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REVIEW



Biological mechanisms underlying the clinical effects of allergen-specific immunotherapy in asthmatic children

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ABSTRACT

Introduction: Allergen-specific immunotherapy (AIT) is indicated for patients with allergic asthma and/or allergic rhinitis, and can be implemented by either subcutaneous injection (SCIT) or sublingual administration (SLIT). AIT reduces asthma symptoms, lowers the use of pharmacologic controller therapy, and decreases the need for rescue medications. SLIT appears to be safer than SCIT, but SCIT seems to be more efficacious and acts earlier in allergic asthmatic children.

Areas covered: This review looks at the pathobiology of allergic asthma as well as the role of regulatory T and B cells in allergen tolerance. It also reviews the immunological mechanisms underlying the clinical effects induced by AIT in allergic asthmatic children.

Expert opinion: AIT is very effective in allergic asthmatic children, who can significantly benefit from this particular type of immunotherapy in order to achieve a better control of their disease. AIT is also capable of modifying the natural history of allergic asthma. Furthermore, AIT can potentially represent a valuable therapeutic tool within the context of precision medicine, as recombinant allergen technology might allow the creation of targeted extracts able to be effective against specific proteins to which individual asthmatic children are allergic, thus helping to implement a personalized approach to treatment.

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1. Introduction

Asthma is a widespread chronic respiratory disease, affecting more than 300 million people worldwide [1–3]. In particular, asthma is the most prevalent pediatric disease: indeed, 1.1 million children in the United Kingdom, about 8.6% children in the United States in 2014, and 11–14% children in Japan in 2015, were estimated to suffer from asthma, respectively [4,5]. Childhood asthma is largely allergic, thus being characterized in most cases by bronchial eosinophilic inflammation sustained by a type 2 inflammatory response consisting of an overproduction of interleukins 4 (IL-4), 5 (IL-5), and 13 (IL-13), mainly secreted by T helper 2 (Th2) lymphocytes and group 2 innate lymphoid cells (ILC2) [5–9]. In addition to eosinophilic inflammation, allergic pediatric asthma is also featured by structural bronchial remodeling, including goblet cell hyperplasia, thickening of subepithelial reticular basement membrane, increased airway smooth muscle mass, and angiogenesis [10,11]. Both inflammatory and structural changes, which are well detectable in children by preschool and school age [12–14], significantly contribute to the onset and progression of airway hyperresponsiveness.

The development of allergic asthma is largely favored by an impaired allergen tolerance due to a defective function of regulatory T (Treg) and B (Breg) cells [15,16]. Treg cells induce immune tolerance against allergens by releasing regulatory cytokines such as interleukin-10 (IL-10), transforming growth

factor- β (TGF- β), and interleukin-35 (IL-35), which contribute to inhibit the activation of allergen-specific Th2 lymphocytes and the development of allergic inflammation [15,16]. IL-10 and TGF- β can be also produced by Breg cells [16]. Restoration of Treg and Breg cell functions is the main mechanism of action by which 'allergen-specific immunotherapy' (AIT) reinstates allergen tolerance in patients with allergic asthma [17]. In allergic asthmatic children, this mechanism makes it possible for AIT to effectively inhibit airway responses to allergens, thus improving asthma symptoms and quality of life, decreasing emergency room visits for asthma attacks, reducing bronchial hyperresponsiveness, lowering the use of rescue medications, as well as ameliorating the symptoms of a frequent comorbidity such as allergic rhinitis [18–20]. Therefore, when introduced quite early during the life of allergic asthmatic children, AIT can prevent asthma progression and potentially modify the natural evolution of this widespread disease.

Within this context, the aim of the present review article is to outline and discuss the pathobiology of allergic asthma, the role of Treg and Breg cells in allergen tolerance, and the mechanisms of action of AIT which underlie its efficacy in allergic asthmatic children.

