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Current Review

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Mechanisms and biomarkers of successful allergen-specific immunotherapy

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ABSTRACT

Allergen-specific immunotherapy (AIT) is considered the only curative treatment for allergic diseases mediated by immunoglobulin E (IgE). Currently, the route of administration depends both on the different types of causal allergens and on its effectiveness and safety profile. Several studies have reported the mechanisms and changes in humoral and cellular response underlying AIT; however, the full picture remains unknown. Knowledge of who can benefit from this type of treatment is urgently needed due to the patient safety risks and costs of AIT. *In vivo* or *in vitro* biomarkers have become a strategy to predict clinical outcomes in precision medicine. There are currently no standardized biomarkers that allow determining successful responses to AIT, however, some studies have found differences between responders and nonresponders. In addition, different candidates have been postulated that may have the potential to become biomarkers. In this review, we aim to summarize the findings to date related to biomarkers in different IgE-mediated allergic diseases (respiratory, food, and venom allergy) with the potential to define who will benefit from AIT.

Keywords: Allergen-specific immunotherapy; Allergy; Biomarkers; IgE; Regulatory T cells; regulatory B cells

INTRODUCTION

Allergen-specific immunotherapy (AIT) is the mainstay treatment that can alter the course of allergic diseases, inducing desensitization and/or tolerance by altering the immunological response to allergens. Although AIT has been used in clinical practice for more than a century, knowledge of the mechanisms underlying the clinical response to this type of treatment was largely gained during the past 2 to 3 decades.

The principle of AIT consists of administration of the culprit allergen at high doses to allergic patients with the aim of inducing tolerance to the allergen [1]. Although AIT is a successful and cost-effective way to treat allergies [2-4], there is undoubtedly room for improvement.

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AIT protocols typically last several years to complete and, as a result, are characterized by low treatment adherence and a high rate of drop-out patients [5]. Therefore, the identification of objective biomarkers with predictive value for the response to treatment is urgently needed. This would allow clinicians to decide early during the treatment which patients are most likely to benefit from the continuation of AIT. Moreover, adjustments in allergen preparations (including the addition of tolerogenic adjuvants and structural modification of allergens) and routes of application are being developed, to reduce the duration of the treatment and increase its effectiveness [6].

In this review, we will provide a brief overview of the different types of AIT that are currently in use in clinical practice as well as novel developments in the field of AIT. Moreover, the basic immunological mechanisms that are at play in the response to AIT will be discussed in order to provide insight into the functional role of the potential biomarkers that are being studied in relation to the outcome of AIT. Then we provide an overview of the biomarker candidates that have been reported in AIT for respiratory allergies (allergic rhinitis, AR), food allergy, and venom allergy.

OVERVIEW OF AIT FEATURES

Allergen manufacturing

Since 1911, immunotherapy based on allergen extracts for the treatment of allergies has been used in clinical practice [7]. These extracts are manufactured from one or more natural allergen sources including pollens, arthropods (mites), animal sources, and venom from Hymenoptera species, and related allergens sources are often used as homologous mixtures [8, 9]. Manufacturing aspects in the production of extracts such as purity, quality, representativeness of the components as well as their storage are important to ensure effectiveness and safety in AIT [8, 10]. Differences in the production of natural allergen extracts frequently occur and this heterogeneity in quality could generate different findings in the clinical and molecular outcomes of AIT [11]. Currently, there is an urgent demand to explore innovative methods for allergen preparation, which has now become possible due to the development of recombinant allergens as a result of the progress that has been made in allergen identification and chemical modifications of allergenic extracts (known as allergoids) which improve the safety profile through hypoallergenic preparations [12-18].

Routes of application for AIT

AIT can be applied through multiple routes depending on the type of allergic disease and the source of sensitization [19]. Likewise, the selected application route leads to particularities in the antigen-presentation process, reflected in differences in efficacy and safety [20]. Subcutaneous, sublingual, and recently oral immunotherapy (OIT) have received U.S. Food and Drug Administration (FDA) approval for use in the treatment of different allergic diseases, however, experimental approaches with other routes of administration such as epicutaneous, intradermal, intralymphatic and local nasal have shown potential as alternatives [21].

Subcutaneous immunotherapy (SCIT) is the oldest and most frequently used application route of AIT, which has been employed for more than a century [7]. SCIT is regarded as a safe and valid therapy for several allergic diseases including venom allergy, AR, and allergic asthma [19]. While adverse reactions occur in up to 71% of patients, severe side effects are

rare [22]. In addition to SCIT, alternative administration routes of AIT are being used and developed to improve the safety and effectiveness of AIT.

Sublingual immunotherapy (SLIT) was approved in 1998 by World Health Organization as an alternative treatment for allergic diseases induced by inhalant allergens [23, 24]. SLIT usually places allergen-containing drops or soluble tablets with extracted allergens under the tongue for a few minutes before being swallowed [25].

OIT could become another needle-free alternative method to treat food allergies by daily swallowing tablets or powders with gradually increasing doses of food allergens, such as cow's milk (CM), egg, and peanuts [26, 27]. FDA authorized the first OIT drug for treating peanut allergies in 2020 [26]. Unlike SLIT, the release of the allergen occurs in the digestive tract where there is a large amount of gut-associated lymphoid tissue [19].

Recently, epicutaneous immunotherapy (EPIT) received increased interest after a trial performed by Senti et al. [28] in 2009, which suggested that EPIT could become a promising method for allergic diseases. EPIT involves the application of a noninvasive and painless patch containing an allergen extract to the skin, which avoids the ingestion of oral allergens improving the safety profile [29-31].

Intralymphatic immunotherapy (ILIT) is a relatively novel AIT application route, which is designed to have a more robust and rapid immune response by injecting a low dose of allergen directly into lymph nodes compared with intramuscular injection [32]. Unlike years of treatment for SCIT, ILIT only needs 3 times of ultrasound-guided injections spaced one month apart, which allows for shortening the duration period of the treatment [33]. However, up to now, there are few studies on ILIT, and its safety and efficacy need to be further demonstrated.

MECHANISMS UNDERPINNING SUCCESSFUL AIT

Allergic sensitization is initiated when allergens are captured by antigen-presenting cells (APCs) in the skin, respiratory or gastrointestinal mucosa. Skin and mucosal epithelial cells produce alarmins such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin as defense mechanisms against allergens. Allergens are processed into peptides and presented by APCs to naïve $CD4^+$ T cells, driving the differentiation into T helper (Th) 2 cells capable of producing type 2 cytokines including IL-4, IL-5, IL-9, and IL-13 [34]. B cells are triggered to undergo IgE class-switching and differentiate into plasma cells secreting allergen-specific IgE (sIgE) antibodies that bind to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Subsequent exposure to the same allergen triggers cross-linking of IgE-FcεRI complexes, resulting in the secretion of histamine, leukotrienes, cytokines, and other inflammatory mediators. These mediators drive type 1 hypersensitivity responses and occasionally result in anaphylaxis. Late-phase reactions and numerous allergen exposures, conserve allergic inflammation, and can progress to tissue remodeling, fibrosis, and the chronic phase of allergic diseases [35, 36].

Successful AIT is characterized by development of clinical tolerance to the allergen. Tolerance may wane over time or could persist long-term, processes that are referred the context of food AIT as desensitization and sustained unresponsiveness (SU), respectively and has

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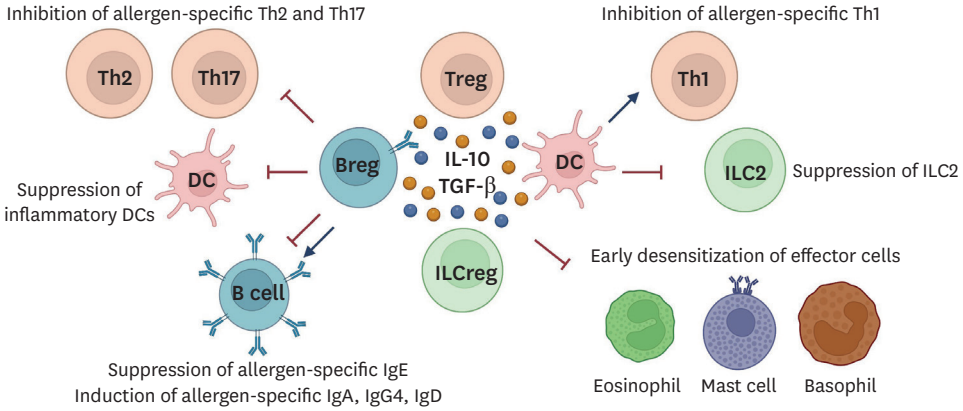

Fig. 1. Mechanisms of immune tolerance induction.
Tregs, Bregs, ILCregs, and tolerogenic DCs produce immunosuppressive cytokines such as IL-10, TGF-β, and IL-35. Tolerogenic DCs express surface molecules that suppress Th2 and Th17 cells as well as inflammatory DCs, and induce allergen-specific Tregs. Tregs suppress early desensitization of effector cells (eosinophils, mast cells, and basophils), effector Th cells (Th1, Th2, and Th17 cells), inflammatory DCs, ILC2, and allergen-sIgE. Through IL-10, TGF-β, and IL-35 cytokines production, allergen-specific IgA, IgG2, IgG4, and IgD antibodies are released and exert IgE-blocking effects. Bregs suppress effector T cells (Th2 and Th17) and induce Treg cell expansion via the release of IL-10, TGF-β, and IL-35 cytokines. Diverse surface molecules on Breg cells including BCR, PDL-1, CD39, CD73, CD80/CD86, CD40, ICOS-L, and AhR are well-expressed and suppress the inflammatory responses. In autoimmune tolerance, Bregs activate iNKT cells with suppressive function. Moreover, Bregs are also the main producer of allergen-specific IgA, IgG2, IgG4, and IgD antibodies that compete with the cross-linking of allergen-sIgE to effector cells. Tregs, regulatory T cells; Bregs, regulatory B cells; ILC, innate lymphoid cell; DC, dendritic cell; IL, interleukin; TGF, transforming growth factor; sIgE, specific IgE; iNKT, Invariant natural killer T; Ig, immunoglobulin.

been associated with Th2-gene networks reprogramming and pathways in the CD4+ T cells [37, 38]. The cellular and molecular mechanisms that underly the development of clinical tolerance in response to AIT have been elucidated to a large extent during the past decades. These mechanisms are mediated by an intricate interplay between different immune cells including mast cells, basophils, innate lymphoid cells (ILCs), dendritic cells (DCs), regulatory T cells (Tregs), and regulatory B cells (Bregs). An overview of the changes that occur in response to AIT are described below and illustrated in **Fig. 1**.

