of IgG⁺CD19⁺CD20⁺CD38⁺ plasmablasts.⁴⁶ The expression of cDNA for sequential ϵ switch circle was detected in nasal biopsies in 3 of 9 LAR patients, suggesting that IgE sequential class switch may operate in the local site of LAR.⁴⁶ Although local ectopic lymphoid tissues (eLTs) contribute to local B cell activation, survival, and antibody production in chronic rhinosinusitis (CRS)^{47,48}; B cells may further enlarge eLTs in nasal polyps via C-X-C motif chemokine ligand 13 (CXCL13) and

lymphotoxin $\alpha_1\beta_2$ (LT $\alpha_1\beta_2$) in nasal mucosa of CRS.⁴⁹ Whilst evidence showing the presence of eLTs in nasal mucosa of AR is lacking, the effect of eLTs on sequential class switch recombination to IgE in AR cannot be excluded.

Regulatory B cell (Breg), a population of suppressor B cells, has been shown to secrete IL-10 in the regulation of allergic airway inflammation.⁵⁰ Studies in AR patients have reported that CD19⁺CD25⁺CD71⁺CD73⁺Breg cells are significantly decreased in seasonal AR patients compared with healthy donors⁵¹ and upon stimulation with CpG, the Breg subset in AR patients secrete lower levels of IL-10 than Breg cells in healthy controls.⁵²

2.4 | DCs as novel therapeutic targets

DCs are regarded as antigen-presenting cells, ingesting the allergens and presenting them to CD4⁺T cells to trigger allergen-induced inflammation. DCs are divided into different subsets including CD11c⁺mDC and CD123⁺plasmacytoid DC (pDC), which are present in the human airway circulation during the disease.⁵³ Increasing evidence suggests that the enhanced antigen-presenting function of mDC in the OVA-sensitized AR mouse model or AR patients was associated with enhanced autophagy⁵⁴ and high expression levels of the maturation markers CD40 and CD83 in DCs.⁵⁵ Additionally, HDM challenge has been shown to promote IL-33 release from mDCs to aggregate local inflammation in HDM-sensitized AR patients.^{5,56} Thus, DCs can be considered therapeutic targets. Nasal administration of genetically engineered DCs, with deficit endocytosis of the mannose receptor by using clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, resulted in a decrease in the type 2 response in a mouse AR model.⁵⁷ Collectively, these findings greatly extend our knowledge of the different subsets of DCs involved in AR.

2.5 | Epithelial cell in AR

The epithelial barrier acts as the first line of defence against harmful substances. Thus, the impairment of the epithelial barrier could contribute to development of multiple allergic conditions and may also be one of the reasons for poor response of AR patients to common treatments.⁵⁸ Recently, it has been demonstrated that high activity of histone deacetylase (HDAC) in the epithelial cell of AR was negatively correlated with epithelial integrity and blocking the activity of HDAC by an inhibitor (JNJ-26481585) could restore deficient expression of tight junctions.⁵⁹ Moreover, reduced epithelial diversity stemming from functional shifts in basal cells in type 2 airway disease may further contribute to barrier dysfunction.⁶⁰ Reports indicate that organoids with in vivo-like tissue architecture have an advantage over the 2D cell culture model to study cell–cell interactions within tissue-like environments and complex tissue remodeling processes in lower airway disease.^{61,62} In this regard, we suggest that establishment of an AR epithelial-organoid model may also help

illustrate the interaction between epithelial cell and non-epithelial cell types present in AR. Nevertheless, the definition of growth media for both epithelial-organoid and immune cell co-culture requires further investigations.

3 | MECHANISM-ORIENTED TREATMENT

3.1 | Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT)

Allergen-specific immunotherapy (AIT), with a history of 110 years (Figure 2), is regarded as the etiological and most effective therapy for AR patients.⁶³ SCIT and SLIT can be used for AR patients who are allergic to HDM,^{14,64} pollen,^{65–67} or other allergens.⁶⁸ A real-world allergy immunotherapy (REACT) retrospective cohort study assessed the long-term and sustained effectiveness of AIT in AR using data collected between 2007 and 2017 and suggested that patients receiving AIT had a reduced likelihood of asthma exacerbation and pneumonia.⁶⁹ Notably, both HDM-SCIT and HDM-SLIT have proven to be safe and efficient in reducing nasal symptoms and corticosteroid use in preschool AR patients; however, multivariate logistic regression analysis has indicated that BMI and high serum HDM-specific IgE represent some of the main risk factors associated with therapy-related side effects.^{17,70–73} Although most patients with HDM sensitivity are co-sensitized with Der p and *Dermatophagoides farinae* (Der f), the consensus regarding the AIT protocol for polysensitized

patients varies among different continents.^{74,75} Furthermore, in Der p and Der f co-sensitized AR patients, treatment with single-mite (Der p) SCIT for up to 36 weeks has been shown to have an effect equivalent to double-mite (Der p: Der f = 1:1) SCIT.⁷⁶ This might be due to the single Der p-SCIT inducing both Der p-sIgG4 and Der f-sIgG4 production, which induces tolerance.⁷⁷ Japanese cedar pollen (JCP) SLIT tablets have been shown to improve the clinical efficacy of JCP pollinosis within a 5-year study period, and a 3-year-treatment provided a longer-term efficacy than an 18-month-treatment, suggesting that JCP-SLIT efficacy is regulated in a treatment duration-dependent manner.⁷⁸

In recent years, several studies have focused on the relationship between the underlying molecular mechanisms and clinical effectiveness of AIT. IL-10 producing ILC2 and Tfr cells have been shown to be lower in GP allergic AR patients, while the induction of IL-10⁺ILC2 and Tfr cells were noticed in patients receiving GP- or HDM-SCIT and SLIT.^{7,32,79} SLIT using *Artemisia annua* extract has also been shown to significantly decrease Th2 cells, while an increase in nTreg and type 1 regulatory T (Tr1) cells has been noted in blood samples collected from seasonal AR (SAR) or JCP allergic patients.^{80,81} Similarly, allergen-specific production of IL-35 from Tregs or Bregs has been shown to be increased after SLIT for JCP.⁸² Besides the number of Th2 cells, T-cell exhaustion was considered to play a role in the tolerance developed during AIT.⁸³ In line with mice data, the exhausted surface marks PD-1 and CTLA4 on Th2A cells decreased in SCIT-treated asthmatic individuals; however, Th2A cells have been shown to persist for a long time in the SCIT