2. Pathobiology of allergic asthma

Airway inflammation in allergic asthma is mediated by complex immune responses, mainly consisting of two phases

including an initial sensitization and memory phase, followed by a subsequent effector phase, respectively (Figure 1) [16,21,22]. Within the airways of genetically predisposed subjects, mucosal dendritic cells capture with their intraepithelial extensions incoming aeroallergens such as tree pollens, dust mites, and animal dander, thus internalizing, processing, and transporting them to draining cervical and thoracic lymph nodes. Here, dendritic cells load the processed antigen peptides within the context of HLA molecules belonging to class II of the major histocompatibility complex (MHC class II), and present them to T-cell receptors of naïve $CD4^+$ T lymphocytes, thereby driving their differentiation into allergen-specific $CD4^+$ Th2 cells. This commitment to Th2 phenotype is dependent on the presence of IL-4 mainly produced by mast cells and basophils, and also requires selective interactions of specific costimulatory molecules, expressed by dendritic cells (CD80/B7.1, CD86/B7.2, ICOS ligand, OX40 ligand), with their respective counter-ligands (CD28, ICOS, OX40) located on T cell surface [23,24]. Activated Th2 lymphocytes then release large amounts of IL-4 and IL-13, which at level of naïve B cells induce Ig class switching toward the synthesis of IgE antibodies. Hence, naïve B cells mature into IgE-producing plasma cells. Subsequently, memory B cells develop, which produce high quantities of allergen-specific IgE, capable of binding to their high-affinity receptors (FcεRI) expressed by mast cells and basophils. During such a sensitization phase (Figure 1,

left panel), patients are asymptomatic, but a clonal expansion of allergen-specific memory Th2 and B cells occurs, which makes allergic subjects prepared to react in case of re-exposure to allergens. In addition to these adaptive immune mechanisms, innate immune pathways involving airway epithelial cells, innate lymphoid cells, and further actions of dendritic cells also contribute to allergic sensitization [25,26]. In particular, inhaled allergens, respiratory viruses, and airborne pollutants stimulate bronchial epithelial cells to produce the innate cytokines thymic stromal lymphopoietin (TSLP), interleukins-25 (IL-25), 31 (IL-31), and 33 (IL-33), which promote Th2-dependent adaptive immune responses and induce both Th2 lymphocytes and ILC2 to express IL-4, IL-13, and IL-5 [9,27]. Dendritic cells also release CCL17 and CCL22 chemokines which bind to CCR4 receptors expressed by Th2 lymphocytes, thus recruiting them into the airways [28].

The effector phase of airway allergic inflammation takes place upon reexposure to allergens, when adjacent allergenic epitopes trigger cross-linking of two or more FcεRI-bound IgE molecules already present on cell membrane of mast cells (Figure 1, right panel). As a consequence, these cells release preformed mediators including histamine and tryptase, which are involved in the induction of immediate asthmatic reactions. Following IgE-mediated stimulation, mast cells also secrete newly synthesized lipid mediators (leukotrienes and prostaglandins) and proinflammatory cytokines, which are