Mast cells and basophils

Mast cells and basophils play a key role in the effector phase of allergic reactions. The allergen-dependent cross-linking of the IgE bound to its high-affinity receptor (FcεRI) on mast cells and basophils initiates type I hypersensitivity reactions through the secretion of several mediators and type 2 cytokines that drive allergic inflammation. AIT induces very rapid desensitization of mast cells and basophils revealed by low responsiveness to allergens despite the high allergen-sIgE levels observed at the beginning of the treatment. However, the reduction of mast cell and basophil infiltration in the tissues and the decreased mediator release occurs in the late phase of AIT [39]. One possible mechanism is the increased production of allergen-specific IgG4 (sIgG4) and the elevated expression of the low-affinity IgG receptor (FcγRIIa and FcγRIIb) on mast cells and basophils. IgG-mediated inhibition also reduces type 2 cytokine secreting from mast cells and basophils [40].

Another mechanism is the quick upregulation of histamine receptor 2, which displays an inhibitory effect on FcεRI-mediated activation and degranulation of basophils. The decrease in basophil responsiveness was demonstrated during many AIT studies [41]. Importantly, the evaluation of basophil responses before, during, and after AIT can help to identify transient desensitization or SU.

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Regulatory T cells

Induction and maintenance of peripheral tolerance to allergens is influenced by the balance between Tregs and effector T cells. Peripheral T-cell tolerance is defined by an increase of Treg cells that can be induced during AIT and a shift of Th2 cell responses to Th1 [39]. Allergen-specific Treg cells can be classified into thymic or natural Treg cells and inducible Treg cells including FOXP3-expressing iTreg cells, IL-10-secreting Tr1 cells, and transforming growth factor (TGF)-β-producing Th3 cells [42, 43]. The suppression of different effector cells by Treg cells is required to completely establish cell-mediated tolerance. Treg cells instituted during and after AIT suppress effector cell function and facilitated the production of blocking antibodies by B cells [35]. Four major mechanisms of Treg cell-mediated suppression have been described: (1) secretion of inhibitory cytokines such as IL-10, TGF-β, and IL-35; (2) metabolic disruption mechanisms; (3) mechanisms involving surface molecules including programmed death 1, cytotoxic T-lymphocyte antigen 4, lymphocyte-activation gene 3, or inducible costimulatory molecule (ICOS); and (4) cytolysis [36, 39, 44]. Increased frequencies of allergen-specific Treg cells and a decrease in Th2 frequencies are associated with natural tolerance in beekeepers during allergen exposure in beekeeping season and AIT-treated allergic patients, respectively [45]. *Ex vivo* analysis of human peripheral blood mononuclear cells (PBMCs) showed that house dust mite (HDM) AIT leads to an increase of functional allergen-specific Tregs and a decrease of allergen-specific immunoglobulin-like transcript (ILT) 3 Treg cells, which display impaired suppressive function [46]. AIT induces long-term Treg cell development by influencing epigenetic changes (hypomethylation) in *FOXP3* regions [47]. IL-10-producing Tregs were induced after birch and grass pollen AIT. In addition, IL-35-inducible Tregs has been identified as a subset of iTregs with the capacity to reduce Th2 inflammation, T-cell proliferation and cytokines produced by ILC2s [48, 49]. Recent studies have demonstrated that successful SCIT increases IL-35 and IL-35-induced Treg cell in blood [39]. All these studies have demonstrated the critical role of the tolerance induced by allergen-specific Treg cells in successful AIT in humans.

Regulatory B Cells

Although B cells play a major role in the immune system through the production of specific antibodies, recent evidence clearly showed that B cells can also regulate immune responses via alternative mechanisms beyond antibody production [50]. Breg cells play a crucial role in producing the immune suppressive cytokines including IL-10, IL-35, and TGF-β, and expressing immune suppressive receptors such as cell membrane-bound molecules such as B cell receptor (BCR), PDL-1, CD39, CD73, CD80/CD86, CD40, inducible costimulatory ligand (ICOS-L), and aryl-hydrocarbon receptor (AhR) [51]. Breg cells can be triggered by several factors, including inflammatory cytokines such as IL-6, IL-1b, and interferon (IFN)-α, microbial compounds such as TLR4 or TLR9 ligands, along with CD40 ligation [52]. During AIT, IL-10–secreting B regulatory 1 (Br1) cells specific to bee-venom allergen phospholipase A_2 show increased frequencies and are skewed toward IgG4 production [53]. IL-10$^+$Br1 cells increased their frequency in allergic patients receiving AIT and naturally exposed to allergen individuals [54]. Furthermore, HDM allergic patients treated with AIT showed significantly increased frequencies of *Dermatophagoides pteronyssinus* (Der P) 1-specific B cells, plasmablasts, and IL-10$^+$IL-1RA$^+$ Breg cells [46]. Thus, Breg cells appear to play an important role in achieving immune tolerance during AIT.

Innate lymphoid cells

ILCs are a relatively recently discovered cell type of the innate immune system. These cells are classified into 2 major subsets; cytotoxic and noncytotoxic (helper) ILCs. The cytotoxic

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ILCs compose of NK cells that display functions of $CD8^+$ cytotoxic T cells and lymphoid tissue inducer cells that are involved in secondary lymphoid structures development. The helper ILCs have been consequently identified into 3 different phenotypes: group 1 ILCs (ILC1s), group 2 ILCs (ILC2s), and group 3 ILCs (ILC3s). These 3 different subsets resemble the functions of Th1, Th2, and Th17 cells, respectively. Interestingly, new discoveries of IL-10–producing ILCs and retinoic acid-mediated pathway of IL-10-producing ILC2s induction has shown the immune regulatory properties of these cells [55, 56]. During the course of AIT, a subset of ILC2 cells regained the capacity to produce IL-10 in grass pollen sublingual treated-patients, indicating that $IL\text{-}10^+$ ILC2s may have disease-regulating effects in AIT [57].

Dendritic cells

DCs are APCs with the dual capacity to induce and preserve allergic inflammation or tolerance. DCs play a major role during the course of AIT. An increase in plasmacytoid DCs, which is a DC subset involved in the induction of Treg cells and oral tolerance is observed in AIT [58, 59]. In addition, reduced frequencies of $CD1c^+$ conventional DCs (cDCs), which support Th2 responses in allergic patients, were also observed after AIT [58]. In mice, $CD11b^+$ cDCs and macrophages transport sublingual allergens to lymph nodes and induce allergen-specific Tregs [39, 60]. Tolerogenic DCs represent a heterogeneous population with an immature or mature phenotype that displays an increased capacity to produce IL-10. Allergoid-mannan conjugates generate tolerogenic IL-10-producing DCs and reprogram monocytes and macrophages into tolerogenic phenotypes [61-63]. Similarly, a nano-vaccine was produced by coupling PGLA-encapsulated ovalbumin (OVA) with mannan induced In vitro IL-10-producing DCs that generated Tregs [64]. Cannabinoids also induce tolerogenic DCs able to generate Tregs by mechanisms depending on autophagy and metabolic reprogramming [65]. Another *in vitro* study showed the capacity of IL-27 produced by DCs to suppress grass pollen-stimulated PBMC proliferation. Interestingly, allergic airway inflammation in mice highlighted the important role of IL-10 signaling in DCs to induce allergen-specific tolerance [66].

Allergen-specific antibodies

The secretion of immunoregulatory cytokines such as IL-10 and TGF-β from previously mentioned cells types results in the suppression of Th2 responses and a shift towards the induction of allergen-specific IgA and IgG4 antibodies [67-69]. Non-IgE allergen-specific and low-affinity IgE antibodies compete with IgE for allergen binding, which at the cellular level inhibits IgE-mediated cross-linking of FcεRI on basophils and mast cells, leading to reduced mast cell and basophil activation [70-72]. While most studies only demonstrated that AIT resulted in increased production of allergen-sIgG4 antibodies, direct evidence for a protective effect against allergic inflammation mediated by allergen-sIgG4 antibodies was recently obtained. Cat-allergic individuals were treated passively immunized with 2 monoclonal anti-Fel d 1 IgG4 antibodies, which resulted in reduced clinical symptoms in response to nasal provocation [73]. Several mechanisms have been described by which IgG4 can regulate the allergic inflammatory response [70]. One of these is its bispecific nature (it has 2 different antigen-binding sites) as a result of a process called Fab-arm exchange which leads to functionally monovalent antibodies and this prevents the formation of immune complexes [74]. In addition, it has a low affinity to activate Fcγ receptors, does not bind to complement, and competes with IgE by blocking its binding to allergens [70]. Similar to IgG4, an IgE-blocking effect has been observed in IgG2. Recent data reveals both IgG2 and IgG4 are induced in patients who received SLIT against grass pollen [75].