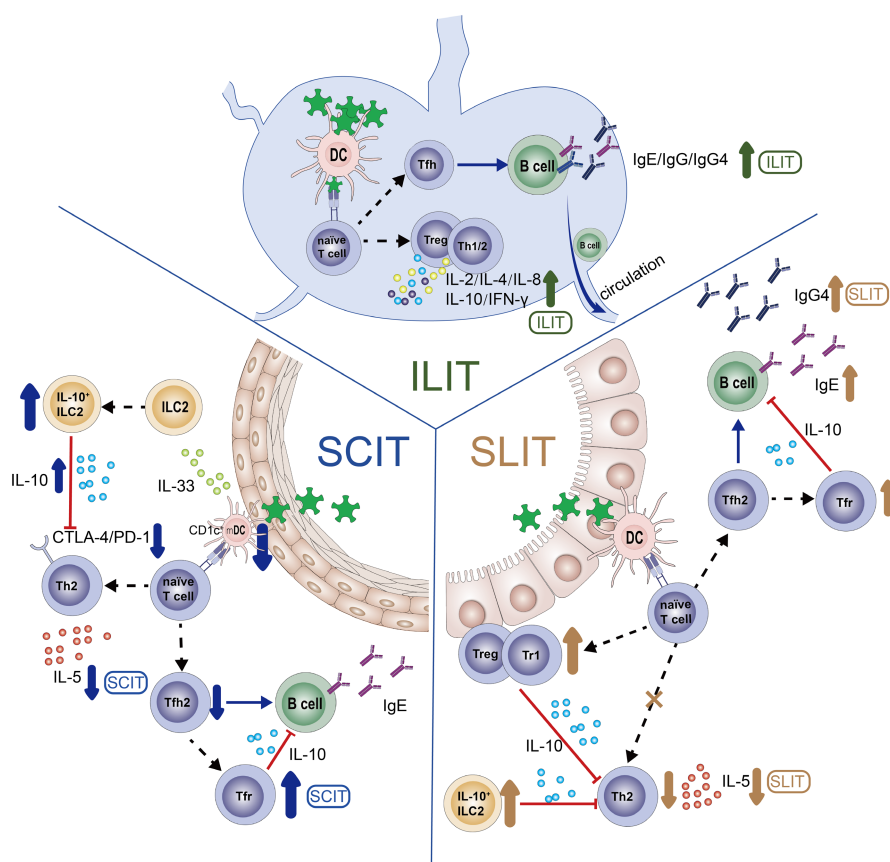


FIGURE 2 Mechanisms underlying the effects of AIT in allergic rhinitis (AR). DC, dendritic cell; ILIT, intra-lymphatic immunotherapy; SCIT, Subcutaneous immunotherapy; SLIT, sublingual immunotherapy; Tfh, follicular helper T cell; Tfr, Follicular regulatory T cells; Tr1, type 1 regulatory T cell

maintenance phase, explaining the long duration of AIT treatment to reduce symptom burden of AR patients.⁸⁴ A novel AIT vaccine BM32, which consists of non-IgE-binding peptides from the B-cell epitopes of GP allergens fused to an immunogenic carrier protein, entailed both the induction of IL-10-secreting T cells and the loss of IL-5-producing Th2 cells.⁸⁵ Although Tfh2 cells play an important role in the induction of antigen-specific IgE in AR, the reduction of Tfh has been shown to be correlated with the clinical efficacy of HDM-SCIT,³³ and elevated levels of Tfr or Tfr/Tfh2 ratio have been observed in AR patients a year after HDM-SCIT.⁸⁶

In terms of biomarkers for AIT, Gotoh et al.⁸⁷ discovered that the levels of antigen-specific IgE and IgG4 were increased in patients with coexisting HDM and JCP AR following SLIT tablet treatment; herein, IgE, IgG4, or IgE/IgG4 ratios have been used to predict the therapeutic effect of SCIT,^{76,88–90} not serum or salivary IgA.⁵⁰ In AR patients, an increase in active antigen-specific CD38⁺ B cells, able to secrete IL-6 to convert Treg cells from Th17 cells in the presence of TGF- β , was also considered an early marker that can be used to predict the outcome of AIT.⁹¹ Moreover, salivary microbiome has been shown to enhance SLIT efficiency by producing IL-10.⁹² An impaired nasal epithelial barrier function is associated with AR pathogenesis,^{58,93} and locally elevated secretory protein 1A1 (SCGB1A1) during pollen SCIT treatment can be used for evaluating long-term immune outcomes.⁹⁴ A decrease in basophil sensitivity after 3 weeks of treatment predicted long-term improvement in seasonal combined symptom and medication scores after SCIT treatment.⁹⁵ To identify the patients who are more responsive to SCIT, IL-4, eotaxin, and IFN- γ might represent robust biomarkers for early prediction of SCIT response in children with HDM-induced AR.⁹⁶

Recently, improvements have been made to reduce adverse events in SCIT. A syringe coated with epinephrine for SCIT is used to minimize potential adverse reactions at the injection site.⁹⁷ Shorter up-dosing schedules such as 7-injection or 11-injection schedules have also been developed.⁹⁸ Comparative studies between the SCIT and SLIT in terms of effectiveness, safety, and cost-effectiveness are limited, and the results are difficult to interpret.^{99–101} Shamji et al.¹⁰² have indicated that blocking the activity of the IgE-allergen complex binding to B cells had similar effects to SLIT and SCIT, while specific IgA production was increased after SLIT and IgG4 production was increased following SCIT. Thus, more head-to-head studies are needed to investigate the differences between SLIT and SCIT, which may aid in selection of a personalized therapy method. In addition to SAR and perennial AR, SCIT has also been shown to improve the symptoms and reduce medicine consumption in LAR.^{103–105} However, larger and multicenter clinical trials are still needed to clarify its safety and long-term efficacy.

3.2 | Intralymphatic immunotherapy (ILIT)

ILIT involves injecting allergen extracts into a subcutaneous lymph node under ultrasound guidance and has been assessed in several recent studies.^{106–108} Intra-lymph node injections of modular allergen

translocation (MAT)-Fel d 1 vaccine (a major category of allergens) has been shown to induce allergen tolerance and promote cellular internalization of the allergen, inflammasome activation, and allergen-specific peripheral T-cell tolerance development.¹⁰⁹ However, this allergen preparation is still under investigation. ILIT using inoculation with aluminum hydroxide-adsorbed allergen extracts showed improved allergic symptoms and reduced rescue medication.¹¹⁰ In contrast, ILIT using tyrosine-adsorbed allergen extracts provided no profound therapeutic effects on AR symptoms induced by HDM, cat, or dog allergens.¹¹¹ It is noteworthy, however, that allergens may leak out of lymph nodes during injection¹⁰⁷ and drain rapidly into the venous system, possibly leading to adverse reactions.¹¹² Considering the comparatively small number of patients recruited for ILIT, the efficacy and potential adverse events of this form of therapy still need to be confirmed. Furthermore, the clinical utility and safety of ILIT remain unknown.