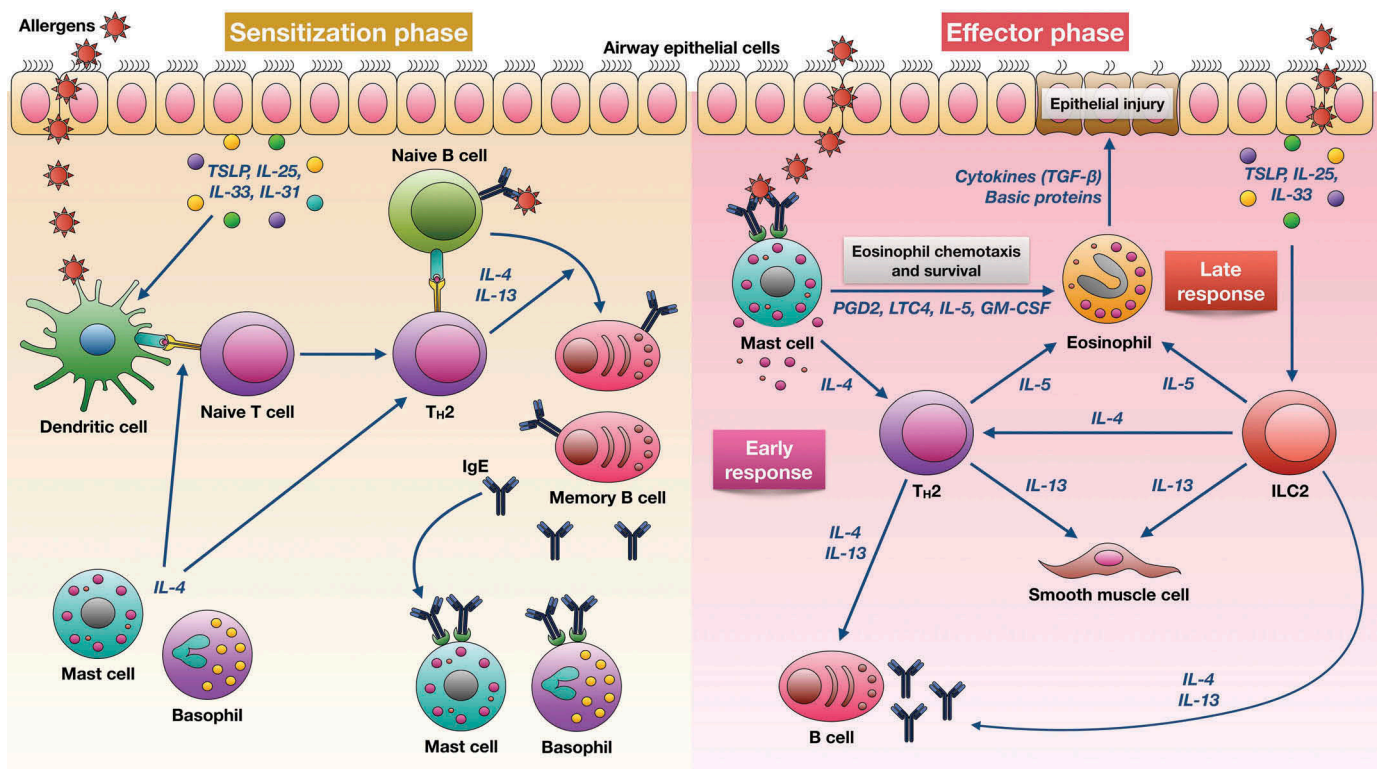


Figure 1. Pathobiology of allergic asthma. During the *sensitization phase* of allergic asthma, dendritic cells capture and process aeroallergens, and transport them to thoracic lymph nodes for presentation to naïve T lymphocytes, which in the presence of IL-4 differentiate into allergen-specific Th2 cells, producing IL-4 and IL-13. These cytokines prime B lymphocytes to synthesize IgE, that bind to their high affinity FcεRI receptors located on the surface of mast cells and basophils. Re-exposure to allergens induces the *effector phase*, characterized by a cross-linking of two or more adjacent FcεRI-bound IgE, which trigger mast cell degranulation as well as the consequent early and late asthmatic responses. Mast cells secrete several lipid mediators (e.g. PGD₂, LTC₄) and cytokines (e.g. IL-5, GM-CSF) that promote survival, proliferation and chemotaxis of eosinophils, which in turn release cytotoxic basic proteins and pro-apoptotic cytokines (TGF-β) causing damage and apoptosis of airway epithelial cells. During this phase, allergen-specific Th2 cells release high amounts of IL-4, IL-13, and IL-5, which is responsible for chronic eosinophilic airway inflammation. IL-4, IL-13, and IL-5 are also produced by group 2 innate lymphoid cells (ILC2), activated by alarmins (IL-25, IL-33, TSLP).

responsible for late asthmatic responses, as well as for further activation of allergen-specific Th2 cells leading to the most severe asthmatic symptoms, due to mucus production and especially to chronic bronchial inflammation sustained by persistence of high allergen-specific IgE levels and IL-5-dependent eosinophilia.