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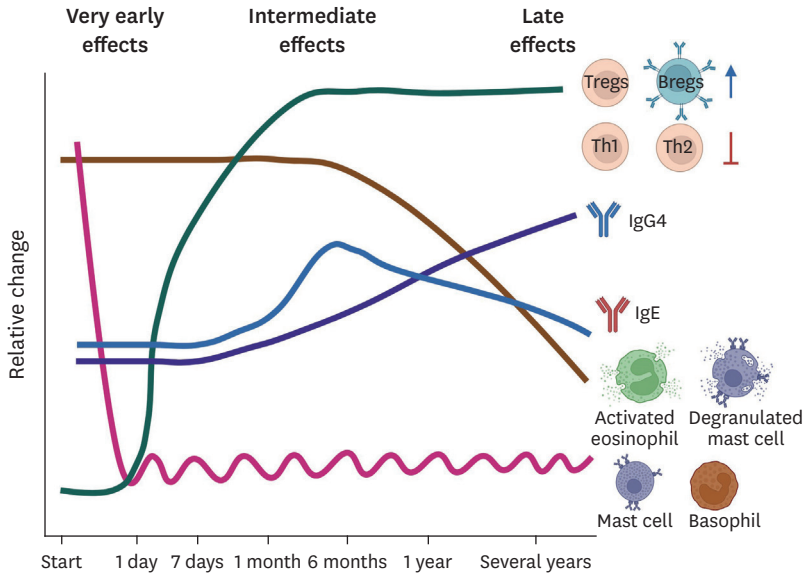

Fig. 2. Kinetics of immune tolerance induction.
AIT dominates the skewing of the T-cell population from allergen-specific Th2 to Treg cells and increases the Bregs population. Both of these cells produce immunosuppressive cytokine IL-10 and suppress allergen-sIgE secretion. In parallel, these cells also induce IgG4 production that displays anti-inflammatory properties. Overall, AIT is considered a successful treatment for allergic inflammation. AIT, allergen immunotherapy; Treg, regulatory T cell; Breg, regulatory B cell; IL, interleukin; sIgE, specific IgE; IgG4, immunoglobulin G4.

Lastly, allergen-specific IgD was recently found to increase in HDM-sensitized asthmatic patients during 30 weeks and more than 2 years of AIT [76]. In addition, allergen-specific IgD was increased in children consuming CM compared to children restricting CM from their daily diet, proposing food antigens may establish humoral IgD responses in humans [77].

The kinetics of the different cellular and humoral processes involved in immune tolerance induction are summarized in **Fig. 2**.

PREDICTIVE BIOMARKERS FOR AIT OUTCOMES IN ALLERGIC DISEASES

Asthma

Asthma is a heterogeneous disease with varying degrees of airway inflammation and response to treatment. Allergic asthma is triggered by inhaled allergens. The incidence of allergic asthma has been continuously increasing over recent decades [78]. While allergic asthma is the dominant phenotype among asthma diagnosed in childhood, allergic sensitization among asthma patients is decreased with increasing age of asthma onset [79, 80]. AIT effectively reduces symptoms and medication needs and improves the quality of life and bronchial hyperresponsiveness in allergic asthma patients [81]. Adolescents and adult asthmatics with AIT exposure are less likely to experience progression of asthma severity [82]. However, a small proportion of patients do not respond to AIT treatments [83]. AIT, either subcutaneously (SCIT) or sublingually (SLIT), with repeated administration for a minimum treatment period of 3 years achieves clinical benefits [84].

Asthma often coexists with rhinitis and is found in up to 38% of patients with AR, which is likely to result in more severe asthma [85, 86]. Global Initiative for Asthma Management and

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Prevention (GINA 2022) considers adding SLIT in adult patients with AR and sensitized to HDM with persisting asthma despite low-medium dose inhaled corticosteroids-containing therapy, provided forced expiratory volume in 1 second is >70% predicted [87]. Post-AIT treatment cessation benefits reduced AR and asthma medication use, and decreased risk of new-onset asthma medication use during treatment [88].

Several immunological biomarkers are applied to measure AIT-induced immune responses and efficacy in asthma (**Table 1**). Among immune cells as biomarkers in AIT, eosinophil, and basophil cells are inhibited by AIT treatment along with allergen-sIgE that are crucial to type 2 inflammation in the airways [89-94].

Cellular biomarkers

In an animal model of asthma, AIT treatment significantly decreased eosinophil-predominated inflammatory cells and type 2 cytokines IL-4, IL-5, and IL-9 in bronchoalveolar lavage fluid, and IL-5 and IL-13 production in lung cells [95, 96]. Periostin, a biomarker of eosinophilic airway inflammation, was reduced after AIT treatment and was correlated with improved lung function in adults with asthma sensitized to HDM [97]. Interestingly, myeloperoxidase (MPO) released from neutrophil activation was also reduced in nasal lavage fluid and blood after 3-year treatment [98, 99]. These findings indicate that AIT actively modifies type 2 airway inflammation and the release of MPO by neutrophils in allergic asthma.

The immunosuppressive role of Tregs is crucial in maintaining the homeostatic balance during dysregulated immune responses of asthma inflammation, and AIT enhances the local functional role of Treg cells. IL-10 produced by Treg cells mediates the changes in sIgE to sIgG4 seen in AIT [100]. Justicia et al. [101] identified increased levels of sIgG4 and sIgE, and IL-10 involved in mechanisms of immune tolerance was induced by AIT specific for HDM. They also found an increased baseline IL-13 in nonresponders which might serve as a biomarker to predict clinical response. In a double-blind placebo-controlled clinical study, Yukselen et al. [94] also found induction of serum IL-10 levels along with improved clinical symptoms in response to SCIT and SLIT. However, SCIT showed a more promising effect with a further decrease in sputum eosinophils and an increase in serum sIgG4. In the airway inflammation model, AIT induced $CD4^+CD25^+Foxp3^+$ Treg cells in peripheral blood and upregulated the expression of IL-10, TGF-β1, and Foxp3 in lung tissues [102]. Tian et al. [103] reported downregulation of Th17 cells in response to AIT in children with allergic asthma. The analysis revealed significant symptom improvement at 12 weeks and changes in Th17 and $CD4^+CD25^+$Treg cells at 24 weeks. Thus, treatment duration should be carefully considered to evaluate the clinical efficacy of AIT, especially when applying T-cell changes as a biomarker.

Numerous publications have described genetic and epigenetic markers as potential biomarkers of allergic asthma. A recent study by Jakwerth et al. [104] investigated epigenetic miR-associated changes in the sputum of grass pollen-allergic patients after one year of AIT. They identified miR-3935 among 4 upregulated miRs in asthmatics, and the mRNA of its target, prostaglandin EP3 receptor, was downregulated in AIT-treated individuals, which might be a therapeutic target for AIT.

Humoral biomarkers

The best-studied predictive biomarkers of humoral immunity including sIgE, sIgG1, sIgG4, and sIgE/total IgE (tIgE) ratio are used to monitor the efficacy of AIT. An initial increment in IgE levels is often observed after AIT treatment followed by a reduction in response to long-

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Table 1. Potential predictive biomarkers for outcome of AIT in asthma with or without rhinitis

Bio marker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with effectiveness to AIT	Ref
Asthma							
Der p 1-sIgG4, -induced TGF-β, and, -induced IFN-γ	SLIT SCIT	HDM (*Dermatophagoides* spp; Der p 1)	Longitudinal prospective RCT (18-mo follow-up)	51 Children with mild/moderate asthma (5–12 yr) underwent different AIT and PT	Antigen-specific IgG4, IFN-γ, and TGF-β levels increased in the SCIT and SCIT plus SLIT compared to the pharmacotherapy group and inversely correlate with clinical symptoms.	N/D	[205]
sIgG1 sIgG4	SCIT	HDM (*D. pteronyssinus*)	Longitudinal prospective RCT (24-mo follow-up)	65 Children between 6–17 yr old were randomized for SCIT plus PT vs. PT alone	Increased levels of specific IgG1 and IgG4 in the SCIT+PT compared to PT	N/D	[206]
sIgE, sIgG4	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective DBCT (24-mo follow-up)	85 Patients with 7–36 yr old were randomized for SLIT vs. placebo.	Increased sIgE and sIgG4 in the SLIT group compared to the placebo	N/D	[207]
sIgE IgG4 SPT	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (18-mo follow-up)	111 Children with mild-to-moderate asthma (5–15 yr) were randomized for SLIT vs. placebo	Increased skin wheal diameter, sIgE, and IgG4 in the SLIT group compared to placebo	N/D	[208]
Th17, Treg	SLIT	HDM (*D. farinae*)	Longitudinal prospective RCT (12-mo follow-up)	Allergic asthma children (4–18 yr); SLIT (n=30) vs. placebo (n=30)	Mean daily symptom scores and percentages of Th17 cells declined, and percentage of Treg increased in peripheral blood.	N/D	[103]
Blood eosinophils sIgE	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (>1-yr follow-up)	16 HDM allergic patients (mean, 11 yr) classified according to improvement of lung function (8:8)	The lung function improved group had lower blood eosinophils and higher HDM-sIgE levels than the declined group.	Associated with unsuccessful AIT Associated with successful AIT	[89]
sIgG4 Blood eosinophils	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (6-mo follow-up)	20 Children with mildly/moderately asthma (aged 6–12 yr)	Decreased blood eosinophil and increased sIgG4 in the SLIT group	N/D	[90]
Blood eosinophil sIgE	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective cohort study (6- and 12-mo follow-up)	31 Patients with mean age of 8.27±2.87 yr with a diagnosis of mild-to-moderate persistent asthma	Total eosinophil count and sIgE decreased compared to baseline.	N/D	[91]
ECP	SCIT	HDM (*D. pteronyssinus*)	Longitudinal prospective DBCT (1-yr follow-up)	129 Asthmatic patients (6–45 yr)	Serum ECP decreased after AIT.	N/D	[92]
Asthma/AR							
tIgE, sIgE/tIgE	SCIT	HDM (*D. pteronyssinus*)	Longitudinal retrospective Cohort study (3 yr follow-up)	185 Asthma and AR children (4–14 yr)	tIgE and sIgE/tIgE ratio associated with clinical response to AIT	Associated with unsuccesful AIT	[110]
tIgE, sIgE/tIgE SPT	SCIT	HDM (*D. pteronyssinus*)	Longitudinal retrospective Cohort study (3-yr follow-up)	81 Asthma and AR children's patients with median age of 7 yr	Treatment-effective cases had lower tIgE and a higher ratio of sIgE/tIgE. SPT grade changes to determine efficacy had a high degree of consistency with symptoms and drug score.	Associated with unsuccessful AIT	[111]
sIgE/tIgE	SCIT SLIT	HDM (*Dermatophagoides* spp.) Grass pollen (*P. judaica*, *O. europea*)	Longitudinal retrospective Cohort study (4-yr follow-up)	279 AR with or without asthma (mean, 29.5 yr)	Higher serum sIgE/tIgE ratio (>16.2) associated with an effective clinical response to AIT	Associated with successful AIT	[109]
sIgE/tIgE	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (2-yr follow-up)	32 Children asthma and/or AR diagnosed (7–15 yr)	Rhinitis symptom scores improved in children with a higher sIgE/tIgE ratio. sIgE/tIgE inversely correlated with visual analogue scales.	Associated with unsuccessful AIT	[209]
sIgE/tIgE	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal retrospective Cohort study (5-yr follow-up)	146 AR patients with/without asthma allergic	Serum sIgE/tIgE ratio significantly increased after SCIT.	N/D	[112]