3.3 | Intradermal immunotherapy (IDIT) and epicutaneous immunotherapy (EPIT)

Intradermal immunotherapy (IDIT) and epicutaneous immunotherapy (EPIT) are different routes for administering the allergen through the skin. Compared to traditional allergen administration routes, IDIT and EPIT have many benefits, such as shorter treatment duration, lower allergen dose, and no need for adjuvants.¹¹³ Rhinoconjunctivitis patients sensitized to grass pollen and receiving IDIT have been shown to have reduced clinical symptoms, medication consumption, and IgE levels,¹¹⁴ with the improved clinical effects lasting for up to 2 years.¹¹⁵ Peanut-allergic children (aged 4–11 years) have also been shown to respond to EPIT with a peanut patch; however, the clinical effect of the patch remains to be fully determined.¹¹⁶ Although a systematic review using the limited number of studies suggested that EPIT might induce desensitization in peanut allergic patients, an increased risk of local adverse events was also noticed in patients.¹¹⁷ Taken together, these findings suggest that IDIT or EPIT may be useful in the management of AR patients; however, this remains to be determined in large well-controlled studies.

3.4 | Biologics treatment for AR

AR is an IgE-mediated response, type 2 inflammatory disease.¹¹⁸ The effects of omalizumab (anti-IgE) and dupilumab (anti-IL-4R α) in the treatment of AR have recently been investigated as monotherapy, as well as in combination with AIT. The therapeutic effects of omalizumab in both SAR and perennial AR (PAR) have been well-demonstrated and validated.¹¹⁹ Two meta-analyses showed that omalizumab was effective and safe to treat uncontrolled AR patients.¹²⁰ Considering the cost-effectiveness, some scholars proposed that omalizumab was more suitable for treatment of SAR with more severe symptoms and shorter duration.

Recently, our group indicated that administration of a single injection of 300 mg of omalizumab 2 weeks before the start of the pollen season could achieve better overall control of symptoms and quality of life (QoL).¹²¹ Furthermore, we observed significantly reduced allergy symptom-relieving medication use, compared to the standard pharmacotherapy for SAR patients.¹²¹ Dupilumab has been found to be effective in improving AR-associated nasal symptoms and RQLQ scores of asthma patients with PAR.¹²² To reduce adverse events and improved efficiency, biologics have been considered supplementary treatments in combination with AIT. Supplementing SCIT with dupilumab for grass pollen-induced AR patients reduced the epinephrine rescue treatment rate from 19.2% to 7.7%,¹²³ and increased sIgG4 levels, indicating maximum responses in patients.¹²⁴ Similarly, omalizumab pretreatment was shown to reduce acute reactions after rush immunotherapy for ragweed-induced SAR.¹²⁵

Although targeted therapies are promising and can target the endotype of AR at the level of pathogenesis, except for omalizumab, which is used in uncontrolled AR patients, other biological agents for T2 inflammation have not been studied well, and the high price of biologics seriously limits their application. In the future, more refractory AR patients would benefit from biologics due to more cost-effective drug design strategies and better targeting in AR patients.

3.5 | Medical therapy

Intranasal corticosteroids (ICS) are considered the first-line treatment for AR patients. A meta-analysis compared the efficacy of ICS, oral antihistamines, and AIT in the treatment of AR. Although all treatments provided a convincing therapeutic effect and improved the symptom scores and QoL, ICS was the only treatment that had a significant impact on nasal airflow and peak nasal inspiratory flow.¹²⁶ A recent phase IV, double-blind, RCT study has reported that intranasal fluticasone furoate was also effective and safe in pediatric patients aged 2 to 12 years,¹²⁷ supporting its use in the clinical treatment of AR children, including children aged 2 to 6 years. Moreover, with the development of information technology, some scholars have proposed that mobile health interventions (MHIs) can effectively improve compliance with ICS treatments; however, individual specificity and clinical stability should still be examined.¹²⁸

Combinations of different targeting medicines are thought to bring additional therapeutic advantages. For instance, montelukast combined with oral antihistamine¹²⁹ and montelukast combined with budesonide¹³⁰ have been shown to be superior to the monotherapies. Twice daily GSP301, a combination of antihistamine (olopatadine 665 µg) and a leukotriene receptor antagonist (mometasone 50 µg), was found to be effective and well-tolerated for AR treatment.¹³¹ Although the combination of ICS and leukotriene receptor antagonists was not shown to provide additional improvements over the ICS therapy in AR, it was nevertheless shown to be advantageous in relieving ocular symptoms.¹³² A recent meta-analysis has suggested that intranasal antihistamine could also offer better

clinical improvements than oral antihistamine when combined with intranasal corticosteroids.¹³³

3.6 | Other therapeutic approaches

In recent years, innovative approaches have continued to be developed, focusing on clinical improvements, such as use of adjuvants, peptides, recombinants, modification of allergens, novel routes of administration, and simultaneous use of biological products.⁶³ Apart from traditional specific allergen extracts, novel medicine, such as allergen-specific antibodies, has also been used in an attempt to treat allergic diseases. Gevaert and colleagues¹³⁴ reported a novel *Betula verrucosa* 1 (Bet v1)-specific antibody cocktail (REGN5713/14/15) provided a significant reduction in nasal symptoms of patients after the birch allergen nasal challenge; a Fel d1-neutralizing IgG antibody significantly improved nasal symptoms of the patients, inhibiting the response between FcεRI and FcεRII, as well as subsequent T cell activation.¹³⁵ Allergen peptides are also used in development for treating allergic diseases. In this regard, a 14-week trial with grass allergen peptide could alleviate AR symptoms, and the efficacy was sustained for the 2-year follow-up period.¹¹⁵

4 | AR PATIENT MANAGEMENT DURING THE COVID-19 PANDEMIC

COVID-19 pandemic has imposed a great challenge on world health systems.¹³⁶ Staying at home for a long time due to lockdown likely increases exposure times to indoor allergens and consequently lead to worsening in rhinitis symptoms in HDM-sensitized asthmatics with AR.¹³⁷ However, numerous studies have demonstrated that AR, regardless of age, is associated with lower rates of COVID-19 infection.^{138,139} Possible underlying protective mechanisms of type 2 inflammation against COVID-19 infection involve increased eosinophils with antiviral activity, expression of cross-reactive T-cell epitopes, and interferon response.¹⁴⁰ Due to the polymorphic COVID-19 symptoms, COVID-19 patients present similar symptoms to the common cold and AR patients.^{141,142} Herein, the ARIA-EAACI study group has recommended the use of a modified Delphi questionnaire to successfully distinguish COVID-19 from common cold and AR.¹⁴³

AR patients with suspected or confirmed COVID-19 diagnosis should discontinue AIT since the induction of Treg and Breg cell responses is not beneficial for the recovery.⁵⁴ In the case of AR patients without a COVID-19 infection, the guideline-based pharmacological treatment should be continued as ICS therapy and the usage of conventional drugs such as antihistamines or β2 adrenoceptor agonists are irrelevant to the COVID-19 infection.¹⁴³ As the success of SCIT is thought to depend on regular injections; a 30% SCIT dropout has been noticed among children and 23.81% among adults due to the fear of contracting COVID-19.^{144,145} The implementation of novel strategies to effectively manage AR patients receiving SCIT

is thus critical as numerous patients delay the treatment during the COVID-19 pandemic.¹⁴⁶ Recently, Xi et al¹⁴⁷ have proposed a novel dose adjustment SCIT schedule beginning with a 10,000 SQ dose (vial 4), and demonstrated that this was equally effective and safe to the conventional schedule beginning with a 10 SQ dose (vial 1) for delayed SCIT of more than 16 weeks.