Airway eosinophilia is a hallmark of allergic asthma. The pivotal cytokine responsible for maturation, activation, survival, and chemotaxis of eosinophils is IL-5, whose action is synergized in chronic allergic asthma by some powerful eosinophil chemoattractants such as eotaxins 1/2 (CCL11/CCL24) and RANTES (CCL5 – regulated upon activation, normal T cell expressed and secreted), that are mainly produced by bronchial epithelial cells, mast cells, and eosinophils themselves [7,29]. With regard to the synthesis and release of IL-5, in addition to Th2 lymphocytes, mast cells and eosinophils, other key cellular sources of this cytokine are ILC2. Besides being activated by the airway epithelial cell-derived innate cytokines IL-25, IL-33 and TSLP, ILC2 are also responsive to activation induced by prostaglandin D₂ (PGD₂), cysteinyl leukotrienes, IL-2, IL-4, IL-7, IL-15, and some ligands of toll-like receptors [9,27,30,31]. In particular, PGD₂ is mainly produced by mast cells and orchestrates a complex intercellular network involving several different immune-inflammatory cells. PGD₂ exerts its biological functions by binding to the CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells) receptor expressed by Th2 cells, ILC2, basophils, and eosinophils. On these latter cells, PGD₂ activates the release of eosinophil cationic protein, stimulates cell migration, and also primes eosinophils to respond to other chemoattractants such as eotaxin [32]. Moreover, PGD₂ significantly contributes to the activation of ILC2, which produce IL-4, IL-13, and especially large amounts of IL-5 [7,29]. In atopic asthmatic patients, ILC2 can be activated within the airways by allergen inhalation challenge [33]. As a consequence, ILC2 can act as early cellular triggers of airway

eosinophilic infiltration and allergic inflammation [33]. Hence, in the pathobiology of allergic asthma a crucial role is played by a multicellular circuit. In particular, inhaled allergens damage airway epithelial cells and induce them to release the so-called alarmins (IL-25, IL-33, and TSLP). Allergens also promote the synthesis and release of mast cell-derived PGD₂. Alarmins and PGD₂ activate ILC2, that in turn stimulate the initial recruitment of eosinophils into the airways [27,33]. ILC2 also promote the subsequent activation of Th2 cells, which further contribute to the pathogenesis of allergic asthma and airway type 2 inflammation, sustained by persistent eosinophilia.

This complex cascade of cellular events results in initiation, maintenance, and amplification of allergen-induced bronchial inflammation, which is mainly expressed by chronic eosinophilic infiltration. Furthermore, eosinophils contribute to damage the airway epithelial layer through the release of cytotoxic proteins [34]. Eosinophils are also a relevant cellular source of transforming growth factor- β (TGF- β), that causes a direct injury to bronchial epithelial cells via induction of apoptosis [35], and stimulates airway fibroblasts to proliferate and produce extracellular matrix proteins [36].

3. Role of Treg and Breg cells in allergen tolerance

In healthy, nonallergic subjects, inhaled allergens are perceived as not harmful because they induce effective mechanisms of immune tolerance, largely mediated by Treg and Breg cells (Figure 2) [15,16].

Treg cells include several different subtypes such as thymus-derived CD25⁺ Foxp3⁺ Tregs (tTregs), peripherally derived Tregs generated outside the thymus after antigenic stimulation (pTregs), peripherally induced Foxp3⁺ T cells, IL-10-producing Treg cells (Tregs1), and TGF- β -producing Th3 cells [16,37,38]. In particular, Foxp3 (forkhead box P3) is the key