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Table 1. (Continued) Potential predictive biomarkers for outcome of AIT in asthma with or without rhinitis

Bio marker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with effectiveness to AIT	Ref
sIgE	SCIT SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (1-yr follow-up)	48 Patients (5–10 yr) with mild persistent asthma/rhinitis classified in 3 groups (SCIT, SLIT, PT)	sIgE reduced in SCIT and SLIT groups.	N/D	[210]
sIgG4	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (6-mo follow-up)	693 Patients uncontrolled asthma and rhinitis (mean, 33 yr)	Increase in allergen-specific IgG4.	N/D	[211]
sIgG4	SLIT SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (3-yrs follow-up)	31 Mild asthmatics ± rhinitis children with a (median age, 10 yr)	Allergen-specific IgG4 was increased in the SCIT group at year 3.	N/D	[108]
sIgG4	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (18-mo follow-up)	90 Participants: rhinitis including 21 asthma positive patients (mean age, 17 yr)	sIgG4 increased after treatment compared to baseline but sIgG4 to HDM components do not qualify as a biomarker to evaluate the efficacy of AIT. The changes of sIgE, sIgG4, sIgE/sIgG4 ratio and the numbers of positive HDM components were not associated with the improvement of combined symptom and medication scores after AIT.	No association with successful AIT	[113]
sIgG2	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (1 yr follow-up)	100 participants AR ± asthma (mean 27 yrs old)	HDM-specific IgG2 increase in hig responders. In high responders, HDM-specific IgG2 and sIgE is correlated	Association with successful AIT	[150]
IL-10 IL-13	SCIT	HDM (*D. pteronyssinus*)	Longitudinal prospective Observational study (1-yr follow-up)	118 Adult patients (18–65 yr) diagnosed with AR ± allergic asthma	Severe patients with poor and no response to treatment had higher baseline IL-13, IL-10, and Th2 cytokines (IL-4 + IL-5 + IL-13).	Associated with unsuccessful AIT	[101]
Basophil IgE	SCIT	Birch pollen (*Betula verrucosa*)	Longitudinal prospective RCT (18- to 20-mo follow-up)	21 Patients with AR with or without mild-to-moderate asthma and 21 placebo control patients (mean age, 32 yr)	Inhibition of basophil activation, IgE binding, and IgE-FAP were correlated with AIT.	N/D	[93]
IL-10, eosinophil, IgG4	SLITSCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (1-yr follow-up)	30 Asthmatic + rhinitis patients (mean age,10 yr)	SLIT and SCIT increased serum IL-10 and decreased nasal eosinophils. SCIT reduced sputum eosinophil and increased serum sIgG4.	N/D	[94]
Periostin + FeNO	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (48-wk follow-up)	Adults with mild/moderate AR and asthma and from 46 SLIT participants 29 were responders and 17 were not responders (20–65 yr)	The proportion of patients with both high periostin and high FeNO levels was significantly higher in responder than in nonresponder.	Associated with successful AIT	[97]
Tregs, IgG4, IFN-γ, TNF-α	SLITSCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (1-yr follow-up)	Sixty-seven patients (age, 5–55 yr) with moderate-severe AR with or without asthma were randomized SLIT (n=27), SCIT (n=26) and placebo (n=14).	% Tregs in CD4+ T cells increased after treatment in both groups. Serum sIgG4 increased and was 30 times higher in SCIT than SLIT after the treatment. Serum IFN-γ increased in SCIT. Treg (SLIT) and IFN-γ (SCIT) inversely correlated with total rhinitis score.	N/D	[212]
CD66b, MPO	Not specified	HDM (*D. pteronyssinus*) Pollens (*D. glomerata*, *O. europea*, *A. vulgaris*)	Longitudinal prospective Experimental study (3-yr follow-up)	AIT-treated atopic patients with allergic asthma and rhinitis (n=15), non-AIT-treated patients with allergic asthma and rhinitis (n=10), and controls (n=10) aged 20–50 yr	Neutrophil cell-surface expression of CD66b is upregulated in vitro in response to allergens and reduced by AIT. AIT also reduced MPO in nasal lavage fluid.	N/D	[98]

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Table 1. (Continued) Potential predictive biomarkers for outcome of AIT in asthma with or without rhinitis

Bio marker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with effectiveness to AIT	Ref
miR-3935, *PTGER3*	SCIT	Grass pollen	Longitudinal prospective Experimental study (>1-yr follow-up)	Rhinitis –AIT 16, rhinitis +AIT 21, asthma –AIT 21, asthma +AIT 22, healthy controls 44, aged 18–70 yr	AIT induces miR-3935 in induced sputum of allergic asthmatics, while mRNA of its target, prostaglandin EP3 receptor, is downregulated in treated patients. PGE2 correlates with ILC2, sputum IL-13, inflammatory cell load, sputum eosinophils, and symptoms in AIT patients.	N/D	[104]
CD29+ Lol p 1-specific memory B cells	SLIT	Grass pollen (*L. perenne*)	Longitudinal prospective Experimental study (4-mo follow-up)	27 AR ± asthma patients, 13 SLIT (median age, 46 yr) and 14 PT (median age, 32 yr)	Associated changes in surface-expressed proteins on memory B cells subsets can be used as early biomarkers for treatment effects.	N/D	[123]
AR							
CD23+ B cells	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (1-yr follow-up)	Adult AR allergic (n=36) and healthy controls (n=31) AIT group (n=23), without AIT group (n=21)	AIT down regulated CD23 expression on memory B cells. Reduction of CD23 expression on switched memory B cells correlated with AIT efficacy in AR patients compared to placebo.	N/D	[122]
ILC2	SCIT	Grass pollen (*P. pratense*)	Longitudinal prospective Cohort study (8- to 36-mo follow-up)	12 Participants with mod-severe SAR, 9 with history of SAR with grass pollen SCIT, 11 nonatopic controls	Suppression of peripheral ILC2s during pollen season in AIT patients. AIT subjects reported markedly less seasonal symptoms than untreated subjects with SAR, correlated with ILC2s proportion.	N/D	[136]
Periostin sIgE	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (48 weeks follow-up)	20 to 65 yr of age with AR AIT group (n=50), control group (n=46)	The proportion of patients with both high serum periostin and s-IgE levels was significantly greater in responder than in nonresponder.	Associated with successful AIT	[116]
MRGPRX2 MMP-12	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (3-yr follow-up)	Moderate to severe persist AR (n=110) and healthy controls (n=40) AIT patients were classified in effective (n=55) and ineffective (n=45).	MRGPRX2 & MMP-12 were significantly higher in the AR ineffective than the effective group-Elevated MMP-12 levels were correlated with VAS and TNSS, MRGPRX2 levels were correlated with VAS.	Associated with unsuccessful AIT	[144]
ALCAM	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal Prospective Cohort study (3-yr follow-up)	Mild AR (n=38), mod-severe AR (n=80), healthy control (n=40) According to response (effective 39, ineffective 29).	ALCAM levels were significantly lower in the effective group than in the ineffective group.	Associated with unsuccessful AIT	[127]
CD63 CD203c (using CD-Sens)	SLIT	Grass pollen (*P. pratense*)	Longitudinal prospective Cohort study (1-yr follow-up)	26 patients with AR sensitized fom at least 2 yr, AIT group (n=16), reference group (n=10)	AIT-treated patients showed a significant decrease in CD63 and CD203c. AIT patients were significant improvement in all symptoms, and no changes in VAS scores were observed in control group.	N/D	[138]
IL-33	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (2-yr follow-up)	60 AR with HDM children, AIT group (n=30), with aging 120–190 mo, placebo group (n=30) with aging 125–185 mo	Suppression of peripheral ILC2s during pollen season in AIT patients	N/D	[132]
Leptin	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (2-yr follow-up)	40 AR (18–60 yr, without obesity) only allergic to HDM at least 2 yr	Serum and nasal leptin protein levels during AIT were decreased. TNSS score after AIT decreased with significant difference compared to placebo group	N/D	[129]

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Table 1. (Continued) Potential predictive biomarkers for outcome of AIT in asthma with or without rhinitis

