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Biomarkers in allergen immunotherapy: Focus on eosinophilic inflammation

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Asthma and allergic rhinitis (AR) are 2 of the most common chronic inflammatory disorders and they appear to be on the rise. Current pharmacotherapy effectively controls symptoms but does not alter the underlying pathophysiology. Allergen immunotherapy (AIT) is an evidence-based therapy for asthma and AR and has been recognized as the only therapeutic method that actually modifies the allergic disease process. There is a lack of objective markers that accurately and reliably reflect the therapeutic benefits of AIT. A biomarker indicating patients that would benefit most from AIT would be invaluable. Eosinophilic inflammation is a cardinal feature of many allergic diseases. Biomarkers that accurately reflect this inflammation are needed to better diagnose, treat, and monitor patients with allergic disorders. This review examines the current literature regarding AIT's effects on eosinophilic inflammation and biomarkers that may be used to determine the extent of these effects.

Keywords: Allergen immunotherapy; allergic rhinitis; asthma; biomarker; eosinophil

1. Introduction

Asthma and allergic rhinitis (AR) are 2 of the most common chronic inflammatory disorders and they appear to be increasing in incidence. AR is a common disease in children, affecting 10% to 30% of this population in developed countries [1, 2]. In the Asia Pacific region, a recent epidemiological study in China found a steadily increasing prevalence of ~18% [3]. AR is closely associated with other allergic diseases, including asthma and allergic conjunctivitis. AR patients frequently have asthma or nonspecific bronchial hyperresponsiveness, while up to 80% of asthma patients also suffer from AR [4]. Consequently, the disease burden in children is substantial and may even include memory deficit, fatigue, sleep deprivation and depression [5-7].

Asthma and AR pharmacotherapy can effectively control symptoms but they cannot affect the underlying immune response. Consequently, when medication is discontinued symptoms may recur [8]. Allergen immunotherapy (AIT) is an evidence-based therapy for AR and asthma [9, 10] and involves the regular administration of gradually increasing doses of allergens over a period of years. AIT works by reducing or eliminating adverse clinical responses to future allergen exposures [11], thus reducing symptoms and medication use in patients with AR and/or asthma. However, it has also been recognized as the only therapeutic method that may affect the underlying immune pathophysiology by slowing or even halting the development of new sensitizations and progression of clinical disease [12, 13]. There are many possible mechanisms of action, including its effect on the T cells closely related to eosinophils and known as T helper 2 (Th2) cells. Though some studies show inhibition of eosinophil increases during seasonal AR, others have produced contradictory results.

The 2 main administration routes for AIT are: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). While SCIT is administered through the skin, SLIT is administered orally in tablet form or an aqueous/liquid extract [14]. SCIT may induce local and systemic side effects. Concerns about safety led to several recommendations to minimize the risk of side effects [15] and also led to the development of SLIT. SLIT appears to be quite safe for pediatric patients, and the incidence of severe reactions does not appear to be dose-dependent, unlike SCIT [16]. There are many studies on SCIT efficacy for allergic disease based on its ability to reduce symptoms and medication use, but evidence for clinical efficacy of SLIT is much less bountiful. There is a novel third route of administration for AIT, directly into the lymph nodes (ie, intralymphatic immunotherapy [ILIT]). The major advantages of ILIT over SCIT/SLIT are its short duration and low allergen doses. Three ultrasound-guided injections are administered into the inguinal lymph nodes 1 month apart [17]. A recent systematic review and meta-analysis found ILIT to be safer than SCIT, and ILIT patients were more compliant [18]. Regardless of the administration route, there is a lack of objective markers that accurately and reliably reflect therapeutic benefit. A biomarker indicating patients that would benefit most from AIT would be invaluable. Difficulties in the management of allergic diseases abound because of their heterogeneity. Identifying clinical and morphological characteristics through phenotyping suggests unique treatment responses. Endotyping, however, involves describing

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mechanisms of disease subgroups, but the relationship between endotype and AIT responsiveness is unclear. Using endotypes to drive AIT strategies will be aided by the discovery of suitable biomarkers so that AIT-responsive patients can be identified as early as possible.

Eosinophils are multifunctional leukocytes and major effector cells of the allergic process. Consequently, measuring eosinophils has been useful for the treatment and monitoring of eosinophil-related diseases like asthma, atopic dermatitis, and AR. However, eosinophil numbers/percentages yield little information about eosinophil activity. Eosinophil activation leads to the extracellular release of 4 granule proteins, with the most promising biomarker of the four being eosinophil-derived neurotoxin (EDN). EDN is more easily recovered than other eosinophil biomarkers because of its weaker electrical charge [19] and greater efficiency in being released from the eosinophil [20]. EDN can be measured in several bodily fluids and is stable for more than 1 year when frozen [21], adding to its utility as a biomarker. For these reasons, EDN has been identified as a good biomarker, both in research and clinical practice [22, 23], for many eosinophil-associated diseases like AR and asthma. Its value as a biomarker has been demonstrated in children and adults [21-24].

Because of the eosinophil's major role in allergic disease and the fact that many treatments target them, reliable and accurate biomarkers for their presence and activity should be identified. In this review, we review the current published literature to assess suitable biomarkers for AIT's ability to reduce eosinophilic inflammation in allergic disease.