Elderly people are more likely to experience more severe forms of COVID-19 than young people. In this regard, COVID-19 vaccines are highly recommended for the elderly to increase protection in advance.¹⁴⁸ To minimize the risk of allergic reactions, individuals who have a history of severe allergic reactions might have to hold off on getting vaccinated.¹⁴⁹ However, limited reports of allergic reactions due to vaccines does not imply that patients suffering from allergic diseases, like AR and asthma, are not suitable for vaccination. Yao et al¹⁵⁰ have indicated that AR patients from China displayed enhanced humoral immune response to the SARS-CoV-2 inactivated vaccine compared to healthy controls due to the upregulated expression of Tfh2 cells, thus supporting the recommendation for vaccination of AR patients to be plausible. However, more studies in different regions are needed to further confirm these findings.

5 | CONCLUSION AND PERSPECTIVE

This review attempts to update our understanding of the role of cells such as ILC2 cells, Th2 cells, Tfr cells, Treg cells, B cells, DCs, and epithelial cells in AR. Thanks to the "omic" data, there has been gradual recognition of the heterogeneity of immune cells such as ILC2 and Th2 cells, which is likely to lead to a better understanding of the pathogenesis of AR and development of mechanism-oriented precision treatments. As AR patients often present with co-morbid mental disorders, the effect of neuro-immune regulation on type 2 immune response in the nasal mucosa is worthy of further investigation. Still, we cannot exclude the influence of type 2 disease on mental disorders of AR patients. Because AIT is increasingly identified as an etiological option with long-term real-life effectiveness for AR patients, further investigations on the biomarkers that can accurately reflect the clinical effect of AIT are also warranted. Although biologics present promising treatment alternatives for AR, future studies are imperative to address the cost-effectiveness, weighing the adverse effects of AR and determining their proper placement in therapy. Whilst still in the midst of the COVID-19 pandemic, distinguishing COVID-19 from AR symptoms promptly and regularly managing AR patients also need to be explored and clarified further; as does the influence of COVID-19 vaccination on clinical symptoms and treatment of AR.

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CONFLICT OF INTEREST

All authors declare no financial or commercial conflicts of interest.

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REFERENCES

- Bousquet J, Anto JM, Bachert C, et al. Allergic rhinitis. *Nat Rev Dis Primers*. 2020;6(1):95.
- Shi W, Gao Z, Ding Y, Zhu T, Zhang W, Xu Y. Clinical characteristics of COVID-19 patients combined with allergy. *Allergy*. 2020;75(9):2405-2408.
- Scadding GK, Scadding GW. Innate and adaptive immunity: ILC2 and Th2 cells in upper and lower airway allergic diseases. *J Allergy Clin Immunol Pract*. 2021;9(5):1851-1857.
- Li Y, Wang W, Ying S, Lan F, Zhang L. A potential role of group 2 innate lymphoid cells in eosinophilic chronic rhinosinusitis with nasal polyps. *Allergy Asthma Immunol Res*. 2021;13(3):363-374.
- Peng YQ, Qin ZL, Fang SB, et al. Effects of myeloid and plasmacytoid dendritic cells on ILC2s in patients with allergic rhinitis. *J Allergy Clin Immunol*. 2020;145(3):855-867.
- Orimo K, Tamari M, Takeda T, et al. Direct platelet adhesion potentiates group 2 innate lymphoid cell functions. *Allergy*. 2022;77(3):843-855.
- Golebski K, Layhadi JA, Sahiner U, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. *Immunity*. 2021;54(2):291-307 e297.
- Shivharaju M, Chitta UK, Grange RMH, et al. Airway stem cells sense hypoxia and differentiate into protective solitary neuroendocrine cells. *Science*. 2021;371(6524):52-57.
- Hewitt RJ, Lloyd CM. Regulation of immune responses by the airway epithelial cell landscape. *Nat Rev Immunol*. 2021;21(6):347-362.
- Velasco E, Delicado-Miralles M, Hellings PW, Gallar J, Van Gerven L, Talavera K. Epithelial and sensory mechanisms of nasal hyperreactivity. *Allergy*. 2022;77:1450-1463.
- Klose CSN, Mählaköiv T, Moeller JB, et al. The neuropeptide neuropeptide U stimulates innate lymphoid cells and type 2 inflammation. *Nature*. 2017;549(7671):282-286.
- Wallrapp A, Riesenfeld SJ, Burkett PR, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature*. 2017;549(7672):351-356.
- Sui P, Wiesner DL, Xu J, et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science*. 2018;360(6393):eaan8546.
- Bozek A, Galuszka B, Gawlik R, et al. Allergen immunotherapy against house dust mites in patients with local allergic rhinitis and asthma. *J Asthma*. 2021;1-9. doi: [10.1080/0277093.2021.1971701](https://doi.org/10.1080/0277093.2021.1971701). Online ahead of print.
- Meng Y, Lu H, Wang C, et al. Naso-ocular neuropeptide interactions in allergic rhinoconjunctivitis, rhinitis, and conjunctivitis. *World Allergy Organ J*. 2021;14(5):100540.
- Rodrigues J, Franco-Pego F, Sousa-Pinto B, Bousquet J, Raemdonck K, Vaz R. Anxiety and depression risk in patients with allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. 2021;59(4):360-373.
- Wang Y, Shi C, Yang Y, et al. Anxiety and depression in allergic rhinitis patients during COVID-19 pandemic in Wuhan, China. *Asian Pac J Allergy Immunol*. 2021. doi: [10.12932/AP-140820-0941](https://doi.org/10.12932/AP-140820-0941). Online ahead of print.
- Morita H, Kubo T, Rückert B, et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells

- by retinoic acid. *J Allergy Clin Immunol.* 2019;143(6):2190-2201. e2199.
19. Walker JA, McKenzie ANJ. TH2 cell development and function. *Nature reviews Immunology.* 2018;18(2):121-133.
 20. Luce S, Chinthrajah S, Lyu SC, Nadeau KC, Mascarell L. Th2A and Th17 cell frequencies and regulatory markers as follow-up biomarker candidates for successful multifood oral immunotherapy. *Allergy.* 2020;75(6):1513-1516.
 21. Luce S, Batard T, Bordas-Le Floch V, Le Gall M, Mascarell L. Decrease in CD38(+) TH2A cell frequencies following immunotherapy with house dust mite tablet correlates with humoral responses. *Clin Exp Allergy.* 2021;51(8):1057-1068.
 22. Hirahara K, Aoki A, Kiuchi M, Nakayama T. Memory-type pathogenic TH2 cells and ILC2s in type 2 allergic inflammation. *J Allergy Clin Immunol.* 2021;147(6):2063-2066.
 23. Wambre E, Bajzik V, DeLong JH, et al. A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders. *Sci Transl Med.* 2017;9(401):eaam9171.
 24. Calise J, Garabatos N, Bajzik V, et al. Optimal human pathogenic TH2 cell effector function requires local epithelial cytokine signaling. *J Allergy Clin Immunol.* 2021;148(3):867-875 e864.
 25. Iinuma T, Okamoto Y, Morimoto Y, et al. Pathogenicity of memory Th2 cells is linked to stage of allergic rhinitis. *Allergy.* 2018;73(2):479-489.
 26. Qi H. T follicular helper cells in space-time. *Nat Rev Immunol.* 2016;16(10):612-625.
 27. Scholz J, Kuhrau J, Heinrich F, et al. Vitamin A controls the allergic response through T follicular helper cell as well as plasmablast differentiation. *Allergy.* 2021;76(4):1109-1122.
 28. Nunokawa H, Murakami Y, Ishii T, et al. Crucial role of stimulator of interferon genes-dependent signaling in house dust mite extract-induced IgE production. *Sci Rep.* 2021;11(1):13157.
 29. Zhang B, Liu E, Gertie JA, et al. Divergent T follicular helper cell requirement for IgA and IgE production to peanut during allergic sensitization. *Sci Immunol.* 2020;5(47):eaay2754.
 30. Varricchi G, Harker J, Borriello F, Marone G, Durham SR, Shamji MH. T follicular helper (Tfh) cells in normal immune responses and in allergic disorders. *Allergy.* 2016;71(8):1086-1094.
 31. Yang J, Geng L, Ma Y, et al. SLAMF6 negatively regulate IL-21 production in Tfh-like cells from allergic rhinitis patients. *J Asthma Allergy.* 2021;14:361-369.
 32. Sharif H, Acharya S, Dhondalay GKR, et al. Altered chromatin landscape in circulating T follicular helper and regulatory cells following grass pollen subcutaneous and sublingual immunotherapy. *J Allergy Clin Immunol.* 2021;147(2):663-676.
 33. Yao Y, Chen CL, Wang N, et al. Correlation of allergen-specific T follicular helper cell counts with specific IgE levels and efficacy of allergen immunotherapy. *J Allergy Clin Immunol.* 2018;142(1):321-324.e310.
 34. Gowthaman U, Chen JS, Zhang B, et al. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science.* 2019;365(6456):eaaw6433.
 35. Kumar S, Fonseca VR, Ribeiro F, et al. Developmental bifurcation of human T follicular regulatory cells. *Sci Immunol.* 2021;6(59):eabd8411.
 36. Long Y, Li W, Feng J, et al. Follicular helper and follicular regulatory T cell subset imbalance is associated with higher activated B cells and abnormal autoantibody production in primary anti-phospholipid syndrome patients. *Clin Exp Immunol.* 2021;206(2):141-152.
 37. Long Y, Xia C, Xu L, et al. The imbalance of circulating follicular helper T cells and follicular regulatory T cells is associated with disease activity in patients with ulcerative colitis. *Front Immunol.* 2020;11:104.
 38. Yao Y, Chen CL, Yu D, Liu Z. Roles of follicular helper and regulatory T cells in allergic diseases and allergen immunotherapy. *Allergy.* 2021;76(2):456-470.
 39. Yao Y, Wang N, Chen CL, et al. CD23 expression on switched memory B cells bridges T-B cell interaction in allergic rhinitis. *Allergy.* 2020;75(10):2599-2612.
 40. Romero-Wolf M, Shin B, Zhou W, Koizumi M, Rothenberg EV, Hosokawa H. Notch2 complements Notch1 to mediate inductive signaling that initiates early T cell development. *J Cell Biol.* 2020;219(10):e202005093.
 41. Jiao WE, Sun L, Xu S, et al. Notch2 suppresses the development of allergic rhinitis by promoting FOXP3 expression and Treg cell differentiation. *Life Sci.* 2021;284:119922.
 42. Mo LH, Luo XQ, Yang G, et al. Epithelial cell-derived CD83 restores immune tolerance in the airway mucosa by inducing regulatory T-cell differentiation. *Immunology.* 2021;163(3):310-322.
 43. Zhang Y, Yang Y, Guo J, et al. miR-146a enhances regulatory T-cell differentiation and function in allergic rhinitis by targeting STAT5b. *Allergy.* 2022;77(2):550-558.
 44. Corrado A, Ramonell RP, Woodruff MC, et al. Extrafollicular IgD+ B cells generate IgE antibody secreting cells in the nasal mucosa. *Mucosal Immunol.* 2021;14(5):1144-1159.
 45. Hoof I, Schulten V, Layhadi JA, et al. Allergen-specific IgG(+) memory B cells are temporally linked to IgE memory responses. *J Allergy Clin Immunol.* 2020;146(1):180-191.
 46. Testera-Montes A, Palomares F, Jurado-Escobar R, et al. Sequential class switch recombination to IgE and allergen-induced accumulation of IgE+ plasmablasts occur in the nasal mucosa of local allergic rhinitis patients. *Allergy.* 2022;77(9):2712-2724. doi: [10.1111/all.15292](https://doi.org/10.1111/all.15292)
 47. Buchheit KM, Hulse KE. Local immunoglobulin production in nasal tissues: A key to pathogenesis in chronic rhinosinusitis with nasal polyps and aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol.* 2021;126(2):127-134.
 48. Wang ZZ, Song J, Wang H, et al. B cell-activating factor promotes B cell survival in ectopic lymphoid tissues in nasal polyps. *Front Immunol.* 2020;11:625630.
 49. Wang ZZ, Song J, Wang H, et al. Stromal cells and B cells orchestrate ectopic lymphoid tissue formation in nasal polyps. *Allergy.* 2021;76(5):1416-1431.
 50. Ma S, Satitsuksanoa P, Jansen K, Cevhertas L, van de Veen W, Akdis M. B regulatory cells in allergy. *Immunol Rev.* 2021;299(1):10-30.
 51. Kim AS, Doherty TA, Karta MR, et al. Regulatory B cells and T follicular helper cells are reduced in allergic rhinitis. *J Allergy Clin Immunol.* 2016;138(4):1192-1195 e1195.
 52. Wirz OF, Globinska A, Ochsner U, et al. Comparison of regulatory B cells in asthma and allergic rhinitis. *Allergy.* 2019;74(4):815-818.
 53. Poposki JA, Peterson S, Welch K, et al. Elevated presence of myeloid dendritic cells in nasal polyps of patients with chronic rhinosinusitis. *Clin Exp Allergy.* 2015;45(2):384-393.
 54. He YQ, Qiao YL, Xu S, et al. Allergen induces CD11c(+) dendritic cell autophagy to aggravate allergic rhinitis through promoting immune imbalance. *Int Immunopharmacol.* 2022;106:108611.
 55. Liu H, Xia J, Chen Y, Ai J, Wang T, Tan G. Immunosuppressive regulation of dendritic cells and T cells in allergic rhinitis by semaphorin 3A. *Am J Rhinol Allergy.* 2021;35(6):846-853.
 56. Peng YQ, Chen DH, Xu ZB, et al. IL-33 receptor expression on myeloid and plasmacytoid dendritic cells after allergen challenge in patients with allergic rhinitis. *Int Immunopharmacol.* 2021;101(Pt B):108233.
 57. Kim B, Lee YE, Yeon JW, et al. A novel therapeutic modality using CRISPR-engineered dendritic cells to treat allergies. *Biomaterials.* 2021;273:120798.
 58. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol.* 2021;21(11):739-751.
 59. Steelant B, Wawrzyniak P, Martens K, et al. Blocking histone deacetylase activity as a novel target for epithelial barrier defects in patients with allergic rhinitis. *J Allergy Clin Immunol.* 2019;144(5):1242-1253.

