Applications and mechanisms of immunotherapy in allergic rhinitis and asthma

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Abstract: Clinical and immunologic tolerance are hallmarks of successful allergen immunotherapy (AIT). Clinical benefits such as reduced symptoms, pharmacotherapy intake and improvement of quality of life persist following cessation of treatment. Successful AIT is associated with suppression of allergic inflammatory cells such as mast cells, eosinophils and basophils in target organs. Furthermore, AIT down-regulates type 2 innate lymphoid cells and allergen-specific type 2 T-helper (Th2) cells. The immunologic tolerant state following AIT is associated with the induction of distinct phenotypes of regulatory T-cells (T-regs) including interleukin (IL)-10-, IL-35- and transforming growth factor (TGF)-β- producing T-regs and FoxP3$^+$ T-regs. B-cell responses, including the induction of IL-10$^+$ regulatory B-cells (B-regs) and the production of IgG4-associated blocking antibodies are also induced following successful AIT. These events are associated with the suppression of antigen-specific Th2 responses and delayed immune deviation in favour of Th1 type responses. Insight into the mechanisms of AIT has allowed identification of novel biomarkers with potential to predict the clinical response to AIT and also novel therapeutic strategies for more effective and safer AIT.

Keywords: allergen immunotherapy, allergic rhinitis, allergy, asthma, biomarkers, blocking antibodies, dendritic cells, IgA, IgG4, regulatory B-cells, regulatory T-cells, tolerance

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Introduction

Allergic rhinitis (AR) and asthma are common diseases with prevalence estimates of up to 30% for AR and 10–20% for asthma [Bauchau and Durham, 2004; Eder *et al.* 2006; Bernstein, 2010; Sullivan *et al.* 2011; Martinez and Vercelli, 2013]. Most patients with asthma have AR while up to 40% of patients with AR also have asthma comorbidity [Cruz *et al.* 2007; Compalati *et al.* 2010; Braunstahl, 2011]. Moreover, AR is an independent risk factor in the development of asthma [Guerra *et al.* 2002]. In western countries, allergic disorders such as AR and asthma have a considerable impact on quality of life [Bauchau and Durham, 2004; Eder *et al.* 2006; Sullivan *et al.* 2011]. They affect school performance in children and work productivity in adults [Simons, 1996; Cockburn *et al.* 1999; Sullivan *et al.* 2011]. Disease burden is mainly caused by responses on exposure to common aeroallergens derived from grass, birch, pet or house dust mite [Bousquet *et al.* 2001; Bauchau and Durham, 2004].

Allergen avoidance and pharmacotherapy such as antihistamines and local corticosteroids are the first line treatment management for controlling symptoms in AR [Bousquet *et al.* 2012; Braido *et al.* 2014; Jutel, 2014; Scadding, 2015; Wheatley and Togias, 2015]. For asthma control, long acting bronchodilators (LABAs) and inhaled corticosteroids (ICSs) are recommended by current guidelines [Reddel *et al.* 2015a, 2015b]. Although therapies for AR with or without asthma have proven effective in controlling symptoms and reducing inflammation, a small proportion of patients do not respond to pharmacotherapy and in these patients, allergen-specific immunotherapy may be of importance.

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Allergen immunotherapy (AIT), first reported by Leonard Noon in the early 20th century, is a highly effective treatment in individuals with immunoglobulin (Ig)E-mediated diseases [Bousquet *et al.* 1998; Durham *et al.* 1999; Calderon *et al.* 2007; Shamji *et al.* 2012]. AIT is associated with the reduction of symptoms [Calderon *et al.* 2007, 2011; Compalati *et al.* 2014], a reduction in the use of rescue medications, improvement of quality of life [Malling and Bousquet, 2008; Burks *et al.* 2013; Canonica *et al.* 2014; Jutel *et al.* 2015] and induces clinical and immunological allergen-specific immune tolerance [Bousquet *et al.* 1998; Durham *et al.* 1999; Bousquet *et al.* 2001; Calderon *et al.* 2007; Bousquet *et al.* 2008; Shamji *et al.* 2012]. AIT can be administered either by a subcutaneous (SCIT) or sublingual (SLIT) route. Although adequate head-to-head studies comparing SLIT and SCIT are limited, there is a tendency to think that SCIT might be superior to SLIT [Di Bona *et al.* 2012; Chelladurai *et al.* 2013; Dretzke *et al.* 2013]. SLIT is considered to have a safer profile compared with SCIT, with a lower number of anaphylactic reactions. However, local side effects have been reported following SLIT [Fujimura and Okamoto, 2010]. AIT is most often applied in mono-allergy but can also be used in multi-allergic patients.