2. Asthma development

A number of factors have been associated with asthma development, including bronchiolitis (a disease primarily in children under 2 years of age). Between 14% and 40% of children having experienced clinically significant bronchiolitis will eventually be diagnosed with asthma [25]. Other factors include type of virus causing bronchiolitis (eg, respiratory syncytial virus [RSV]), atopy and/or family history of atopy, elevated blood eosinophils, serum EDN levels at 3 months after hospitalization for RSV bronchiolitis, exposure to secondhand smoke, and no daycare attendance [26]. Certain respiratory viruses, like human rhinovirus and RSV, have a well-documented association with asthma development and exacerbation. RSV infection may promote a Th2 bias in human and other animal responses, including a weakened T helper 1 (Th1) response during viral infection (eg, significantly lower levels of Interferon-gamma [IFN-γ] and tumor necrosis factor-alpha). The weaker Th1 response in these individuals may lead to reduced viral clearance and prolonged or more severe disease. RSV infection induces chemokines, and RANTES and eotaxin in particular have been associated with increased eosinophilia and disease severity. Eotaxin is a key component of Th2-driven disease and its levels correlate well with eosinophil degranulation in pediatric asthma [27]. Abnormal regulatory T-cell (Treg) function and/or numbers have been identified as a major cause of allergic asthma (AA), and defective Tregs have even been observed in umbilical cord blood in newborns genetically predisposed to allergy [28, 29]. Ninety percent of asthmatics are diagnosed by 6 years of age, which suggests early life events like atopic diseases and respiratory virus-induced wheezing illnesses exert a strong influence on asthma development [28, 30]. It is therefore imperative to precisely diagnose and treat allergic disorders at an early age. Early therapeutic interventions would be greatly aided by validated and reliable biomarkers that can be used for identifying those patients most likely to benefit from AIT.

3. Atopic march and allergic disease

In childhood, the progression from 1 allergic disease to the next that sometimes occurs is referred to as the "atopic march." There is a connection between upper and lower respiratory tract allergic diseases, which has been coined united airway disease [31]. There is much epidemiologic, anatomic, pathophysiologic, and clinical evidence for this. Localized inflammatory changes in the upper and lower airways can lead to systemic responses [32, 33]. Gene-environment interactions are important risk factors for developing asthma and atopy in childhood and a defect in Tregs at birth predisposes a child by enhancing the release of Th2 cytokines in response to allergens [34]. Asthma has many phenotypes (clinical features) and pathophysiological mechanisms (endotypes), with the early-onset asthma phenotype being strongly associated with atopy and a Th2-driven mechanism. The Th2 endotype is characterized by atopy, elevated immunoglobulin (Ig)E, and airway eosinophilic inflammation. Sensitization to aeroallergens and respiratory infections synergistically increases asthma risk [35]. Atopy is also a major risk factor for exercise-induced bronchospasm (EIB), with up to 40% of children with EIB having AR and 30% of those children having asthma [36]. Sensitization to animal, perennial, airborne, or food allergens is linked to a higher risk for asthma development in young children [37]. The important role of allergen sensitization in allergic disease cannot be overstated and it is imperative to diagnose and control early on to slow or even inhibit disease progression.

4. AIT mechanisms of action

AIT involves the systematic administration of extracts, with the main ingredient being allergenic proteins from pollen, dander, dust mites, insects, mold, and others. The cellular and molecular mechanisms through which AIT act include suppression of inducible CD4(+), CD25+, and Treg cells, along with suppression of eosinophils, mast cells, and basophils and the switching of antibodies from IgE to IgG4 blocking antibodies (ie, the IgG4 antibody binds to the allergen without initiating an allergic reaction). A switch from a Th2 to a Th1 immune deviation has also been noted [38]. The main idea behind AIT is that gradually increasing doses of these allergenic extracts will desensitize the patient, leading to a reduction in symptoms and may even halt the development of new sensitizations. The resulting "immune tolerance" implies changes in memory type allergen-specific T and B cell responses, as well as mast cell and basophil activation thresholds [39]. The beneficial effects of AIT can last a long time, as it is the only known allergen therapy to permanently alter the underlying immunologic response. From the very first administration of AIT, mast cell and basophil activity, degranulation, and systemic anaphylaxis degranulation decrease. However, little is known about the exact mechanisms by which AIT modifies and/or suppresses basophil and mast cell responses. Anaphylaxis mediators are released during AIT and sting challenges without inducing systemic anaphylaxis [40]. Piecemeal release of mediators by mast cells and basophils may decrease the granule content of these mediators. Piecemeal degranulation involves the selective release of portions of granule contents, with no granule-to-granule and/

or granule-to-plasma membrane fusions [41]. This may also decrease the activation threshold of mast cells and basophils, as decreased mediator release in these cells is a well-established finding early on in AIT [42]. Throughout the course of AIT, mast cell and basophil suppression continues to be affected by immunological changes such as the generation of allergen-specific Treg cells and decreased IgE [39].

SCIT and SLIT have been associated with transient early increases in serum allergen-specific IgE antibody levels may occur after SCIT/SLIT followed by suppression of the usual seasonal increases in IgE levels during natural allergen exposure [43]. It has been suggested that early Th2 priming by high allergen exposure may be a key to successful immunotherapy [44]. Three years of continuous SCIT has been shown to decrease allergen-specific IgE concentrations, which may contribute to long-term allergen tolerance [45]. IgG, IgG4, and IgA may have serum and nasal inhibitory activity for IgE after SCIT [46-48], with large increases in serum concentrations of IgG, especially IgG4. SLIT administration has also shown induction of allergen-specific IgG1, IgG4, and IgA antibodies [44]. The inhibitory effects of IgG4 on IgE-dependent events have been demonstrated in several studies. IgG can compete with IgE for allergen [49], which blocks allergen-IgE complex formation and prevents cross-linking of high-affinity IgE receptors on basophils and mast cells. This inhibits histamine release. IgE-facilitated antigen presentation (FAP) to T cells, a major pathway for allergen-specific Th2 responses, can be inhibited by IgG/IgG4 blocking the binding of allergen-IgE complexes to low-affinity receptors on B cells [50, 51]. These inhibitory blocking antibodies are maintained by both SCIT and SLIT even after AIT is stopped [46, 52].