Bio marker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with effectiveness to AIT	Ref
IL-4 Eotaxin IFN-γ	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (2-yr follow-up)	69 of 72 children AR, completed 1-yr follow-up schedule with 46 included in effective group and 23 in ineffective group	Eotaxin, IFN-r, IL-4 levels closely associated with the efficacy of AIT in pediatric HDM-induced AR patients	Associated with successful AIT Associated with unsuccessful AIT	[134]
CXCL13	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (6-mo follow-up)	80 Children with AR treated with AIT were categorized into effective group (n=56), ineffective group (n=24)	CXCL13 in the effective group were higher than those in the ineffective group.	Associated with successful AIT	[124]
MIF	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (3-yr follow-up)	160 Persistent HDM-induced AR, including 48 mild AR (MAR), 112 mod-severe AR (MSAR), 77 healthy controls MSAR group, 106 receive SLIT for 3 yr → 45 good response, 35 poor responses	MIF were significantly lower in the good response group than in the poor response group. Circulating MF levels were positively correlated with TNSS, VAS, specific IgE, blood eosinophil count.	Associated with unsuccessful AIT	[130]
LTA4H	Not specified	Grass pollen (*Arteminsa* spp.)	Longitudinal prospective Cohort study (1-yr follow-up)	Age between 6 and 60, with artemisia pollen allergen AR After treatment 1 yr, patients were classified as responders (n=30), nonresponses (n=15).	LTA4H level in the responders increased significantly after 1yr therapy, that of nonresponders remained unchanged.	Associated with successful AIT	[139]
HDM-reactive ST2+CD45RO+ CD4+ cells, IL-5+IL-13+CD27-CD161+CD4+	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective RCT (52-wk follow-up)	89 HDM-AR patients placebo (43), HDM 300IR (46)	HDM-reactive CD27-CD4+ cells, IL-5+IL-13+CD27-CD161+C4+cells, ST2+CD45RO+CD4+cells were detected in all patients with HDM-AR, were significantly decreased after AIT.	Associated with unsuccessful AIT	[125]
JC-pollen spicific IL-10+Foxp3+	SLIT	Pollen JC (*C. japonica*)	Longitudinal prospective RCT (52 weeks follow-up)	40 Patients age 12–64 yr JC pollen extract AIT group and placebo group 1:1	JC-pollen specific IL-10+Foxp3+ cells were increased after initiation of SLIT in good responders	Associated with successful AIT	[126]
ILC2	SCIT	HDM (*Dermatophagoides* spp.)	Transversal Experimental study	40 Participants, 9 AR untreated group, 24 AR receiving *D. p teronyssinus* AIT 7 healthy control	Levels of ILC2 in the AIT group were significantly reduced compared with untreated group	N/D	[137]
TAFI	SLIT	Pollen JC (*C. japonica*)	Longitudinal retrospective Cohort study (3-yr follow-up)	9 JCP undergoing AIT	Serum levels of TAFI increased gradually over time, a significant change was observed in 2 yr of AIT Serum C3a levels decreased significantly over the same interval.	N/D	[141]
Lactic acid, creatinine, sphingosine	SLIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (3-yr follow-up)	72 Assigned to receive AIT, 68 patients completed, 39 into effective group, 29 into ineffective group	Lactic acid, ornithine, sphingosine and creatine levels were elevated in the serum of ineffective group	Associated with unsuccessful AIT	[152]
Arachidonic and linolenic acid					Arachidonic and linolenic acid were higher in effective group	Associated with successful AIT	
13-HODE, 9-HPODE, 5(S)-HETE, 8S(S)-HETE, 11(S)-HETE, 15(S)-HETE, 11-hydro TXB2	SCIT	HDM (*Dermatophagoides* spp.)	Longitudinal prospective Cohort study (42-wk follow-up)	73 AR patients: 35 received Der p. single; 38 received mixed Der p, Der f.	Following the AIT, levels of AA and down-stream metabolic molecules (13-HODE, 9-HPODE, 5(S)-HETE, 8S(S)-HETE, 11(S)-HETE, 15(S)-HETE, 11-hydro TXB2) decreased.	N/D	[153]

AIT, allergen immunotherapy; AR, allergic rhinitis; ECP, eosinophil cationic protein; PT, pharmacotherapy; RCT, randomized clinical trial; DBCT, double blinded clinical trial; FAP, CD23-mediated IgE facilitated allergen presentation; HDM, house dust mite; ECP, eosinophil cationic protein; PTGER3, prostaglandin EP3 receptor; SPT, skin prick test; IFN-γ, Interferon γ; GP, grass pollen; MPO, myeloperoxidase; cytotoxic; ALCAM, activated leukocyte cell adhesion molecule; N/D, not determined; MIF, macrophage migration inhibitory factor; LTA4H, leukotriene A4 hydrolase; TAFI, thrombin-activatable fibrinolysis inhibitor; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; TGF, transforming growth factor; FeNO, fractional exhaled nitric oxide; SAR, seasonal allergic rhinitis; MMP-12, matrix metalloproteinase-12; MRGPRX2, mas-related G protein-coupled receptor-X2; TAFI, thrombin-activatable fibrinolysis inhibitor; PGE2, prostaglandin E2; VAS, visual analog scale; TNSS, total nasal symptom score; JCP, Japanese cedar pollen.

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term AIT treatment [105, 106]. This change is accompanied by induced blocking antibodies (particularly, of the subclass IgG4) [107]. The sIgE/tIgE ratio is often increased following AIT treatment [108-112], however, no changes are observed when evaluated less than 2 years of AIT treatment [113]. The blocking activity of IgG antibodies maintains unchanged for at least 2 years of discontinuation of AIT, despite the reduction in the IgG1 and IgG4 levels [114], suggesting long-term immune tolerance following cessation of AIT treatment.

In vivo biomarkers

Changes in skin prick test (SPT) have a high degree of diagnostic performance in the evaluation of efficacy in HDM-SCIT according to tIgE levels [111]. Recently, one study reported the increased sensitivity and clinical relevance of the intradermal test compared to SPT to predict AIT effectiveness in respiratory allergic diseases [115]. Hoshino et al. [116] report an interesting finding where the proportion of responders to AIT had high periostin and high fractional exhaled nitric oxide levels, which opens a window to explore the combination of *in vivo* and *in vitro* biomarkers.

Allergic rhinitis

AR is a highly prevalent health problem in childhood, adolescence, and adult life [117]. Susceptibility to other allergic comorbidities in AR has been described [118-121]. AIT has been shown to reduce the symptoms of rhinitis and prevent the development of allergic comorbidities, therefore the possibility to reduce pharmacological treatment. Different biomarkers have been proposed for the evaluation of the response to AIT in AR (**Table 1**).

Cellular biomarkers

The understanding of the role of B and especially, allergen-specific ones, in AR-AIT remains limited. Yao et al. [122] demonstrated that CD23 expression on switched memory B cells, positively correlated with disease severity and clinical efficacy of HDM-SCIT in patients with AR, and also correlated with improvement of the symptom scores. Consistently, grass pollen SLIT induces Lol p 1-specific memory B cells with upregulated expression of surface IgG4, CD23, and CD29 [123]. The serum C-X-C motif ligand 13(CXCL13) but not B cell-activating factor after HDM-SCIT in pediatric AR have clinical values for biomarkers, being CXCL13 level higher in effective AIT group [124].

Regarding T cells, Ihara et al. [125] reported significantly decreased memory Th2 cell subsets (HDM-reactive $CD27^-CD4^+$, $IL\text{-}5^+IL\text{-}13^+CD27^-CD161^+CD4^+$, $ST2^+CD45RO^+CD4^+$) in HDM-AR patients after SLIT. Japanese cedar (JC) (*Cryptomeria japonica*) pollinosis patients who received SLIT significantly increased JC-specific $IL\text{-}10^+Foxp3^+$ cells, and good responders of the immunotherapy group had significant suppression of IL-4 and IL-5-producing Th2 cells [126]. Activated leukocyte cell adhesion molecule (ALCAM, also known as CD166) plays an important role in T-cell activation and immune response. Xie et al. [127] demonstrated that moderate to severe HDM-AR received the sublingual AIT at least 3 years, and the ALCAM levels were significantly lower in the effective group and exhibited better for predicting SLIT clinical efficacy. Leptin is known for being involved in the apoptosis and activation of T cells [128]. The leptin concentration in serum and nasal lavage was significantly decreased after SLIT treatment in 40 HDM-AR patients without obesity [129]. The macrophage migration inhibitory factor (MIF) is a T-lymphocyte-derived protein and the serum concentrations of MIFs were significantly lower in HDM-induced AR patient's good-response sublingual AIT group than in the poor-response group [130].

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Proinflammatory cytokines such as IL-4, IL-5, IL-13, eotaxin, and IL-33 are usually expressed at high levels in chronic allergic diseases including AR. They induce inflammation and contribute to the Th2 response [131]. The children who received HDM SLIT decreased significantly both serum and nasal lavage of IL-33 levels after 12 months of treatment compared to the control group, and correlation with symptom score and Th2 cytokines (IL-4, IL-5, IL-13) [132]. Nasr et al. [133] found that AR patients who were treated with SLIT to palm trees for more than 6 months significantly had lower serum IL-33 levels than immunotherapy naïve AR patients. The serum level of IL-33 in patients with intermittent AR (IAR) was correlated with disease severity and could be a part of the pathogenesis of IAR. Periostin is the down-stream molecule of IL-13, and cytokine of type 2 inflammation allergic disease. The age between 20 and 65 with a history of HDM-induced AR, had sublingual administration for alleviated symptoms. The serum periostin level decreased after immunotherapy treatment and it was also found that high serum periostin is an independent factor for improvement in quality of life. Therefore, periostincould be a predictor of clinical response to AIT [116]. Xie et al. [134] prospectively recruited 72 children with moderate to severe persistent HDM-induced AR and treated them with SCIT. Based on treatment efficacy, they found that serum eotaxin, IL-4, and Th1 cytokines IFN-γ levels were closely correlated with the efficacy of AIT in patients.

ILC2 are morphologically similar to lymphocytes, and represent an alternative source of Th2 cytokines in the nasal mucosa [135]. In patients with seasonal AR, sensitized to *Phleum pretense*, the proportions of ILC2 cells were increased during the pollen season. And they also found that SCIT for 8–36 months can induce a reduction of ILC2 cells, correlation with less seasonal symptoms compared to the subcutaneous AIT [136]. The frequencies of ILC2 cells in HDM-sensitized patients with AR who received immunotherapy were significantly reduced compared with the untreated group [137].

Basophil activation can be studied by monitoring the expression of surface markers such as CD63 and CD203c, using flow cytometry-based analysis [135]. Caruso et al. [138] measured CD63 and CD203c expression in AR patients who were treated with *Parietaria officinalis* SLIT using CD-Sens, which can detect the minimum dose for activating basophils with increasing doses of allergen. The patients who received SLIT showed a significant decreased in CD-Sens for CD63 and CD203c expression, and found a correspondence in clinical symptoms more with CD203c marker.