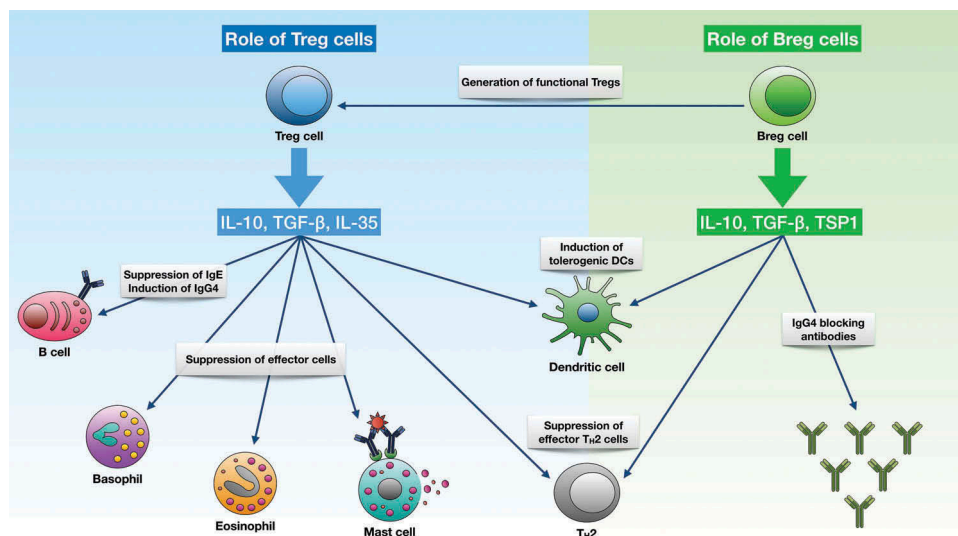


Figure 2. Role of Treg and Breg cells in allergen tolerance. Treg and Breg cells prevent and suppress allergic inflammation by inhibiting the functions of several effector cells such as Th2 lymphocytes, IgE-producing B lymphocytes, eosinophils, basophils, and mast cells. Moreover, Treg and Breg cells stimulate the activity of tolerogenic dendritic cells (DCs), and also induce the production of blocking IgG4 antibodies. All these regulatory effects are mainly mediated by the anti-inflammatory cytokines IL-10 and transforming growth factor- β (TGF- β).

transcription factor responsible for differentiation and development of various Treg cells [39–41]. Treg cells prevent and suppress allergic inflammation by inhibiting allergen-dependent bioactivity and degranulation of mast cells and basophils, and also by negatively regulating the cell functions of eosinophils, dendritic cells, and both T and B lymphocytes (Figure 2) [42]. These suppressive effects of Treg cells are mediated by multiple mechanisms including release of regulatory cytokines (IL-10, TGF- β , IL-35), as well as inhibition of dendritic cell activation operated by membrane-bound cytotoxic T-lymphocyte antigen 4 (CTLA-4), and induction of tolerogenic dendritic cell subsets [43]. Furthermore, Treg cells suppress activation of allergen-specific Th2 lymphocytes, downregulate the expression of Fc ϵ RI receptors on mast cells, decrease allergen-specific IgE synthesis, and promote B-cell production of the anti-inflammatory IgG4 antibody [44]. Treg cells, whose generation is induced by both immature and mature dendritic cells, can thereby inhibit the functions of the main cellular elements involved in both sensitization and effector phases underlying allergic asthma.

Besides Treg cells, Breg cells also play a relevant role in the induction of allergen tolerance. Breg cells can develop at various levels of maturation and differentiation of B lymphocytes, including immature B cells and highly differentiated plasmablasts and plasmacells [16,45]. Human Breg cells include several different subtypes such as CD27⁺CD24^{high}CD148^{high}CD48^{high} B10/pro-B10 cells, CD24^{hi}CD38^{hi} immature transitional B cells, CD73⁻CD25⁺CD71⁺ Br1 cells, and CD27^{int}CD38⁺ plasma cells [46]. In particular, Breg cells induce the synthesis of IgG4 blocking antibodies, inhibit activation and proliferation of effector T lymphocytes, suppress Th2-dependent inflammation, as well as promote T-cell expression of Foxp3 and generation of functional Treg cells (Figure 2). These effects of Breg cells are largely mediated by their ability to produce the inhibitory cytokines IL-10 and TGF- β , and the TGF- β -activating multifunctional protein thrombospondin 1 (TSP1) [47–51]. In addition to being dependent on secreted cytokines, the immunosuppressive effects of Breg cells are also mediated by other factors including membrane-associated proteins (CD19, CD62L, MHC-II) and intracellular signaling molecules (signal transducer and activation of transcription 3, myeloid differentiation response gene 88) [52].