SCIT and SLIT inhibit early- and late-phase responses by effector cells. Inhibition of late responses has been associated with decreased eosinophil numbers [53] and Th2 cytokine levels, including IL-4, IL-5, IL-9, and IL-13 [54, 55]. AIT also has an effect on levels of the CC chemokine eotaxin, which is known for eosinophil recruitment. Grass pollen SCIT has been shown to decrease mast cell, basophil, and eosinophil numbers in the nasal mucosa, with concomitant decreases in seasonal symptoms and rescue medication use [44]. Direct correlations between IL-5 reductions and nasal mucosal eosinophil numbers and between eosinophil numbers and seasonal symptom severity were also noted. SLIT for HDM inhibited local mucosal VCAM-1 expression and decreased local eosinophilia [56]. SCIT and SLIT are effective in decreasing recruitment and activation of effector cells in tissues affected by the allergic process.

AIT causes a significant decrease in Th2 cytokines and Th2 effector cell activity, increased numbers and activity of T regulatory cells, and increased secretion of anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor-beta (TGF-β), all which diminish the allergic reaction to specific allergens [57]. The Th2-associated allergic inflammation found in both AR and AA is strongly associated with eosinophils [58], which infiltrate the upper and lower airways and release proinflammatory mediators. Eosinophil numbers correlate well with spirometric findings FEV_1 and BHR [59, 60]. Studies have shown AIT may inhibit increases in nasal eosinophilia in seasonal AR [61]; however, reductions in sputum eosinophilia have not been found [62, 63]. Patients receiving SCIT or SLIT for 2 years experienced clinical improvement in their AR with decreases in Th2 cell numbers, along with decreased levels of Th2-associated cytokines IL-4, IL-5, and IL-13 in nasal fluid. However, Th2 cell numbers and Th2 cytokine levels rebounded during the 3rd year, along with an increase in seasonal symptoms once AIT was stopped. This is in contrast to several studies that have shown AIT of at least 3 years duration being essential for long-lasting benefits [52, 64, 65]. After 3 years of AIT, benefits lasted for at least 2 years [66], suggesting disease modification in addition to effective symptomatic treatment.

Increases in allergen-specific Treg cell numbers during AIT have also been noted in a number of studies [39, 67, 68]. Treg cells release regulatory cytokines like IL-10 and TGF-β, thereby reducing Th2-driven immune responses. The suppressive effects of Treg cells on Th2 cells result in immune deviation toward a Th1 response [69]. Regulatory B (Breg) cells also produce IL-10 and are able to inhibit T-cell- and DC-mediated inflammatory responses and main natural immunologic tolerance. Bregs are also able to suppress specific immune responses through the production of TGF-β and IL-35 [70].

Th2 immunity suppression during SCIT and SLIT has also been associated with immune deviation and induction of Th1 cells [71, 72]. In a study by Durham et al. [72], grass pollen SCIT significantly increased IFN-γ $mRNA^+$ cells, with significant negative correlations found between these cells and hay fever symptoms and rescue medication requirements during the 11-week pollen season. SCIT inhibited immediate (0 to 60 minutes) increases in sneezing and nasal blocking and late (0 to 24 hours) nasal symptoms. There were significant reductions in total eosinophils and activated (ie, eosinophil cationic protein [ECP]-releasing) eosinophils.

SCIT and SLIT induce similar, but not identical changes in immune response. SCIT and SLIT share the following cellular immunity features: induction of allergen-specific Tregs, Th2-to-Th1 immune deviation, and induction of IL-10 and TGF-β. In addition to these mechanisms, SCIT also induces selective apoptosis of $CD27^-$ allergen-specific T cells and reduction of group 2 innate lymphoid cells, whereas SLIT induces TGF-β^+ allergen-specific T helper 3 cells. Humoral immunity mechanisms activated by both SCIT and SLIT include transient rise and long-term inhibition of allergen-specific IgE and increase in allergen-specific IgA and IgG4. SCIT also rapidly decreases allergen component IgE and inhibits FAP [73]. The difference in therapeutic mechanisms may occur because of the difference in administration but also because of the level of allergen exposure. Although the dose administered through SLIT is significantly higher, the effective dose is much lower than SCIT due to the reduced absorption through the oral mucosa because of the neutralizing effects of saliva. SCIT also uses adjuvants that boost immune response. Because of the difference in immune response, SCIT is often reported as being more efficacious than SLIT.

5. Efficacy

Recommended treatments for AR are: (1) avoiding allergens; (2) symptomatic therapy; and (3) AIT [74]. Of the 3, AIT is the only treatment for AR and asthma with a disease-modifying effect [75]. Continuous AIT for at least 3 years may modify the underlying pathophysiology of the disease [64, 65]. In children with AR due to grass pollen, both types of AIT (SCIT and SLIT) have been effective in preventing asthma onset [8]. And for pediatric patients with asthma, AR treatment may also improve asthma control [76]. A recent systematic review and

meta-analysis by Dhami et al. [77] found dozens of published studies demonstrating the positive effects of AIT on asthma. Benefits included significantly reduced symptom and medication scores, increased asthma control, and improved quality of life.