Several other chemokines, and arachidonic acid pathway molecules also play roles in allergic inflammation. Patients with Artemisia pollen AR were treated with AIT for 1 year, and AIT responders increased leukotriene A4 hydrolase levels significantly than nonresponders [139]. Thrombin-activatable fibrinolysis inhibitor (TAFI) is known for the regulation of coagulation and fibrinolysis and also inactivates other inflammatory mediators [140, 141]. Yoshida et al. [141] demonstrated that in AR patients with allergies to JC pollen who were undergoing SLIT, the serum TAFI levels were increased gradually and significantly changes over the 2 years of SLIT and correlated with improvements in the symptoms-related scores. They also suggested that TAFI could suppress the degranulation of mast cells via an IgE-mediated mechanism.

Mas-related G protein-coupled receptor-X2 (MRGPRX2) is expressed by mast cells, and associated with IgE-independent activation of mast cells [142]. Matrix metalloproteinase-12 (MMP-12) can be induced by M2 macrophages, and promote the proliferation of Th2 cells, and secretion of IL-4 and IL-13 [143]. Zhou et al. [144] found that circulating serum MRGPRX2 and MMP-12 levels were lower in the AR SLIT-treated group and useful for evaluating the disease severity.

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Humoral biomarkers

One of the main features of AR is elevated concentrations of allergen-sIgE to clinically suspected allergens [135]. Both SCIT and SLIT are associated with transient increases in serum allergen-sIgE antibody levels that are followed by blunting of seasonal increases in sIgE levels [135, 145, 146]. Di Lorenzo et al. [109] reported that adult patients with AR and/or asthma symptoms had a significant positive correlation between serum sIgE/tIgE ratio (>16.2) and the clinical response. However, Fujimura et al. [147] found that patients with a low sIgE/tIgE ratio showed a better response to AIT than patients with a higher ratio. Liu et al. [148] found that after 6 months SLIT in HDM-AR children serum tIgE levels, serum sIgE levels, and serum sIgE/tIgE ratios and the levels of IL-10 and IL-35 were correlated with clinical response. Adults and adolescents who underwent SCIT and were monosensitized to birch pollen had a sustained and long-term (5 years) efficacy of the treatment [149]. Bordas-Le Floch et al. [150] report a higher concentration of sIgG2 to HDM in high responders to AIT, assuming a key role of this isotype in immune tolerance. Finally, successful AIT increased allergen sIgG4 levels and correlated with decreased allergen-sIgE levels in grass pollen AIT. Also the pre-existing Phl p 1 and Phl p 5 sIgE levels predict increases in sIgG4 levels after updosing the AIT [151].

Metabolic biomarkers

A recent prospective study of serum metabolomics has demonstrated that after 3 years of Der P and *Dermatophagoides farinae* SLIT, the effective group exhibited 6 metabolites (lactic acid, ornithine, linolenic acid, creatinine, arachidonic acid, and sphingosine) that showed good performance to evaluate the efficacy of SLIT. These metabolites are mainly involved in glycolysis and fatty acid metabolism pathways, so they may provide a better understanding of the mechanisms of SLIT in AR patients [152]. Interestingly, on metabolic reactions between AIT with single-species mite and double-species mite allergens, 6 metabolites (13-HODE, 9-HPODE, 5(S)-HETE, 8S(S)-HETE, 11(S)-HETE, 15(S)-HETE, 11-hydro TXB2) associated with ω-6 related arachidonic acid and linoleic acid pathway showed significant changes and correlated with symptoms scores. Additionally, a decreased serum 11(S)-HETE level more with single-species mite-SCIT, may serve as a distinguishable marker for options of SCIT [153].

Food allergy

AIT for food allergy is currently under development and OIT is the most-studied approach. OIT is less frequently associated with adverse effects than SCIT [154]. The assessment of food AIT efficacy is typically based on SU evaluation, which is the lack of immune response in subjects treated with AIT after occasional doses of allergen. Different biomarkers have been used to predict the achievement of SU after food AIT, mostly allergen-specific antibodies in serum (**Table 2**).

Cellular biomarkers

Contradictory results have been reported for the usefulness of basophil activation as a predictor for the response to food AIT. In a phase II clinical trial, achievement of SU against peanut was associated with lower basophil activation response [155]. More recently, it was reported that grouping participants based on the clinical outcome at any oral food challenge moment over time were possible, indicating that basophil activation does not correlate with AIT success [156]. Another study observed similar basophil sensitivities at baseline in subjects with SU and those with transient desensitization, but also found that an early decrease in basophil sensitivity correlates with SU [157]. In addition to peanut AIT, CM AIT studies have assessed basophil activity as a biomarker. A CM-OIT study with

Table 2. Potential predictive biomarkers for outcome of AIT in food allergy

Biomarker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with with effectiveness to AIT	Ref
Food Allergy							
sIgA for EW and OVA	OIT	Whole egg	Longitudinal prospective Cohort study (12-mo follow-up)	26 Egg-allergic patients divided in a high-desensitization group (n=21, 5–12 yr old) and a low-desensitization/failure group (n=5, 5–11 yr old)	Baseline IgA levels specific for EW and OVA were higher in the high-desensitization group than in the low-desensitization/failure group.	Associated with successful AIT	[160]
sIgA for EW, OVA and OVM	OIT	Solid EW	Longitudinal prospective	37 Egg-allergic patients that underwent OIT divided in clinical responders (n=19) and nonresponders (n=18)	No significant differences in baseline sIgA1 and sIgA2 between responders achieving SU and nonresponders were observed.	No association with successful AIT	[161]
sIgE for EW and OVM sIgG4/sIgE for OVM			Phase II trial (4-yr follow-up)		In children that received egg OIT and obtained SU after 4 yr, lower baseline IgE levels were measured specific for EW and OVM.	Associated with unsuccessful AIT	
					Children who developed SU had increased sIgG4/sIgE for ovomucoid at baseline compared to nonresponders.	Associated with successful AIT	
sIgA to CM, casein and β-lactoglobulin	OIT	CM	Longitudinal prospective Phase I trial (3 months follow-up)	40 CM-allergic patients (6–17 yrs old) that underwent CM OIT (32 achieved desensitization)	High sIgA prior to OIT predicts failure to achieve desensitization.	Associated with unsuccessful AIT	[213]
sIgA for peanut	OIT	Peanut	Longitudinal prospective Phase II trial (160-wk follow-up)	69 Peanut-allergic patients (1–4 yr) completed OIT. Patients were divided into 3 categories: desensitized/remission (n=19), desensitized/no remission (n=40), and not desensitized/no remission (n=10)	In the not desensitized/no remission group the baseline sIgA levels were higher than in the desensitized/remission group.	Associated with unsuccessful AIT	[162]
IgE for CM and casein SPT wheal diameter	OIT	CM	Transversal, analytic study (2-yr follow-up)	70 CM-allergic patients (1–5 yr), 18 of them underwent OIT, 44 underwent accelerated milk introduction, and 8 had no intervention	High baseline levels of IgE specific to milk and casein are associated with persistence of CMA.	Associated with unsuccessful AIT	[163]
					SPT wheal diameter was not a predictive marker for AIT outcome.	No association with successful AIT	
sIgE for CM, casein, and β-lactoglobulin	OIT	CM	Longitudinal prospective Cohort study expansion on clinical trial (12-mo follow-up)	85 CM-allergic children (6–18 yr) divided in OIT group (n=48) and control group (n=37)	Showed a reduced likelihood of reaching a maintenance dose in children (9–15 yr) with elevated baseline levels of sIgE.	Associated with unsuccessful AIT	[164]
sIgE for peanut	OIT	Peanut	Longitudinal prospective	146 Children (1–3 yr) divided in OIT group (n=96) and control group (n=50)	The predictive role of lower baseline sIgE in remission was shown by use of multivariable regression analysis.	Associated with unsuccessful AIT	[166]
sIgG4/sIgE ratio for peanut			Phase II trial (2-yr follow-up)		The desensitization/remission group showed highest peanut sIgG4/sIgE ratio at baseline.	Associated with successful AIT	
sIgE/total IgE ratio for Ara h 1 and h 2	OIT	Peanut	Longitudinal prospective Pilot clinical trial (3- to 56-mo follow-up)	24 Children (1–16 yr) (12 achieved SU)	Achievement of SU was associated with lower IgE baseline levels specific for Ara h 1 and Ara h 2.	Associated with unsuccessful AIT	[167]
sIgG4/sIgE ratio for peanut					Higher baseline sIgG4/sIgE ratios were found in children achieving SU.	Associated with succesful AIT	
SPT wheal diameter					Smaller SPT wheal diameter was associated with successful OIT outcome.	Associated with unsuccessful AIT	

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Table 2. (Continued) Potential predictive biomarkers for outcome of AIT in food allergy