4. AIT: mechanisms of action and clinical effects in allergic asthmatic children

AIT has been practiced for more than 100 years, with the aim of inducing tolerance to allergens in patients with IgE-mediated diseases [53–55]. Currently, AIT can be implemented by two main modalities, based on subcutaneous injection (SCIT) or sublingual administration (SLIT), respectively. SCIT consists of repeated subcutaneous injections of weekly increasing doses of extracts of the causal allergen, followed by maintenance doses separated by 4–8 weeks [56]. SLIT is performed by sublingual administration of allergen extracts prepared as dissolvable tablets or liquid formulations, often given accordingly to a once-daily schedule [57,58]. Both SCIT and SLIT are very effective in inducing immune tolerance to inhaled allergens via several mechanisms responsible for regulation of T/B cell-mediated and IgE-dependent responses, as well as for suppression of effector cells including mast cells, basophils, and eosinophils (Figure 3) [59].

AIT-induced immune tolerance depends on suppression of the functions of allergen-specific T and B memory cells, on modulation of allergen-specific IgE and IgG-mediated responses, as well as on inhibition of mast cell and basophil degranulation. In addition, AIT reduces airway eosinophilic infiltration and also lowers blood levels of a reliable marker of eosinophil activation such as eosinophil cationic protein [60]. Indeed, AIT suppresses Th2 lymphocytes and stimulates the generation and activation of Foxp3⁺ Treg cells, thus increasing their production of the inhibitory cytokines IL-10 and TGF- β [61,62]. AIT also enhances the number of Breg cells, such as Br1 cells expressing IL-10 [63]. AIT-induced IL-10 producing Breg cells are able to inhibit IgE synthesis and to suppress T lymphocytes and proinflammatory dendritic cells [47]. AIT shifts the Th2 secretory profile to a Th1 cytokine pattern [64]. Moreover, by driving an immune deviation from allergen-specific Th2 polarization to Treg cell commitment, as well as by inducing Breg cell proliferation, AIT effectively represses the production of allergen-specific IgE, and concomitantly stimulates the synthesis of IgG4 antibodies, thereby significantly decreasing the IgE/IgG4 ratio [44]. These effects of AIT are largely mediated by IL-10 [65]. IgG4 plays a key role in AIT-dependent modulation of immune responses. Indeed, an allergen-specific IgG4 competitively binds to the same

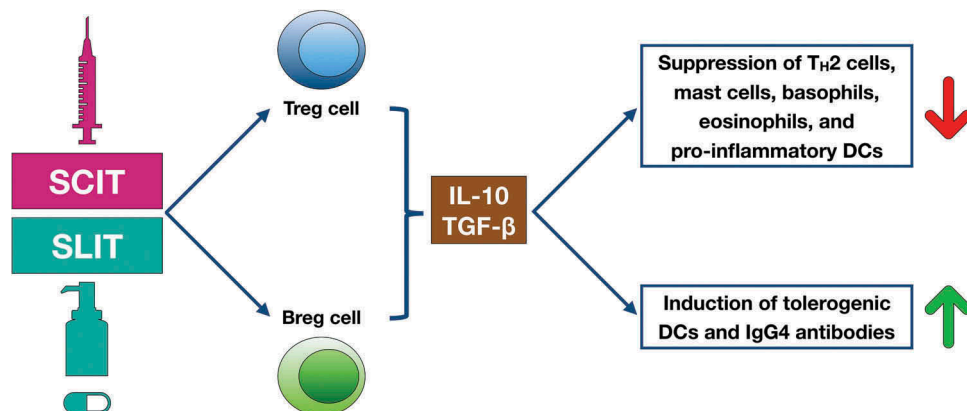


Figure 3. Mechanisms of action of allergen-specific immunotherapy (AIT). Both subcutaneous (SCIT) and sublingual (SLIT) AIT modalities prevent allergen sensitization and inhibit allergic inflammation mainly by inducing the generation and activation of Treg and Breg cells.