6. Biomarkers for eosinophilic inflammation

Eosinophilic inflammation is a hallmark of many allergic diseases, including AA, AR, atopic dermatitis (AD), and eosinophilic esophagitis. Many studies have demonstrated associations between AIT administration and reductions in eosinophilic numbers and/or activity [41, 49, 53, 59, 61, 72, 74, 75, 78, 79]. The increased adhesion of peripheral blood eosinophils and increased chemotactic activity of eosinophils into the airways during seasonal birch pollen exposure in asthmatics were suppressed by AIT [80, 81]. AIT has also been shown to attenuate eosinophil adhesion, chemotactic, and transendothelial migration activity in house dust mite (HDM)-sensitized allergic asthmatics [80, 82]. A recently published study [79] of children with AA and AR compared traditional therapy (ie, inhaled corticosteroids [ICS] + short-acting beta$_2$-agonist) versus traditional therapy + AIT using eosinophils as a biomarker for efficacy. The addition of AIT to the 2nd group resulted in a greater reduction in nasal eosinophilia over the 3-year treatment period than in the traditional therapy group and a significant reduction in sputum eosinophilia. Significantly greater improvements in bronchial hyperresponsiveness, symptom scores, and skin reactivity were also observed in the AIT group. Another published study [83] comparing ICS and AIT for treatment of mild persistent asthma and AR. ICS was administered during the pollen season while SLIT was administered continuously for 5 years. Both groups had significantly reduced bronchial symptom scores and bronchodilator use, but the improvements were greater in the SLIT group at 3 and 5 years. Nasal symptom scores, nasal steroid use, and nasal eosinophilia significantly decreased in only in the SLIT group. Because of its major role in allergic disease, the eosinophil has been the gold standard for measuring underlying inflammation. Along with eosinophils, IgE plays a vital role in many allergic diseases. Together, they have been proposed as a simple, economical, and reliable diagnostic duo for AR [84, 85], and correlations between the two have been found in AR patients [86, 87]. Playing such an important role in allergic disease both locally and systemically, and with the ease of obtaining it from a number of different bodily fluids (eg, blood, serum, nasal and sputum secretions), the eosinophil should be utilized more often as a good biomarker for AIT efficacy.

The mere presence of eosinophils in tissues yields very little information on their activity. Atopic inflammation is a complex process with the release of various cytokines affecting eosinophil activation, proliferation, differentiation, and survival. Thus, it would be challenging using peripheral eosinophilia alone as a biomarker for atopic disease activity. Instead, eosinophil activity is best measured by eosinophil degranulation [88], which is the extracellular release of granule proteins like EDN and ECP. There is a serious lack of studies using these eosinophil granule proteins as biomarkers in AIT. One such study used ECP as a biomarker investigating AIT efficacy in AR patients. Again, traditional therapy (budesonide spray) was compared to AIT (SLIT) and significant decreases in ECP were found in both groups after treatment [89]. ECP was at 1 time the most studied of the eosinophil granule proteins but times have changed, as EDN appears to be superior in a multitude of studies on its use as a biomarker for allergic disease [22, 90, 91]. It has been concluded by many research groups that the presence of increased EDN levels in active allergic disease suggests it has a role in pathogenesis and could be useful as a diagnostic and even prognostic biomarker. Elevated levels have been found in patients with asthma [22, 90, 91], AD [22, 92], AR [22], chronic rhinosinusitis [93], and urticaria [94]. EDN is more easily recovered from measuring instruments and cell surfaces than other eosinophil biomarkers, it can be measured in a number of bodily fluids (blood, serum, urine, sputum, nasal secretions, and bronchoalveolar lavage), and is also stable for extended periods when frozen. Its use as a biomarker has been validated in the above specimen types [22-24, 91, 92], with serum being the most common [22, 24, 91]. In addition, fecal EDN shows promise as a biomarker for food allergy [23]. All these characteristics add to its utility as a biomarker. Despite this, there appears to be no published studies using EDN as a biomarker for AIT efficacy. Future studies should be done to explore this possibility.

7. Other biomarkers for AIT

Increased IgE levels are a key patient characteristic for initiating AIT [15, 95, 96]. Some long-term AIT studies have shown specific IgE (sIgE) levels decrease over time [48, 97], while other studies have shown no change or even an increase [44]. The ratio of sIgE to total IgE (sIgE/tIgE ratio, hereafter referred to as the "IgE ratio") has been used as a predictive marker for treatment efficacy in patients receiving either grass pollen or HDM AIT for 4 years. The IgE ratio in this study predicted successful AIT with a sensitivity of 97.2% and specificity of 88.1% [98]. Other studies have shown similar correlations between IgE ratio and clinical outcomes of AIT [50, 99]. A study by Fujimura et al. [100] found the IgE ratio to be a good candidate as a biomarker for treatment response and prognosis in SLIT. IgE ratio has not been validated as a biomarker for AIT efficacy; therefore, further validation studies are needed.

IL-4 is a typical Th2 cytokine, along with IL-5 and IL-13, and has elevated levels in AR patients with associated allergic symptoms. A recent study found Th2 cytokine levels decreased after AIT and the change in cytokine levels was closely associated with efficacy [69]. A very recent study by Xie et al. [101] found IL-4 levels to be closely associated with SCIT efficacy in pediatric AR patients and was predictive for treatment response. Treatment efficacy was based on improvement of clinical symptoms and reduction in rescue drug consumption. After the initial study on the discovery cohort was completed and potential biomarkers were identified, an independent validation cohort was created. After 1 year of SCIT treatment, the validation cohort was divided into 2 groups: "effective" and "ineffective." For the treatment to be considered "effective," a >30% reduction in symptom and medication score was required. In the effective group, baseline IL-4 levels were higher than in the ineffective group, and serum IL-4 demonstrated a strong ability to predict SCIT efficacy. When a ROC curve was done for IL-4's potential as a biomarker for SCIT efficacy, the calculated area under the curve (AUC) was 0.840 with a $P < 0.001$.

Eotaxin, a CC chemokine ligand, is a key mediator of eosinophil migration, activation, and maturity and is known to facilitate local and systemic eosinophil recruitment in many inflammatory diseases [102-104]. Serum eotaxin levels were elevated in pediatric HDM-induced AR patients who responded to SCIT, suggesting eotaxin may be involved with SCIT mechanisms

[101]. Furthermore, Xie et al. [101] validated the use of eotaxin as a biomarker capable of predicting AIT efficacy (AUC = 0.681, P = 0.006). Type 2 inflammation and eosinophilia are key components of AR pathogenesis and may be the basis for the therapeutic mechanism of SCIT [105-107]. It is known that AIT regulates Th1/Th2 response balance and attenuates eosinophilic inflammation in AR, and upregulation of Th1 Bregs and Tregs has been considered prognostic [108, 109].