Biomarker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with with effectiveness to AIT	Ref
sIgE/total IgE for CM	OIT	CM	Longitudinal prospective Phase II trial (32 months follow-up)	57 CM-allergic patients (7–35 yr old) that underwent OIT (combined with omalizumab) were divided in treatment group with omalizumab (n=28) and placebo group (n=29). 13 Patients of the treatment group and 10 of the placebo group achieved SU	Lower baseline sIgE/total IgE correlated with the likelihood of achieving SU in the treatment group.	Associated with unsuccessful AIT	[159]
Ara h 2-specific IgG, IgG4 and IgE Basophil sensitivity to Ara h 2	OIT	Peanut	Longitudinal prospective single-center, open-label trial (13-mo follow-up)	30 Subjects with peanut allergy (7- to 13-yr old)	Ara h 2-specific IgG and IgG4 showed no correlation with OIT outcome; sIgE is greater in unsuccessful OIT patients compared to those that reached SU; basophil sensitivity decreases in patients with SU.	sIgG and IgG4: N/D sIgE associated with unsuccessful OIT Basophil sensitivity associated with successful OIT	[157]
Peanut- and Ara h 2-specific IgE	OIT	Peanut	Longitudinal prospective Cohort study (Not specified time of follow-up)	49 subjects with suspected or known peanut allergy (9–36 mo old)	Measurement of peanut-specific IgE and IgE binding to Ara h 2 at baseline may allow prediction of OIT success.	Associated with successful OIT	[168]
IgE- and IgG4-binding peptides	CM-OIT	CM allergens	Longitudinal prospective cohort study (2-yr follow-up)	25 CM-allergic children who underwent CM-OIT and 7 nontreated CM-allergic children as control (>4 yr old)	CM-OIT induces increase of IgG4-binding epitopes and decrease in IgE-binding epitopes; 2 sets of IgE-binding peptides can predict efficacy and safety of OIT	N/D	[169]
IgE- and IgG4-binding peptides	CM-OIT	CM	Longitudinal prospective cohort study (28-mo follow-up)	55 Patients with milk allergy (7–35 yr old) randomized 1:1 to receive omalizumab or placebo during CM-OIT	IgE and IgG4 binding to epitopes were altered by OIT regardless of outcome; SU is associated with lower levels of baseline epitope-specific IgE	No association IgE and IgG4 binding to epitopes Epitope-specific IgE associated with unsuccessful OIT	[170]
IgE- and IgG-binding peptides	OIT	Soy (rBet v 1)	Secondary analysis of a double-blind placebo-controlled trial (not specified time of follow-up)	34 Patients (mean age, 38 yr)	Binding to allergen epitopes is clinically relevant in sub-groups of patients only; IgE-binding to one of the epitopes was correlated with stronger symptoms after ingesting soya	Associated with unsuccessful OIT	[171]
Basophil activation response, sIgE	OIT	Peanut	Longitudinal prospective RCT phase II study (approximately 2-yr follow-up)	120 Patients (7–55 yr old) with peanut allergy, with a positive result from a double-blind, placebo-controlled, food challenge (≤500 mg of peanut protein), a positive SPT result (≥5-mm wheal diameter above the negative control), and peanut-specific IgE concentration of more than 4 kU/L	Higher IgE, higher risk of OIT failure; low basophil activation response, high success rate	Associated with unsuccessful OIT	[155]
Basophil activation, peanut-specific IgE, IgA and IgG4	OIT	Peanut	Double-blind, placebo-controlled food challenge (9-mo follow-up)	20 Patients (4–12 yr old), with peanut-specific IgE ≥ 0.35 kU/L, peanut SPT wheal ≥ 3 mm compared to the negative control, and a positive double-blind, placebo-controlled food challenge	Suppression of basophil activation occurs within the first 90 days of OIT; sIgG4 and IgA increased throughout therapy	Not associated with successful OIT	[156]

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Table 2. (Continued) Potential predictive biomarkers for outcome of AIT in food allergy

Biomarker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with with effectiveness to AIT	Ref
CM-specific IgE and IgG4; CD63 and CD203c expression; basophil histamine release	OIT and SLIT	CM	Longitudinal prospective RCT (around 60-wk follow-up)	30 Subjects (6–17 yr) with CM allergy	OIT was more efficacious for desensitization to CM than SLIT alone, but it had more side effects; CD63 and CD203c expression decreased after therapy; CM-specific IgG4 levels increased in all groups; CM-specific IgE and histamine release decreased in the OIT group	N/D	[158]
Hazelnut-specific IgE, SPT wheal diameter	OIT	Hazelnut	Longitudinal Retrospective Single-center study (at least 6-mo follow-up)	100 Subjects (3–9 yr old) who underwent at least 6 months of hazelnut OIT for IgE-mediated allergy; 6-mo follow-up	Hazelnut OIT is associated with hazelnut desensitization. IgE negatively correlated with OIT success; smaller SPT wheal diameter at baseline positively correlated with OIT success	Associated to unsuccessful OIT	[172]
CM-specific IgE, SPT wheal diameter	OIT	CM	Longitudinal prospective cohort study (5 yrs)	74 Subjects (2–18 yr old) with CM allergy;	Lower sIgE and smaller SPT wheal diameter at baseline correlated with complete desensitization. IgE negatively correlated with OIT success; smaller SPT wheal diameter at baseline positively correlated with OIT success	Associated to unsuccessful OIT	[173]
Baseline sIg	OIT	CM (casein and α and β-lactoglobulin)	Longitudinal prospective open label study (median 6 yrs follow-up)	Children (n=168) with CM allergy	Baseline and sIgG4/IgE ratio to casein, and ß-lactoglobulin sIgE concentrations were higher in the group that had a positive challenge.	Associated to unsuccessful OIT	[165]
sIgG4 /IgE ratio					Higher casein sIgE remains in reactive patients. Casein sIgG4/IgE ratio is important to define the outcome of milk OIT	Associated to successful OIT	

AIT, allergen immunotherapy; CM, cow's milk; CMA, cow's milk allergy; EW, egg white; N/D, not determined; OIT, oral immunotherapy; OVA, ovalbumin; OVM, ovomucoid; RCT, randomized clinical trial; sIgA, specific IgA; sIgE, specific IgE; sIgG4, specific IgG4; SPT, skin prick test; SU, sustained unresponsiveness; tIgE, total IgE.

30 children showed that baseline expression of the basophil markers CD63 and CD203c as well as histamine release at baseline could not predict tolerance [158]. Nevertheless, a CM-omalizumab OIT study found that baseline basophil activation might still help identify subjects in whom omalizumab can enhance SU development, but in combination with other serological markers [159].

Humoral biomarkers

Serum sIgA has been studied as a potential predictive biomarker of food AIT in different studies, although with contradicting results. In one study with egg-allergic patients undergoing OIT, baseline sIgA levels against egg white (EW) and OVA were higher in high-desensitized patients that tolerated one hard-boiled egg after one year compared to those who could not (low-desensitized/failure group). This indicated that high sIgA levels before OIT could predict treatment effectiveness [160]. In contrast, another study showed that there were no significant differences in baseline sIgA1 and sIgA2 between responders and nonresponders [161]. sIgA levels may also be predictive of therapy failure, being higher in patients not achieving SU to CM and peanut after OIT [161, 162].

The role of sIgE as a potential predictive biomarker has been investigated in several food AIT studies. A recent study with 70 allergic children to CM showed that high baseline levels of

sIgE to CM and casein are associated with persistence of CM allergy despite AIT [163]. This is consistent with the findings of Cohen et al. [164] and Kauppila et al. [165], demonstrating that elevated baseline levels of sIgE to total CM and its allergens are associated with a lower chance of reaching a maintenance dose of 200 mL of CM due to adverse reactions. In line with these findings, lower baseline sIgE levels for EW and ovomucoid (OVM) were measured in children that received egg AIT and obtained SU after 4 years [161] and lower sIgE to total peanut extract and Ara h 2 had a predictive role in peanut-allergic children [166]. Furthermore, achievement of SU in children that underwent peanut AIT was associated with lower sIgE baseline levels for Ara h1 and Ara h 2 [167]. Additionally, these children had a lower sIgE/tIgE ratio at baseline, suggesting that this ratio can also be used as a predictive biomarker for treatment response. This was also observed in subjects enrolled in a trial of CM AIT combined with omalizumab, but only for subjects treated with omalizumab and not for placebo-treated subjects [159]. In contrast, another study showed that, even though Ara h 2-sIgE was lower in subjects that reached SU, the difference in the ratio of Ara h 2-sIgE/tIgE was not significant between the groups [157]. Overall, there is a consensus in the literature that lower sIgE and sIgE/tIgE ratios at the start of AIT are associated with treatment success.

In addition to the levels of sIgE at baseline and the ratio between sIgE and tIgE, analysis of antibody epitope binding may contribute to predicting the outcome of AIT. In an AIT study with 49 peanut-allergic children, Dreskin et al. [168] revealed that the binding of IgE to specific linear Ara h 2 epitopes at baseline can be useful in predicting the success of SU. Furthermore, through bioinformatic analysis, 2 baseline sets of 16 IgE-binding peptides were identified for predicting the safety and efficacy of CM-OIT before treatment [169]. Another CM-OIT study developed predictive models based on epitope-specific antibody binding and showed that having lower diversity and lower binding of IgE at baseline to specific epitopes can predict SU [170]. Lastly, a study investigating the efficacy of subcutaneous injection of birch pollen allergen Bet v 1 in soya allergy reported the potential of IgE- and IgG-binding to epitopes as a biomarker for successful AIT [171].

As the levels of both sIgG4 and sIgE play an important role in AIT, the ratio of sIgG4/sIgE is also of interest as a potential predictive biomarker [165]. Several peanut AIT studies found a higher sIgG4/sIgE ratio at baseline in subjects that achieved desensitization or SU compared with subjects that did not [155, 157, 166, 167], and this was more recently confirmed in a phase II clinical trial with 146 participating children [166]. Furthermore, similar findings have been observed in an egg AIT study, in which children who developed SU had increased sIgG4/sIgE for OVMat baseline compared to nonresponders [161].

In vivo biomarkers

The association between smaller SPT wheal diameter at baseline and successful OIT outcome has been reported in studies using peanut, hazelnut, and CM [167, 172, 173]. However, this association was not found in a peanut AIT study with 120 participants, which could be due to the recruitment criterium of SPT wheal diameter of ≥5 mm above the negative control instead of the conventional ≥3 mm [155]. Furthermore, the SPT wheal diameter was not a predictive marker for AIT outcome in a recent study with 70 CM-allergic children undergoing AIT or a more rapid introduction of baked milk [163]. Collectively, the contradictory results of these studies suggest that more work is needed to confirm the role of SPT wheal diameter as a predictive biomarker in AIT.

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Venom allergy

Allergy to the venom of Hymenoptera species presents with severe manifestations and is potentially life-threatening. Similarly, Hymenoptera venom immunotherapy (VIT) is one of the riskiest since there is a high probability of severe adverse events (8%–20%) [174-176], however, it is the only treatment that can change the course of the disease by inducing immunomodulation and tolerance in most patients with effectiveness around 80%–95% depending on the allergen source [177-179]. According to the geographical location and environmental factors, different insects of this order may be the cause of the reaction [180] and endotypes and phenotypes have been described, not always mediated by IgE [181]. VIT is recommended in sensitized adults and children with severe reactions to the stings as well as in adults with generalized skin symptoms if the quality of life is impaired [177]. For VIT, subcutaneous injection is the only route of administration that is used in clinical practice, compared to aeroallergen and food-allergen IT which can be administered SC but also sublingually [182].