According to the AR and its Impact on Asthma (ARIA) guidelines [Brozek *et al.* 2010; Bousquet *et al.* 2012], AIT is indicated in moderate-to-severe intermittent AR if patients are unresponsive to pharmacotherapy. However, ARIA guidelines only give a conditional recommendation for AIT (both SLIT and SCIT) in allergic asthma due to moderate and low quality evidence [Brozek *et al.* 2010; Bousquet *et al.* 2012], while Global Initiative for Asthma (GINA) guidelines indicate that AIT should be considered after pharmacological treatment and allergen avoidance [Reddel *et al.* 2015a]. Current guidelines state that in clinical practice, uncontrolled asthma is a contraindication for both SCIT and SLIT [Di Bona *et al.* 2012; Pitsios *et al.* 2015].

Effects of allergen immunotherapy on early and late phase responses

Both the early and the late phase allergic responses are suppressed after AIT, starting with the late phase response already 2 weeks after the start of treatment [Francis *et al.* 2008]. Suppression of the IgE-mediated early cutaneous responses is less pronounced and occurs 8–12 weeks after the first dose [Durham *et al.* 1999; Francis *et al.* 2008]. Interestingly, mast cell and basophil degranulation is decreased soon after the first injection of AIT [Iliopoulos *et al.* 1991; Akdis and Akdis, 2015]. In other studies, skin biopsies following AIT have shown reduced numbers of eosinophilic, neutrophilic and basophilic infiltration after AIT [Varney *et al.* 1993; Nish *et al.* 1994]. The suppression of late phase responses have been reported in skin, nose and in the lungs [Warner *et al.* 1978; Pienkowski *et al.* 1985; Iliopoulos *et al.* 1991]. Reduction in nasal responses have also been reported for grass pollen, and cat allergens [Nanda *et al.* 2004; Puggioni *et al.* 2005]. Allergic asthmatics demonstrated a reduction in late responses after AIT in mite and birch studies [Warner *et al.* 1978; Arvidsson *et al.* 2004].

Mechanisms of allergen immunotherapy

A variety of immune cells, such as T-helper lymphocytes type 2 (Th2), eosinophils, mast cells and basophils [Arvidsson *et al.* 2004; Novak *et al.* 2011; Shamji *et al.* 2011], are responsible for the inflammation observed in allergic diseases. Th2 cells play an essential role by producing cytokines such as interleukin (IL)-4, IL-5 and IL-13 that subsequently are responsible for the induction of effector cells. Furthermore, Th2 cells drive B-cells to produce allergen-specific IgE (sIgE). Cellular and humoral responses associated with AIT are presented in Figure 1.

Cellular changes

In allergic individuals, cytokines and mediators such as TSLP, IL-25, IL-33 derived from epithelial cells induce dendritic cells (DCs) to polarize naïve T-cell responses towards a Th2 response [Bellinghausen *et al.* 2001; Hurst *et al.* 2002; Soumelis *et al.* 2002; Ito *et al.* 2005; Schmitz *et al.* 2005]. AIT results in an induction of tolerant DCs that skew naïve T-cells towards IL-10-producing regulatory T-cells (Tregs) subsequently leading to a Th1 response [Shamji *et al.* 2011; Akdis and Akdis, 2015]. Several studies have reported the increase of Th1 cytokines and chemokines such as eotaxin, or tumour necrosis factor (TNF)α, paralleled by an upregulation of Th1 [interferon (IFN)-γ, IL-12] and regulatory cytokines [IL-10, transforming growth factor (TGF)β] [Faith *et al.* 2003; Jutel *et al.* 2003] although others report no changes [Wachholz *et al.* 2002; Francis *et al.* 2003]. It is still believed that these changes in serum cytokines as well as chemokines are immunological