60. Ordoñas-Montanes J, Dwyer DF, Nyquist SK, et al. Allergic inflammatory memory in human respiratory epithelial progenitor cells. *Nature*. 2018;560(7720):649-654.
61. Pat Y, Ruckert B, Ogulur I, et al. Differentiation of bronchial epithelial spheroids in the presence of IL-13 recapitulates characteristic features of asthmatic airway epithelia. *Allergy*. 2022;77:2229-2233.
62. Sachs N, Papaspyropoulos A, Zomer-van Ommen DD, et al. Long-term expanding human airway organoids for disease modeling. *EMBO J*. 2019;38(4):e100300.
63. Pfaar O, Bousquet J, Durham SR, et al. One hundred and ten years of Allergen Immunotherapy: a journey from empiric observation to evidence. *Allergy*. 2022;77(2):454-468.
64. Huang Y, Wang C, Wang X, Zhang L, Lou H. Efficacy and safety of subcutaneous immunotherapy with house dust mite for allergic rhinitis: a meta-analysis of randomized controlled trials. *Allergy*. 2019;74(1):189-192.
65. Demoly P, Corren J, Creticos P, et al. A 300 IR sublingual tablet is an effective, safe treatment for house dust mite-induced allergic rhinitis: an international, double-blind, placebo-controlled, randomized phase III clinical trial. *J Allergy Clin Immunol*. 2021;147(3):1020-1030.e1010.
66. Boldovjakova D, Cordoni S, Fraser CJ, et al. Sublingual immunotherapy vs placebo in the management of grass pollen-induced allergic rhinitis in adults: A systematic review and meta-analysis. *Clin Otolaryngol*. 2021;46(1):52-59.
67. Lou H, Wang X, Wei Q, et al. Artemisia Annu sublingual immunotherapy for seasonal allergic rhinitis: A multicenter, randomized trial. *World Allergy Organ J*. 2020;13(9):100458.
68. Jutel M, Bruggenjurgen B, Richter H, Vogelberg C. Real-world evidence of subcutaneous allergoid immunotherapy in house dust mite-induced allergic rhinitis and asthma. *Allergy*. 2020;75(8):2050-2058.
69. Fritzsche B, Contoli M, Porsbjerg C, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: Results from the REACT study, a retrospective cohort study. *Lancet Reg Health Eur*. 2022;13:100275.
70. Pavon-Romero GF, Larenas-Linnemann DE, Xochipa Ruiz KE, Ramirez-Jimenez F, Teran LM. Subcutaneous allergen-specific immunotherapy is safe in pediatric patients with allergic rhinitis. *Int Arch Allergy Immunol*. 2021;182(6):553-561.
71. Kim CK, Callaway Z, Park JS, Kwon E. Efficacy of subcutaneous immunotherapy for patients with asthma and allergic rhinitis in Korea: effect on eosinophilic inflammation. *Asia Pac Allergy*. 2021;11(4):e43.
72. Proctor T, Morrough E, Fenske O, et al. Impact on quality of life and safety of sublingual and subcutaneous immunotherapy in children with severe house dust mite and pollen-associated allergic rhinoconjunctivitis. *Clin Transl Allergy*. 2020;10:10.
73. Xiang L, Liu F, Zhi L, et al. Safety of semi-depot house dust mite allergen extract in children and adolescents with allergic rhinitis and asthma. *Immunotherapy*. 2021;13(3):227-239.
74. Zhao L, Zhang Y, Zhang S, Zhang L, Lan F. The effect of immunotherapy on cross-reactivity between house dust mite and other allergens in house dust mite -sensitized patients with allergic rhinitis. *Expert Rev Clin Immunol*. 2021;17(9):969-975.
75. Calderon MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol*. 2012;129(4):929-934.
76. Zheng P, Yan G, Zhang Y, et al. Metabolomics reveals process of allergic rhinitis patients with single- and double-species mite subcutaneous immunotherapy. *Metabolites*. 2021;11(9):613.
77. Feng M, Luo T, Xian M, et al. Suppression function against environmental dust exposure after Dermatophagoides pteronyssinus immunotherapy is associated with production of specific and cross-reactive immunoglobulin G4. *Clin Exp Allergy*. 2021;52(7):878-887.
78. Yonekura S, Gotoh M, Kaneko S, Maekawa Y, Okubo K, Okamoto Y. Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets. *J Allergy Clin Immunol Pract*. 2021;9(11):4103-4116.
79. Boonpiyathad T, Tantilipikorn P, Ruxrungtham K, et al. IL-10-producing innate lymphoid cells increased in patients with house dust mite allergic rhinitis following immunotherapy. *J Allergy Clin Immunol*. 2021;147(4):1507-1510.
80. Lou H, Huang Y, Ouyang Y, et al. Artemisia annua-sublingual immunotherapy for seasonal allergic rhinitis: a randomized controlled trial. *Allergy*. 2020;75(8):2026-2036.
81. Terada T, Matsuda M, Inaba M, et al. Sublingual immunotherapy for 4 years increased the number of Foxp3(+) Treg cells, which correlated with clinical effects. *Inflamm Res*. 2021;70(5):581-589.
82. Kouzaki H, Arikata M, Koji M, et al. Dynamic change of anti-inflammatory cytokine IL-35 in allergen immune therapy for Japanese cedar pollinosis. *Allergy*. 2020;75(4):981-983.
83. Wambre E. Effect of allergen-specific immunotherapy on CD4+ T cells. *Curr Opin Allergy Clin Immunol*. 2015;15(6):581-587.
84. Wang SH, Zissler UM, Buettner M, et al. An exhausted phenotype of T(H) 2 cells is primed by allergen exposure, but not reinforced by allergen-specific immunotherapy. *Allergy*. 2021;76(9):2827-2839.
85. Rauber MM, Mobs C, Campana R, et al. Allergen immunotherapy with the hypoallergenic B-cell epitope-based vaccine BM32 modifies IL-10- and IL-5-secreting T cells. *Allergy*. 2020;75(2):450-453.
86. Yao Y, Wang ZC, Wang N, et al. Allergen immunotherapy improves defective follicular regulatory T cells in patients with allergic rhinitis. *J Allergy Clin Immunol*. 2019;144(1):118-128.
87. Gotoh M, Okubo K, Yuta A, et al. Safety profile and immunological response of dual sublingual immunotherapy with house dust mite tablet and Japanese cedar pollen tablet. *Allergol Int*. 2020;69(1):104-110.
88. He Y, Liu J, Zhao D, et al. The IgE blocking activity induced by dermatophagoides pteronyssinus subcutaneous immunotherapy does not correlate with specific IgA but with IgG4 in both serum and saliva. *Int Arch Allergy Immunol*. 2021;182(12):1231-1244.
89. Zheng P, Bian X, Zhai Y, et al. Metabolomics reveals a correlation between hydroxyicosatetraenoic acids and allergic asthma: evidence from three years' immunotherapy. *Pediatr Allergy Immunol*. 2021;32(8):1654-1662.
90. Bordas-Le Floch V, Berjont N, Batard T, et al. Coordinated IgG2 and IgE responses as a marker of allergen immunotherapy efficacy. *Allergy*. 2022;77(4):1263-1273.
91. Tian GX, Peng KP, Liu MH, et al. CD38(+) B cells affect immunotherapy for allergic rhinitis. *J Allergy Clin Immunol*. 2022;149:1691-1701.e9.
92. Oka A, Kidoguchi M, Kariya S, et al. Role of salivary microbiome in IL-10 production and efficacy of sublingual immunotherapy. *Allergy*. 2021;76(8):2617-2620.
93. Nur Husna SM, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Nasal epithelial barrier integrity and tight junctions disruption in allergic rhinitis: overview and pathogenic insights. *Front Immunol*. 2021;12:663626.
94. Zissler UM, Jakwerth CA, Gueth F, et al. Allergen-specific immunotherapy induces the suppressive secretoglobulin 1A1 in cells of the lower airways. *Allergy*. 2021;76(8):2461-2474.
95. Schmid JM, Würtzen PA, Siddhuraj P, et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. *Allergy*. 2021;76(5):1528-1538.
96. Xie S, Fan R, Tang Q, et al. Identification of robust biomarkers for early predicting efficacy of subcutaneous immunotherapy in children with house dust mite-induced allergic rhinitis by multiple cytokine profiling. *Front Immunol*. 2021;12:805404.