To date, no complete overview exists of the mechanisms by which VIT induces tolerance, and information that explores predictive biomarkers of response to VIT is scarce [183]. Associations have been described between changes in some components of the immune system and the tolerance to stings or effectiveness of Hymenoptera VIT. However, many of the reported mechanisms also have been studied in beekeepers, who are exposed to high doses of bee venom as a result of their occupation. Few studies have carried out designs to identify biomarkers of successful VIT (**Table 3**).

Cellular biomarkers

Changes in basophil markers, tryptase levels, and histamine release were among the first approaches to determine the effectiveness of immunotherapy [184, 185]. VIT could modulate the mast cell function where it has been reported a decreased baseline serum tryptase concentration over time after VIT [186]. Basophils also downregulate the expression of surface activation markers (CD11c, CD32, CD35, CD63, CD116, CD122, CD124, CD130, and CD132) and histamine release after VIT [184, 185, 187]. However, monitoring these cells as an *in vitro* method does not offer an alternative for determining successful immunotherapy when compared to the sting challenge [188].

VIT also has effects on the adaptive response mediated by T and B cells. The directing of the Th2 response of allergic patients towards a Th1 profile after immunotherapy is one of the most recognized mechanisms of action, where the levels of VIT are increased. IFN-γ in parallel with the decrease of IL-4 and IL-13 [189, 190]. Akdis et al. showed how the development of epitope-specific T cells (Th1 and Tregs) to bee major allergen, phospholipase A2, in VIT which are capable to suppress cells of the T2 allergic response [45, 191]. VIT was found to be related to the progressive expansion of circulating $CD4^+CD25^+Foxp3^+$ Treg cell numbers [192]. IL-10-producing antigen-specific Tregs also appear in the context of high-dose exposure to allergens; this was demonstrated in beekeepers whose cells were measured in and out of beekeeping season [193].

In a study conducted on patients in VIT rush, samples were taken at 5 days to analyze markers of immune tolerance. Among the findings, tryptophan degradation was observed, which is related to suppression in T cells and the induction of tolerance. In addition, elevated ILT 3 and ILT4, which are inhibitory receptors expressed on monocytes, and elevated levels of IL-10 by monocytes and $CD3^+$ T cells were found [194]. These mechanisms may explain the early response to VIT.

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Table 3. Potential predictive biomarkers for outcome of AIT in venom allergy

Bio marker	Type of AIT	Allergen source of study	Study type	Study population	Main finding	Association with with effectiveness to AIT	Ref
Venom allergy							
Kynurenine	SCIT	*A. mellifera*	Longitudinal prospective	20 BV allergic patients older than 18 yr and 20 beekeepers as tolerant group	Markers studied have proven helpful for monitoring the early response to VIT, such as IgG4 to Api m 1.	Associated with successful AIT	[198]
Api m 1-sIgG4 IL-10 Helios$^-$ Tregs basophil degranulation			Cohort study (12-mo follow-up)		In contrast, others, such as kynurenine, the basophil degranulation test, or the Treg Helios$^-$ cells, are useful for the late phase.	Associated with unsuccessful AIT	
sCD30	SCIT	*Polistes*, *Apis*, and *Vespula* spp.	Longitudinal prospective Cohort study (12-mo follow-up)	14 Patients with Hymenoptera venom allergy who had undergone VIT and 61 healthy controls	sCD30 levels are higher in patients with Hymenoptera venom allergy and expression decreases during VIT.	N/D	[196]
PLA and peptide specific T cells anti-PLA IgE anti-PLA IgG4	SCIT	*A. mellifera* and phospholipase A2 (group 1 allergen)	Longitudinal prospective Experimental study (2-mo follow-up)	Five BV allergic individuals (mean age, 47 yr)	VIT for 2 months of individuals suffering from bee sting allergy is associated with a significant reduction in T-cell proliferative response and cytokine secretion to the epitopes of the major BV allergen, PLA.	N/D	[45]
BTC	SCIT	*Vespula* and *Apis* spp.	Longitudinal retrospective Cohort study (4.7 yr mean of follow-up)	302 Patients diagnosed with Hymenoptera venom allergy and undergone VIT	Significant decrease of BTC by 2.5% per year after VIT.	N/D	[186]
Basophils surface markers	SCIT	*Vespula* spp.	Longitudinal prospective Experimental study (2 wk)	Forty-eight patients whom had been treated with rush VIT	Decreased in the expression of CD11c, CD32, CD35, CD63, CD116, CD122, CD124, CD130, and CD132 surface markers in basophils after one week after rush VIT	N/D	[185]
Mast cells tryptase Histame by leucocytes	SCIT	*A. mellifera*	Transversal Experimental study	58 Patients hyposensitized with bee venom were challenged with the sting of a living bee	Patients which not react to the sting challenge had lower histamine and tryptase levels compared to still reactive ones	Associated with unsuccessful AIT	[184]
Api m 10-sIgE	SCIT	*A. mellifera*	Longitudinal retrospective Experimental study (at least 6 months of VIT)	VIT patients (n=115) were included; responders (n=79) or treatment failure (n=36)	Allergic patients with dominant sensitization to Api m 10 are at increased risk for treatment failure in VIT	Associated with unsuccessful AIT	[204]
Helios$^-$ Tregs	SCIT	*A. mellifera*	Transversal comparative study	Allergic patients with reactions after bee stings; tolerant beekeepers receiving ≥50 stings/yr; and healthy nonexposed controls	Tolerant Beekepers showed higher levels of sIgG4 and IL-10 as well as an enhanced CTLA-4+ and Helios- Treg, and reduced Th1, Th2 and Th17 subsets. Helios- Treg population could be a novel candidate biomarker useful for monitoring tolerance.	N/D	[214]
sCD30 sTNF-R1	SCIT	*Vespula* and *Apis* spp.	Transversal comparative study	21 Patients allergic to wasp and/or honey bee venom and 42 healthy participants	sCD30(TNFRSF8), and sTNF-R1 may be considered as effective prognostic factors	N/D	[197]
CD30 CD154 CD152	SCIT	*A. mellifera*, *Polistes*, and *Vespula* spp.	Longitudinal prospective Experimental study (4-mo follow-up)	Seven patients underwent VIT	Downregulation of the markers in CD4+ T cells after 4 months of VIT	N/D	[183]

AIT, allergen immunotherapy; BV, bee venom; BTC, baseline tryptase concentration; IL, interleukin; N/D, not determined; SCIT, subcutaneous immunotherapy; sIgE, specific IgE; sTNF-R1, soluble tumor necrosis factor receptor 1; sCD30, soluble CD30; PLA, phospholipase A2; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; VIT, venom immunotherapy.

Among the most-studied mechanisms of VIT is the increase in IL-10, which can be produced by different cell types. In PBMCs from VIT patients, IL-10 was produced initially by activated $CD4^+CD25^+$, allergen-specific T cells, followed by B cells and monocytes [195]. Recently, human IL-10-secreting Br1 cells (identified by surface markers $CD73^-CD25^+CD71^+$) were described in beekeepers, healthy donors, and allergic patients. Among their functions is the

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production of high levels of IL-10, suppressed antigen-specific $CD4^+$ T-cell proliferation, and the production of IgG4 [53].

Soluble CD30 (sCD30) is a glycoprotein that is expressed and secreted by Th2 lymphocytes. In patients with an allergy to Hymenoptera venom, sCD30 concentrations are elevated and their levels decrease during AIT [196, 197]. Additionally, Packi et al. [197] proposed that a decrease in the level of both TNFR1 and sCD30 markers in patients suffering from Hymenoptera venom allergy may be considered an effective prognostic factor for VIT. In $CD4^+$ cells, downregulated markers have been described after 4 months with VIT, such as CD30, CD154, and CD152. In this same study, VIT was shown to be effective, with an increase in IFNγ-producing $CD4^+$ cells and a decrease in basophil degranulation [183]. Recently, tolerance status in bee-venom-allergic patients after immunotherapy was invariably associated with a significant regulatory response characterized by the expansion of $Helios^-$ Tregs subpopulation and increased IL-10, sIgG4, and kynurenine levels [198].

Humoral biomarkers

Increased levels of serum sIgE during the beginning of the VIT is a common finding, however, this decreases after a year [198-201]. On the other hand, in natural exposure to high doses of hymenopteran venom, as is the case in beekeepers, IgG4 levels are over one hundred times higher than in subjects allergic to the venom and even in unexposed subjects [202]. In the case of VIT, the persistent role of IgG4 antibodies has been discussed for many decades, although successful desensitization is accompanied by increases in the inhibitory activity of both IgG4 and IgE, these return to baseline within months upon discontinuation of treatment, however, subsequent follow-up revealed a more sustained decline in venom-sIgE levels [203]. This also proposes alternative memory mechanisms other than the humoral response that may be involved in the persistence of tolerance.

In contrast, dominant sensitization to some specific allergens, like Api m 10, in bee-venom allergy may be a risk factor for immunotherapy failure showing the importance of component resolved profiles in the prediction of treatment results [204].

CONCLUSION

Biomarkers with predictive value for the success of AIT are highly sought after because their identification will allow a personalized assessment on a per-patient basis of the likelihood that AIT will result in amelioration of the disease. While many biomarker candidates have been identified, as outlined in this review article, none of these have thus far been validated and proven sufficiently accurate predictors of response to treatment. Currently, studies designed to determine biomarkers for a successful response to AIT remain limited in food and venom allergies. The humoral response (assessed levels of sIgE and sIgG4, and ratios with tIgE) seems to be promising (especially in respiratory allergies) however, there are still contradictory findings. It is necessary to propose strategies where *in vitro* and *in vivo* markers are combined.

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