8. Conclusion

The benefits of AIT for treatment of some of the most common immunologic diseases in the world like AA and AR are evident. Eosinophilic inflammation is a cardinal feature of the allergic process; consequently, when using AIT as treatment it is imperative to find biomarkers that accurately and reliably represent the underlying inflammation responsible for many of the short- and long-term debilitating effects of allergic diseases. Eosinophils have been used in the past, but their mere presence gives little information on their activity. Eosinophil granule proteins like EDN and ECP are easily obtainable and accurately reflect the eosinophil activity so commonly found in allergic diseases. It is imperative clinicians use validated biomarkers for diagnosis, treatment, and monitoring of allergic disease. A biomarker such as EDN can be used to identify patients that would benefit most from treatments like AIT, thus optimizing critically scarce health funding and minimizing the ill effects of using treatments that don't work.

Conflicts of interest

The authors have no financial conflicts of interest.

Authors contributions

Chang-Keun Kim: conception of study, writing of manuscript, revisions, approval of final draft. Zak Callaway: conception of study, writing of manuscript, revisions, approval of final draft. Jin-Sung Park: writing of manuscript and approval of final draft. Ruby Pawankar: writing of manuscript and approval of final draft. Takao Fujisawa: writing of manuscript and approval of final draft.

References

1. Papadopoulos NG, Aggelides X, Stamataki S, Prokopakis E, Katotomichelakis M, Xepapadaki P. New concepts in pediatric rhinitis. Pediatr Allergy Immunol 2021;32:635-46.
2. Schuler Iv CF, Montejo JM. Allergic rhinitis in children and adolescents. Immunol Allergy Clin North Am 2021;41:613-25.
3. Wang XD, Zheng M, Lou HF, Wang CS, Zhang Y, Bo MY, Ge SQ, Zhang N, Zhang L, Bachert C. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. Allergy 2016;71:1170-80.
4. Navarro A, Valero A, Julia B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. J Investig Allergol Clin Immunol 2008;18:233-38.
5. Liu W, Zeng Q, He C, Chen R, Tang Y, Yan S, Luo X, Luo R. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. Pediatr Allergy Immunol 2021;32:86-91.
6. Sultesz M, Horvath A, Molnar D, Katona G, Mezei G, Hirschberg A, Gálffy G. Prevalence of allergic rhinitis, related comorbidities and risk factors in schoolchildren. Allergy Asthma Clin Immunol 2020;16:98.
7. Yavuz ST, Oksel Karakus C, Custovic A, Kalayci O. Four subtypes of childhood allergic rhinitis identified by latent class analysis. Pediatr Allergy Immunol 2021;32:1691-99.
8. Tsabouri S, Mavroudi A, Feketea G, Guibas GV. Subcutaneous and sublingual immunotherapy in allergic asthma in children. Front Pediatr 2017;5:82.
9. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group. Allergic rhinitis and its impact on asthma. ARIA. WHO initiative. J Allergy Clin Immunol 2001;108:S147-S334.
10. Nelson HS. Immunotherapy for inhalant allergens. In: Adkinson Jr NF, Bochner BS, Busse WW, Holgate ST, Lemanske Jr, RF, Simons FER, editors. Middleton's allergy. 7th ed. Atlanta: Elsevier; 2008. p. 1657-77.
11. Atkins D, Leung DYM. Principles of treatment of allergic disease. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007. p. 942-49.
12. Harmanci K, Razi CH, Toyran M, Kanmaz G, Cengizlier MR. Evaluation of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. Asian Pac J Allergy Immunol 2010;28:7-13.
13. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007;17:85-91.
14. Creticos P, Esch R, Couroux P, Gentile D, D'Angelo P, Whitlow B, Alexander M, Coyne TC. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitiis. J Allergy Clin Immunol 2014;133:751-58.
15. Cox L, Li J, Lockey F, Nelson HS. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007;120:S25-S85.
16. Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, Varga EM, Valovirta E, Moreno C, Malling HJ, Alvarez-Cuesta E, Durham S, Demoly P. European Academy of Allergy and Clinical Immunology task force report on "dose-response relationship in allergen-specific immunotherapy". Allergy 2011;66:1345-59.
17. Senti G, Freiburghause AU, Larenas-Linnemann D, Hoffmann HJ, Patterson AM, Klimek L, et al. Intralymphatic immunotherapy: update and unmet needs. Int Arch Allergy Immunol 2019;178:141-49.
18. Wang W, Wang X, Wang H, Wang X. Evaluation of safety, efficacy, and compliance of intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Int Arch Allergy Immunol 2023;184:754-66.
19. Venge P, Bystrom J, Carlson M, Hakansson L, Karawacjzyk M, Peterson C, Sevéus L, Trulson A. Eosinophil cationic protein (ECP): molecular and biological properties and the use of ECP as a marker of eosinophil activiation in disease. Clin Exp Allergy 1999;29:1172-86.
20. Saitoh O, Kojima K, Sugi K, Matsuse R, Uchida K, Tabata K, Nakagawa K, Kayazawa M, Hirata I, Katsu K. Fecal eosinophil granule-derived proteins reflect disease activity in inflammatory bowel disease. Am J Gastroenterol 1999;94:3513-20.
21. Rutten B, Young S, Rhedin M, Olsson M, Kurian N, Syed F, Beech A, Fidock M, Newbold P, Singh D, Platt A, Hughes G. Eosinophil-derived neurotoxin: a biologically and analytically attractive asthma biomarker. PLoS One 2021;16:e0246627.
22. Kim CK, Kang DY, Callaway Z, Kim KS, Kwon EM, Yamaide F, Nakano T, Suzuki Y, Mashimo Y, Hata A, Okamoto Y, Shimojo N. Increase in eosinophil-derived neurotoxin level in school children with allergic disease. Asia Pac Allergy 2022;12:e25.
23. Kim CK, Callaway Z, Pawankar R. Eosinophil granule proteins as a biomarker in managing asthma and allergies. Asia Pac Allergy 2023;13:66-71.
24. Lee Y, Lee JH, Yang EM, Kwon EM, Jung CG, Kim SC, Choi Y, Cho YS, Kim CK, Park HS. Serum levels of eosinophil-derived neurotoxin: a biomarker for asthma severity in adult asthma. Allergy Asthma Immunol Res 2019;11:394-405.
25. Piippo-Savolainen E, Korppi M. Wheezy babies-wheezy adults: review on long-term outcome until adulthood after early childhood wheezing. Acta Paediatr 2008;97:5-11.
26. Luo G, Nkoy FL, Stone BL, Schmick D, Johnson MD. A systematic review of predictive models for asthma development in children. BMC Med Inform Decis Mak 2015;15:99.
27. Kim CK, Callaway Z, Gern JE. Viral infections and associated factors that promote acute exacerbations of asthma. Allergy Asthma Immunol Res 2018;10:12-17.
28. Lloyd CM, Hawrylowicz CM. Regulatory T cells in asthma. Immunity 2009;31:438-49.
29. Smith M, Tourigny MR, Noakes P, Thornton CA, Tulic MK, Prescott SL. Children with evidence of reduced neonatal CD4(+)CD25(+) CD127(lo/-) regulatory T cell funciton. J Allergy Clin Immunol 2008;121:1460-6-66.e1.
30. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, Gern JE, Gerritsen J, Hamelmann E, Helms PJ, Lemanske RF, Martinez F, Pedersen S, Renz H, Sampson H, von Mutius E, Wahn U, Holt PG.