97. Sapsaprang S, Boonard K, Pacharn P, Srisuwatthari W, Visitsunthorn N, Jirapongsananuruk O. Epinephrine-coated syringe for SCIT reduced local reactions: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol Pract.* 2020;8(4):1465-1467.
98. Horn A, Fernández-Rivas M, Wolf H, et al. Shortened up-dosing with 7 injections of subcutaneous allergy immunotherapy (Alutard SQ) is safe and well tolerated. *J Investig Allergol Clin Immunol.* 2021;31(1):80-83.
99. Liu W, Zeng Q, He C, et al. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. *Pediatr Allergy Immunol.* 2021;32(1):86-91.
100. Chen H, Gong GQ, Ding M, et al. Dropouts from sublingual immunotherapy and the transition to subcutaneous immunotherapy in house dust mite-sensitized allergic rhinitis patients. *Front Allergy.* 2021;2:810133.
101. Tie K, Miller C, Zanation AM, Ebert CS Jr. Subcutaneous versus sublingual immunotherapy for adults with allergic rhinitis: a systematic review with meta-analyses. *Laryngoscope.* 2022;132(3):499-508.
102. Shamji MH, Larson D, Eifan A, et al. Differential induction of allergen-specific IgA responses following timothy grass subcutaneous and sublingual immunotherapy. *J Allergy Clin Immunol.* 2021;148(4):1061-1071.
103. Hoang MP, Samuthpongton J, Chitsuthipakorn W, Seresirikachorn K, Snidvongs K. Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis. *Rhinology.* 2022;60(1):11-19.
104. Zhu W, Gao P, Zhang Q, Chen J. Efficacy and safety of subcutaneous immunotherapy for local allergic rhinitis: a meta-analysis of randomized controlled trials. *Am J Rhinol Allergy.* 2022;36(2):245-252.
105. Eguiluz-Gracia I, Ariza A, Testera-Montes A, Rondon C, Campo P. Allergen immunotherapy for local respiratory allergy. *Curr Allergy Asthma Rep.* 2020;20(7):23.
106. Werner MT, Bosso JV. Intralymphatic immunotherapy for allergic rhinitis: A systematic review and meta-analysis. *Allergy Asthma Proc.* 2021;42(4):283-292.
107. Hellkvist L, Hjalmarsson E, Weinfeld D, et al. High-dose pollen intralymphatic immunotherapy: Two RDBPC trials question the benefit of dose increase. *Allergy.* 2022;77(3):883-896.
108. Skaarup SH, Schmid JM, Skjold T, Graumann O, Hoffmann HJ. Intralymphatic immunotherapy improves grass pollen allergic rhinoconjunctivitis: a 3-year randomized placebo-controlled trial. *J Allergy Clin Immunol.* 2021;147(3):1011-1019.
109. Zaleska A, Eiwegger T, Soyer O, et al. Immune regulation by intralymphatic immunotherapy with modular allergen translocation MAT vaccine. *Allergy.* 2014;69(9):1162-1170.
110. Park HJ, Kim SH, Shin YS, et al. Intralymphatic immunotherapy with tyrosine-adsorbed allergens: a double-blind, placebo-controlled trial. *Respir Res.* 2021;22(1):170.
111. Aini NR, Mohd Noor N, Md Daud MK, Wise SK, Abdullah B. Efficacy and safety of intralymphatic immunotherapy in allergic rhinitis: a systematic review and meta-analysis. *Clin Transl Allergy.* 2021;11(6):e12055.
112. Lee SP, Choi SJ, Joe E, et al. A pilot study of intralymphatic immunotherapy for house dust mite, cat, and dog allergies. *Allergy Asthma Immunol Res.* 2017;9(3):272-277.
113. Rondon C, Sanchez-Borges M, Cupello ER, Fabiano F, Capriles-Hulett A. Aqueous intradermal low-dose house dust mite immunotherapy in tropical settings: a valid cost-effective approach for developing nations? *Allergol Immunopathol.* 2021;49(2):31-39.
114. Sola Martinez FJ, Barranco Jimenez RM, Martin Garcia C, et al. Intradermal Phleum pratense allergoid immunotherapy. Double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy.* 2020;50(12):1352-1361.
115. Ellis AK, Frankish CW, Armstrong K, et al. Persistence of the clinical effect of grass allergen peptide immunotherapy after the second and third grass pollen seasons. *J Allergy Clin Immunol.* 2020;145(2):610-618 e619.
116. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: The PEPITES randomized clinical trial. *JAMA.* 2019;321(10):946-955.
117. Xiong L, Lin J, Luo Y, Chen W, Dai J. The efficacy and safety of epicutaneous immunotherapy for allergic diseases: a systematic review and meta-analysis. *Int Arch Allergy Immunol.* 2020;181(3):170-182.
118. Eschenbacher W, Straesser M, Knoedder A, Li RC, Borish L. Biologics for the treatment of allergic rhinitis, chronic rhinosinusitis, and nasal polyposis. *Immunol Allergy Clin North Am.* 2020;40(4):539-547.
119. Dantzer JA, Wood RA. Update on omalizumab in allergen immunotherapy. *Curr Opin Allergy Clin Immunol.* 2021;21(6):559-568.
120. Tsabouri S, Ntritsos G, Koskeridis F, Evangelou E, Olsson P, Kostikas K. Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis. *Rhinology.* 2021;59(6):501-510.
121. Zhang Y, Xi L, Gao Y, et al. Omalizumab is effective in the pre-seasonal treatment of seasonal allergic rhinitis. *Clin Transl Allergy.* 2022;12(1):e12094.
122. Busse WW, Maspero JF, Lu Y, et al. Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis. *Ann Allergy Asthma Immunol.* 2020;125(5):565-576.
123. Corren J, Saini SS, Gagnon R, et al. Short-term subcutaneous allergy immunotherapy and dupilumab are well tolerated in allergic rhinitis: a randomized trial. *J Asthma Allergy.* 2021;14:1045-1063.
124. Kamal MA, Franchetti Y, Lai CH, et al. Pharmacokinetics and concentration-response of dupilumab in patients with seasonal allergic rhinitis. *J Clin Pharmacol.* 2022;62(5):689-695.
125. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2006;117(1):134-140.
126. Zhang K, Li AR, Miglani A, Nguyen SA, Schlosser RJ. Effect of medical therapy in allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy.* 2022;36(2):269-280.
127. Zhang Y, Wei P, Chen B, et al. Intranasal fluticasone furoate in pediatric allergic rhinitis: randomized controlled study. *Pediatr Res.* 2021;89(7):1832-1839.
128. Baxter MS, Tibble H, Bush A, Sheikh A, Schwarze J. Effectiveness of mobile health interventions to improve nasal corticosteroid adherence in allergic rhinitis: a systematic review. *Clin Transl Allergy.* 2021;11(9):e12075.
129. Krishnamoorthy M, Mohd Noor N, Mat Lazim N, Abdullah B. Efficacy of montelukast in allergic rhinitis treatment: a systematic review and meta-analysis. *Drugs.* 2020;80(17):1831-1851.
130. Chen H, Zhang L, Lou H, Wang Y, Cao F, Wang C. A randomized trial of comparing a combination of montelukast and budesonide with budesonide in allergic rhinitis. *Laryngoscope.* 2021;131(4):E1054-e1061.
131. Andrews CP, Mohar D, Salhi Y, Tantry SK. Efficacy and safety of twice-daily and once-daily olopatadine-mometasone combination nasal spray for seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2020;124(2):171-178.
132. Seresirikachorn K, Mullol J, Limitlaohaphan K, Asvapoositkul V, Snidvongs K. Leukotriene receptor antagonist addition to intranasal steroid: systematic review and meta-analysis. *Rhinology.* 2021;59(1):2-9.
133. Du K, Qing H, Zheng M, Wang X, Zhang L. Intranasal antihistamine is superior to oral H(1) antihistamine as an add-on therapy to intranasal corticosteroid for treating allergic rhinitis. *Ann Allergy Asthma Immunol.* 2020;125(5):589-596.