epitopes selectively recognized by IgE, thereby preventing the interactions between cell membrane-bound IgE and allergens [66]. Of course, this 'immunologic blockade' operated by IgG4 results in inhibition of mast cell and basophil degranulation. Moreover, IgG4 inhibits IgE-mediated facilitation of allergen presentation by antigen presenting cells to T lymphocytes [64]. Furthermore, AIT could also affect ILC2 bioactivity and proliferation. In this regard, it is noteworthy that AIT performed through subcutaneous injections of grass pollen extracts is able to suppress the seasonal increases in ILC2 numbers [67].

Therefore, AIT-induced immunologic tolerance is mainly mediated by Treg and Breg cells via their cytokine products, including IL-10 and TGF- β . The latter suppress both activity and proliferation of Th2 cells and ILC2, thus inhibiting the production of Th2 cytokines (IL-4, IL-5, IL-9, IL-13), and consequently decreasing the activation of eosinophils, basophils, mast cells, and IgE-secreting B lymphocytes [64,67,68]. In addition to the very well-documented ability of AIT to blunt allergic airway inflammation, recent data obtained using experimental murine models of allergic asthma suggest that SCIT can also affect bronchial remodeling, thus reducing goblet cell metaplasia, collagen deposition, and smooth muscle thickness [69]. These structural changes appear to be mediated by an AIT-induced increase of IL-10-producing Treg cells.

Both SCIT and SLIT are indicated for children with uncontrolled allergic asthma [18,19]. AIT is currently considered also by Global Initiative for Asthma guidelines as a possible option for management of allergic asthma in adults and children [70]. In particular, allergic asthmatic children are the main candidates for AIT when environmental measures and standard drug treatments are not sufficient to guarantee a satisfactory asthma control. However, pharmacological therapies must be continued even during AIT. AIT should be prescribed for the aeroallergens which are really responsible for allergic disease in a given subject. In this regard, in addition to clinical history, skin prick tests, and eventual detection of allergen-specific IgE antibodies in peripheral blood, identification of the major allergens which are the true antigenic triggers of allergic respiratory symptoms can also require the use of molecular diagnostic methods such as component-resolved diagnostics (CRD) [71–75]. Indeed, instead of utilizing crude allergen extracts, as in conventional allergy diagnosis, CRD uses purified or recombinant allergens for detection of specific causative molecules. Hence, CRD could be especially useful in polysensitized allergic patients. However, despite these promising perspectives, so far no study has shown that AIT based on CRD is more effective.

The efficacy of SCIT has been evaluated in several trials carried out in asthmatic children monosensitized to house dust mite (HDM) [19].

In addition to HDM-SCIT, specific SCIT for *Alternaria* also resulted to be effective in decreasing seasonal symptoms of allergic asthma [18].

In spite of the widespread concerns about the potential risk of adverse events eventually triggered by SCIT, this AIT is quite safe and well tolerated in children, and anaphylactic reactions rarely occur [19,76].

SLIT is particularly useful for allergic asthmatic children because does not need injections, can be performed at home rather than in a medical center, and especially because of its excellent safety and tolerability profile, which makes the risk of severe adverse events practically irrelevant [77–79]. In fact, one of the most commonly reported adverse reactions is just mild oral itch [80]. Many trials have documented the effectiveness of HDM-SLIT in asthmatic children. A recent meta-analysis showed that SLIT significantly improved asthma symptom score and enhanced serum IgG4 levels in asthmatic children sensitized to HDM [81]. HDM-SLIT also decreased the number of acute asthma attacks, as well as the use of inhaled corticosteroids (ICS) and rescue medications [82–84]. In addition to HDM-SLIT, grass pollen-SLIT has also been shown to be efficacious in the management of allergic asthma in children, regardless of its continuous or co-seasonal use [19]. In this regard, it has been recently shown that SQ grass SLIT tablets decreased the development of asthma symptoms and the use of asthma medication, but did not induce any effect on the time to asthma onset [85].