Early identification of atopy in the prediction of persistent asthma in children. Lancet 2008;372:1100-106.
31. Licari A, Castagnoli R, Denicolo CF, Rossini L, Marseglia A, Marseglia GL. The nose and lung: united airway disease? Front Pediatr 2017;5:44.
32. Wang Y, McCusker CT. Interleukin-13-dependent bronchial hyperresponsiveness following isolated upper-airway allergen challenge in a murine model of allergic rhinitis and asthma. Clin Exp Allergy 2005;35:1104-11.
33. Braunstahl G, Overbeek SE, Keinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001;107:469-76.
34. Martin-Orozco E, Norte-Munoz M, Martinez-Garcia J. Regulatory T cells in allergy and asthma. Front Pediatr 2017;5:117.
35. Caffarelli C, Priftis K, Mastrorilli C, Garcia-Marcos L. Editorial: the parallel march of asthma and allergy in childhood: a multi-perspective approach. Front Pediatr 2018;6:135.
36. Caggiano S, Cutrera R, Di Marco A, Turchetta A. Exercise-induced bronchospasm and allergy. Front Pediatr 2017;5:131.
37. Moustaki M, Loukou I, Tsabouri S, Douros K. The role of sensitization to allergen in asthma prediction and prevention. Front Pediatr 2017;5:166.
38. Nelson HS. The evolution of allergy immunotherapy. Ann Allergy Asthma Immunol 2021;126:357-66.
39. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and imune tolerance to allergens. World Allergy Organ J 2015;8:17.
40. Eberlein-Konig B, Ullmann S, Thomas P, Przybilla B. Tryptase and histamine release due to a sting challenge in bee venom allergic patients treated successfully or unsuccessfully with hyposensitization. Clin Exp Allergy 1995;25:704-12.
41. Moon TC, Befus AD, Kulka M. Mast cell mediators: their differential release and the secretory pathways involved. Front Immunol 2014;5:569.
42. Plewako H, Wosinska K, Arvidsson M, Bjorkander J, Skov PS, Hakansson L, Rak S. Basophil interleukin 4 and interleukin 13 production is suppressed during the early phase of rush immunotherapy. Int Arch Alergy Immunol 2006;141:346-53.
43. Shamji MH, Francis JN, Wurtzen PA, Lund K, Durham SR, Till SJ. Cell-free detection of allergen-IgE cross-linking with immobilized phase CD23: inhibition by blocking antibody responses after imunotherapy. J Allergy Clin Immunol 2013;132:1003-5.e1.
44. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, Bohle B, Chaker AM, Till SJ, Valenta R, Poulsen LK, Calderon MA, Demoly P, Pfaar O, Jacobsen L, Durham SR, Schmidt-Weber CB. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy 2017;72:1156-73.
45. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol 1982;70:261-71.
46. James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, Jacobson MR, Kimber I, Till SJ, Durham SR. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. J Allergy Clin Immunol 2011;127:509-16.e1.
47. Renand A, Archila LD, McGinty J, Wambre E, Robinson D, Hales BJ, Thomas WR, Kwok WW. Chronic cat allergen exposure induces a TH2 cell-dependent IgG4 response related to low sensitization. J Allergy Clin Immunol 2015;136:1627-35.e13.
48. Pilette C, Nouri-Aria KT, Jacobson MR, Wilcock LK, Detry B, Walker SM, Francis JN, Durham SR. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol 2007;178:4658-66.
49. Rispens T, Ooijevaar-de Heer P, Bende O, Aalberse RC. Mechanisms of immunoglobulin G4 fab-arm exchange. J Am Chem Soc 2011;133:10302-311.
50. Wurtzen PA, Lund G, Lund K, Arvidsson M, Rak S, Ipsen H. A double-blind placebo-controlled birch allergy vaccination study II: correlation between inhibition of IgE binding, histamine release and facilitated allergen presentation. Clin Exp Allergy 2008;38:1290-301.
51. Burton OT, Tamayo JM, Stranks AJ, Koleoglou KJ, Oettgen HC. Allergen-specific IgG antibody signaling through FcγRIIb promotes food tolerance. J Allergy Clin Immunol 2018;141:189-201.e3.
52. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, Scadding GK, Andersen JS, Riis B, Dahl R. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 2010;125:131-8.e1.
53. Furin MJ, Norman PS, Creticos PS, Proud D, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 1991;88:27-32.
54. Scadding GW, Eifan AO, Lao-Araya M, Penagos M, Poon SY, Steveling E, Yan R, Switzer A, Phippard D, Togias A, Shamji MH, Durham SR. Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. Allergy 2015;70:689-96.
55. Amadee R, Shamji MH, Harris KM, Qin T, Wambre E, Scadding GW, Wurtzen PA, Till SJ, Togias A, Nepom GT, Kwok WW, Durham SR. Synchronous immune alterations mirror clinical response during allergen immunotherapy. J Allergy Clin Immunol 2018;141:1750-60.
56. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, Canonica GW. Randomised controlled trial of local allergoid immunotherapy on allergic inflamation in mite-induced rhinoconjunctivitis. Lancet 1999;351:629-32.
57. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2007;119:780-91.
58. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. Clin Exp Allergy 2004;34:891-96.
59. Ciprandi G, Cirillo I, Vizzaccaro A, Monardo M, Tosca MA. Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity. Respir Med 2005;99:1606-12.
60. Ciprandi G, Cirillo I, Klersy C, Marseglia GL, Vizzaccaro A, Pallestrini E, Tosca M. Role of FEF 25-75 as an early marker of broncial impairment in patients with seasonal allergic rhinitis. Am J Rhinol 2006;20:641-47.
61. Wilson DR, Irani AM, Walker SM, Jacobson MR, Mackay IS, Schwartz LB, Durham SR. Grass pollen immunotherapy inhibits seasonal increases in basophils and eosinophils in the nasal epithelium. Clin Exp Allergy 2002;31:1705-13.
62. Polosa R, Gotti FL, Mangano G, Paolino G, Mastruzzo C, Vancheri C, Lisitano N, Crimi N. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy 2004;59:1224-28.
63. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol 2006;117:263-68.
64. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, Bousquet J, Calderón M, Compalati E, Durham SR, van Wijk RG, Larenas-Linnemann D, Nelson H, Passalacqua G, Pfaar O, Rosário N, Ryan D, Rosenwasser L, Schmid-Grendelmeier P, Senna G, Valovirta E, Van Bever H, Vichyanond P, Wahn U, Yusuf O. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014;7:6.
65. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, Ryan D, Agache I, Ansotegui IJ, Arasi S, Du Toit G, Fernandez-Rivas M, Geerth van Wijk R, Jutel M, Kleine-Tebbe J, Lau S, Matricardi PM, Pajno GB, Papadopoulos NG, Penagos M, Santos AF, Sturm GJ, Timmermans F, van Ree R, Varga E-M, Wahn U, Kristiansen M, Dhami S, Sheikh A, Muraro A. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 2017;28:728-45.
66. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, Wurtzen PA, Andersen JS, Tholstrup B, Riis B, Dahl R. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129:717-25.e5.
67. Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol 2007;120:707-13.
68. Rolland JM, Gardner LM, O'Hehir RE. Functional regulatory T cells and allergen imunotherapy. Curr Opin Allergy Clin Immunol 2010;10:559-66.
69. Shamji MH, Layhadi JA, Sharif H, Penagos M, Durham SR. Immunological responses and biomarkers for allergen-specific immunotherapy against inhaled allergens. J Allergy Clin Immunol Pract 2021;9:1769-78.
70. Rosser EC, Mauri C. Regulatory B cells: origin, phenotype, and function. Immunity 2015;42:607-12.
71. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, Klotz F, Ebner H, Kraft D, Scheiner O. Immunological changes during specific immunotherapy of grass pollen allergy: reduced