134. Gevaert P, De Craemer J, De Ruyck N, et al. Novel antibody cocktail targeting Bet v 1 rapidly and sustainably treats birch allergy symptoms in a phase 1 study. *J Allergy Clin Immunol*. 2022;149(1):189-199.
135. Shamji MH, Singh I, Layhadi JA, et al. Passive prophylactic administration with a single dose of anti-Fel d 1 monoclonal antibodies REGN1908-1909 in cat allergen-induced allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med*. 2021;204(1):23-33.
136. Yeğit OO, Demir S, Ünal D, et al. Adherence to subcutaneous immunotherapy with aeroallergens in real-life practice during the COVID-19 pandemic. *Allergy*. 2022;77(1):197-206.
137. Yucel E, Suleyman A, Hizli Demirkale Z, Guler N, Tamay ZU, Ozdemir C. 'Stay at home': Is it good or not for house dust mite sensitized children with respiratory allergies? *Pediatr Allergy Immunol*. 2021;32(5):963-970.
138. Du H, Dong X, Zhang JJ, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. *Allergy*. 2021;76(2):510-532.
139. Ren J, Pang W, Luo Y, et al. Impact of allergic rhinitis and asthma on COVID-19 infection, hospitalization, and mortality. *J Allergy Clin Immunol Pract*. 2022;10(1):124-133.
140. Ding M, Dong X, Sun YL, et al. Recent advances and developments in COVID-19 in the context of allergic diseases. *Clin Transl Allergy*. 2021;11(7):e12065.
141. Ferrel F, Gaino F, Russo E, et al. Clinical presentation at the onset of COVID-19 and allergic rhinoconjunctivitis. *J Allergy Clin Immunol Pract*. 2020;8(10):3587-3589.
142. Hagemann J, Onorato GL, Jutel M, et al. Differentiation of COVID-19 signs and symptoms from allergic rhinitis and common cold: an ARIA-EAACI-GA(2) LEN consensus. *Allergy*. 2021;76(8):2354-2366.
143. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK(PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855.
144. Aytekin ES, Soyer Ö, Şekerel BE, Şahiner ÜM. Subcutaneous allergen immunotherapy in children: real life compliance and effect of COVID-19 pandemic on compliance. *Int Arch Allergy Immunol*. 2021;182(7):631-636.
145. Koca Kalkan I, Ates H, Aksu K, et al. Real-life adherence to subcutaneous immunotherapy: What has changed in the era of the COVID-19 pandemic. *World Allergy Organ J*. 2021;14(7):100558.
146. Zhang Y, Zhang L. Management practice of allergic rhinitis in china during the COVID-19 pandemic. *Allergy Asthma Immunol Res*. 2020;12(4):738-742.
147. Xi L, Wang C, Gao Y, Zhang Y, Zhang L. Comparative study of novel dosing schedules for interrupted immunotherapy for allergic rhinitis. *Clin Transl Allergy*. 2022;12(4):e12147.
148. Bousquet J, Agache I, Blain H, et al. Management of anaphylaxis due to COVID-19 vaccines in the elderly. *Allergy*. 2021;76(10):2952-2964.
149. Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - An EAACI-ARIA Position Paper. *Allergy*. 2021;76(6):1624-1628.
150. Yao Y, Wang ZZ, Huang A, et al. TFH 2 cells associate with enhanced humoral immunity to SARS-CoV-2 inactivated vaccine in patients with allergic rhinitis. *Clin Transl Med*. 2022;12(1):e717.

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