Overall, in allergic asthmatic children, SCIT appears to be more effective than SLIT, whereas SLIT is safer than SCIT [19]. SLIT may have a positive impact on the quality of life of pediatric patients [86]. With regard to health economic analysis, a recent systematic overview further corroborates current evidence that both SLIT and SCIT can be cost-effective for patients with allergic asthma and rhinitis [87].

5. Concluding remarks

Taken together, currently available data suggest that AIT is quite effective in children with allergic asthma whose disease is not adequately controlled by standard pharmacological treatment. In particular, the benefits of both SCIT and SLIT in pediatric asthmatic patients include relevant improvements in respiratory symptoms, lung function, quality of life, and drug intake. AIT efficacy is due to its ability to interfere with key cellular and molecular pathways underlying the IgE-mediated immune cascade responsible for allergic asthma. In asthmatic children AIT efficacy is associated, especially with regard to SLIT, with a very good safety and tolerability profile. Therefore, all these features make AIT a therapeutic and preventive approach particularly useful for the management of allergic pediatric asthma.

6. Expert opinion

For allergic asthmatic children, AIT provides a valuable further therapeutic option, in addition to the widely used pharmacological treatments [88]. Indeed, pediatric asthma may be particularly susceptible to the potential disease-modifying properties of AIT. AIT restores an impaired allergic tolerance mainly by inducing the generation and activation of Treg and Breg cells, thus making it possible to shut down Th2-dependent and ILC2-mediated cellular and molecular pathways underlying allergic asthma. Through its peculiar mechanisms of action, AIT works as an upstream silencer of the immune cascade leading to IgE-mediated asthma. As a consequence of these powerful interferences with the pathogenic circuits responsible for allergic asthma, AIT induces a very effective inhibition of both

sensitization and effector phases, thereby remarkably increasing the activation threshold of mast cells and basophils, and also significantly reducing airway eosinophilic infiltration. Moreover, in addition to dampening the inflammatory substrate of allergic asthma, AIT can also potentially modulate the bronchial structural changes elicited by several cytokines released by immune cells. Of course, the positive impact of AIT might be especially effective in childhood and adolescence, when an early influence on the natural history of asthma could really slow down the progressive disease evolution. Such successful features of AIT are convincingly confirmed by its ability to attenuate asthma severity and to provide a prolonged curative action, documented by the persistent clinical benefits as well as by the prevention of further allergen sensitization, observable even after AIT interruption.

In addition, the relevant AIT-induced reduction of ICS usage is very advantageous in asthmatic children, who can be particularly exposed to the systemic side effects of ICS treatment. A decreased ICS intake, allowed by AIT, is also very useful in view of the well-known inability of glucocorticoids to affect the progressive deterioration of lung function in asthma [89], despite their excellent therapeutic actions with regard to disease control.

In the next future, the disease-modifying properties of AIT could be further potentiated by possible associations with the modern biological therapies of asthma [90]. Indeed, the currently available biologics for asthma treatment, as well as those which will be introduced in the coming years, are mainly directed against molecular targets involved in Th2-driven allergy and type 2 airway inflammation. Hence, AIT can exert an upstream blockade of Th2 cell polarization and activation, whereas anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab), anti-IL-5 receptor (benralizumab), and anti-IL-4/13 receptor (dupilumab) monoclonal antibodies may synergize with AIT downstream by inhibiting the proinflammatory and remodeling effects of IgE and Th2 cell-derived cytokines. In support of these concepts, preliminary findings also referring to children and adolescents suggest that the concomitant administration of the anti-IgE monoclonal antibody omalizumab can enhance AIT safety and efficacy [91,92].

On the basis of the above considerations, it should be helpful to bring more attention to the benefits of AIT in children with allergic asthma. In this regard, SLIT can be extremely useful because of its high safety and feasibility, which may significantly improve treatment adherence in the pediatric population of allergic asthmatic patients. An additional development of AIT regards the possibility of improving the implementation of personalized therapeutic options, based on recombinant antigen technology aimed to realize allergen extracts targeted to the specific proteins toward which an individual young asthmatic is allergic.

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