lymphoproliferative responses to allergen and shit from TH2 to TH1 in T-cell clones specific for ph1 p 1, a major grass pollen allergen. Clin Exp Allergy 1997;27:1007-15.
72. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, Kay AB, Hamid QA. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol 1996;97:1356-65.
73. Lawrence MG, Steinke JW, Borish L. Basic science for the clinician: mechanisms of sublingual and subcutaneous immunotherapy. Ann Allergy Asthma Immunol 2016;117:138-42.
74. Huang FL, Liao EC, Yu SJ. House dust mite allergy: its innate immune response and immunotherapy. Immunobiology 2018;223:300-02.
75. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, Halken S, Larenas-Linnemann D, Pawankar R, Pitsios C, Sheikh A, Worm M, Arasi S, Calderon MA, Cingi C, Dhami S, Fauquert JL, Hamelmann E, Hellings P, Jacobsen L, Knol EF, Lin SY, Maggina P, Mösges R, Oude Elberink JNG, Pajno GB, Pastorello EA, Penagos M, Rotiroti G, Schmidt-Weber CB, Timmermans F, Tsilochristou O, Varga E-M, Wilkinson JN, Williams A, Zhang L, Agache I, Angier E, Fernandez-Rivas M, Jutel M, Lau S, van Ree R, Ryan D, Sturm GJ, Muraro A. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy 2018;73:765-98.
76. De Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. Thorax 2012;67:582-87.
77. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, Muraro A, Roberts G, Akdis CA, Bonini M, Cavkaytar O, Flood B, Gajdanowicz P, Izuhara K, Kalayci O, Mosges R, Palomares O, Pfaar O, Smolinska S, Sokolowska M, Asaria M, Netuveli G, Zaman H, Akhlaq A, Sheikh A. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy 2017;72:1825-48.
78. Wilson DR, Nouri-Aria KT, Walker SM, Pajno B, O'Brien F, Jaconbson MR, Mackay IS, Durham SR. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. J Allergy Clin Immunol 2001;107:971-76.
79. 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:e43.
80. Nagata M, Nakagome K. Allergen immunotherapy in asthma: current status and future perspectives. Allergol Int 2010;59:15-19.
81. Hakansson L, Heinrich C, Rak S, Venge P. Priming of eosinophil adhesion in patients with birch pollen allergy during pollen season: effect of immunotherapy. J Allergy Clin Immunol 1997;99:551-62.
82. Nagata M, Saito K, Kikuchi I, Tabe K, Hagiwara K, Kanazawa M, Sakamoto Y. Immunotherapy attenuates eosinophil transendothelial migration induced by the supernatuants of antigen-stimulated mononuclear cells from atopic asthmatics. Int Arch Allergy Immunol 2004;134:21-24.
83. Marogna M, Spadolini I, Massolo A, Berra D, Zanon P, Chiodini E, Canonica GW, Passalacqua G. Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. Ann Allergy Asthma Immunol 2009;102:69-75.
84. Small P, Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol 2011;7:S3.
85. Sonawane R, Ahire N, Patil S, Korde A. Study of eosinophil count in nasal and blood smear in allergic respiratory diseases. MVP J Med Sci 2016;3:44-51.
86. Sharma M, Khaitan T, Raman S, Jain R, Kabiraj A. Determination of serum IgE and eosiniophils as a diagnostic indicator in allergic rhinitis. Indian J Otolaryngol Head Neck Surg 2019;71:S1957-61.
87. Brakhas SA, Atia MR, Aziz YJ, Al-Sharqi SAH. Study of total IgE levels and eosinophil count according to age and gender in patients with allergic rhinitis. World J Pharm Res 2015;4:295-303.
88. Venge P. Monitoring the allergic inflammation. Allergy 2004; 59:26-32.
89. Chen J, Zhou N, Huang Z. [The changes of serumal eosinophil cationic protein of patients will allergic rhinitis with specific imunotherapy]. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;25:347-48.
90. Kim CK, Callaway Z, Kim DW, Kita H. Eosinophil degranulation is more important than eosinophilia in identifying asthma in chronic cough. J Asthma 2011;48:994-1000.
91. Kim CK, Callaway Z, Fletcher R, Koh YY. Eosinophil-derived neurotoxin in childhood asthma: correlation with disease severity. J Asthma 2010;47:568-73.
92. Gomulka K, Medrala W. Serum levels of vascular endothelial growth factor, platelet activating factor and eosinophil-derived neurotoxin in chronic spontaneous urticaria -- a pilot study in adult patients. Int J Mol Sci 2022;23:9631.
93. Tsuda T, Maeda Y, Nishide M, Koyama S, Hayama Y, Nojima S, Takamatsu H, Okuzaki D, Kinehara Y, Kato Y, Nakatani T, Obata S, Akazawa H, Shikina T, Takeda K, Hayama M, Inohara H, Kumanogoh A. Eosinophil-derived neurotoxin enhances airway remodeling in eosinophilic chronic rhinosinusitis and correlates with disease severity. Int Immunol 2019;31:33-40.
94. Gomulka K, Wojcik E, Szepietowski JC. Serum levels of eosinophil-derived neurotoxin, platelet-activating factor and vascular endothelial growth factor in adult patients with atopic dermatitis -- a pilot study. Biomedicines 2022;10:3109.
95. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, Nelson H, Akdis CA. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013;131:1288-96.e3.
96. Calderon MA, Casale T, Cox L, Akdis CA, Burks AW, Nelson HS, Jutel M, Demoly P. Allergen immunotherapy: a new semantic framework from the European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL consensus report. Allergy 2013;68:825-28.
97. Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK, Staple SQ, Aalberse RC, Till SJ, Durham SR. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol 2004;172:3252-59.
98. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, Ditta V, Lo Bianco C, Leto-Barone MS, D'Alcamo A, Di Fede G, Rini GB, Ditto AM. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol 2009;123:1103-10-10.e1.
99. Li Q, Li M, Yue W, Zhou J, Li R, Lin J, Li Y. Predictive factors for clinical response to allergy immunotherapy in children with asthma and rhinitis. Int Arch Allergy Immunol 2014;164:210-17.
100. Fujimura T, Yonekura , Horiguchi S, Taniguchi Y, Saito A, Yasueda H, Inamine A, Nakayama T, Takemori T, Taniguchi M, Sakaguchi M, Okamoto Y. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. Clin Immunol 2011;139:65-74.
101. Xie S, Fan R, Tang Q, Cai X, Zhang H, Wang F, Xie S, Gao K, Zhang J, Xie Z, Jiang W. 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 Imunol 2022;12:805404.
102. Polosukhina D, Singh K, Asim M, Barry DP, Allaman MM, Hardbower DM, Piazuelo MB, Washington MK, Gobert AP, Wilson KT, Coburn LA. CCL11 exacerbates colitis and inflammation-associated colon tumorigenesis. Oncogene 2021;40:6540-46.
103. Wakabayashi K, Isozaki T, Tsubokura Y, Fukuse S, Kasama T. Eotaxin-1/CCL11 is involved in cell migration in rhematoid arthritis. Sci Rep 2021;11:7937.
104. Zhu WX, Chen Y, Liu DG, Yu GY. Eosinophilic sialodochitis: a type of chronic obstructive sialadenitis related to allergy. Laryngoscope 2021;131:E800-06.
105. Zissler UM, Schmidt-Weber CB. Predicting success of allergen-specific immunotherapy. Front Immunol 2020;11:1826.
106. Celebi Sozener Z, Mungan D, Cevhertas L, Ogulur I, Akdis M, Akdis C. Tolerance mechanisms in allergen immunotherapy. Curr Opin Allergy Clin Immunol 2020;20:591-601.
107. Han X, Krempski JW, Nadeau K. Advances and novel developments in mechanisms of allergic inflammation. Allergy 2020;75:3100-11.
108. Berings M, Karaaslan C, Altunbulakli C, Gevaert P, Akdis M, Bachert C, Akdis CA. Advances and highlights in allergen immunotherapy: on the way to sustained clinical and immunologic tolerance. J Allergy Clin Immunol 2017;140:1250-67.
109. Breiteneder H, Peng YQ, Agache I, Diamant Z, Eiwegger T, Fokkens WJ, Traidl-Hoffmann C, Nadeau K, O'Hehir RE, O'Mahony L, Pfaar O, Torres MJ, Wang D-Y, Zhang L, Akdis CA. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. Allergy 2020;75:3039-68.