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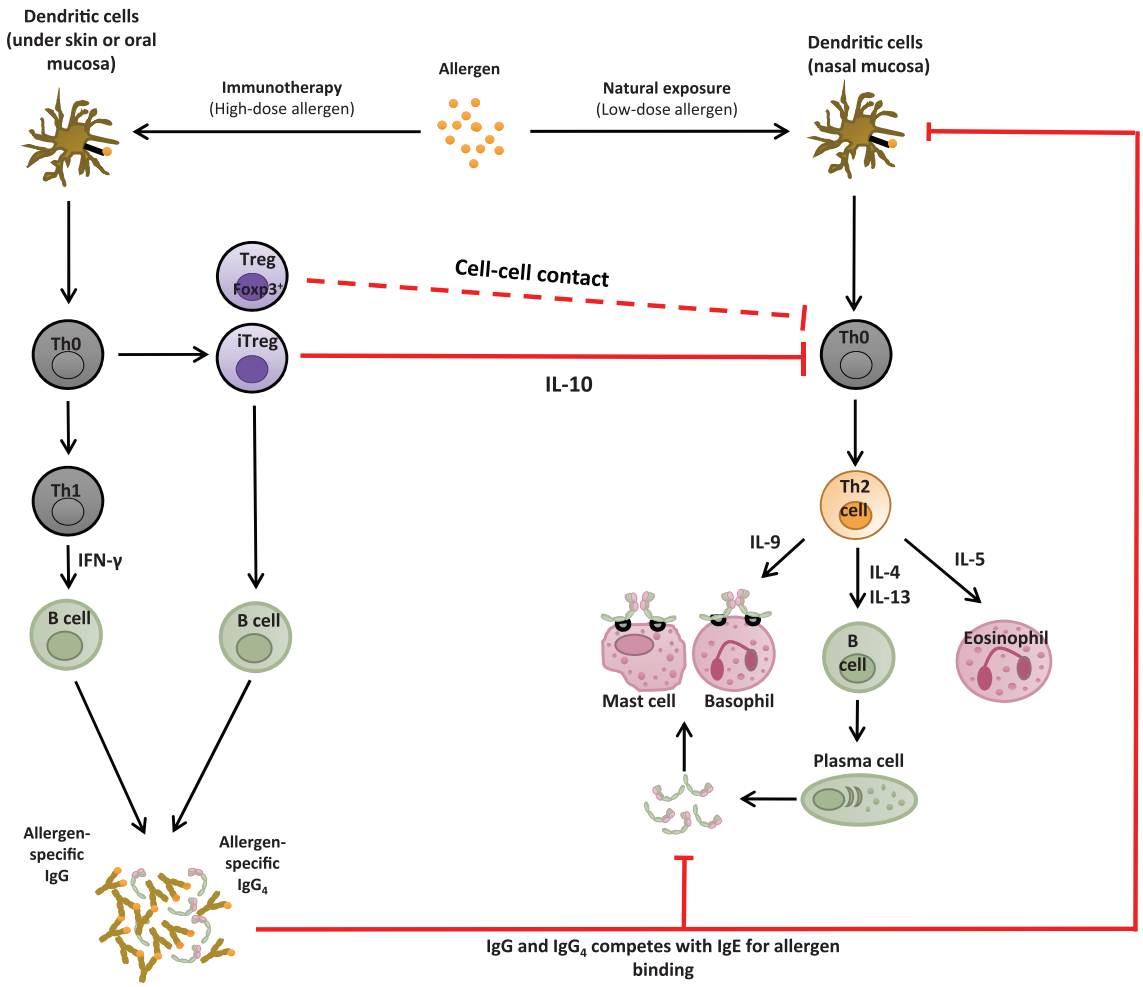

Figure 1. Mechanisms of immunological and clinical tolerance in AIT. Natural (low-dose) allergen exposure at mucosal surfaces results in a Th2-driven allergic inflammation with mast-cells, basophils and eosinophilic activity. High-dose allergen administered by SLIT or SCIT immunotherapy results in immune deviation from a Th2 to a Th1-driven response. This is accompanied by an increase in the ratio of Th1 cytokines such as IFN-γ and an induction of Treg cells and inducible Treg cells (iTregs) and an increase in the regulatory cytokines such as IL-10. Furthermore, AIT leads to allergen-specific IgG, in particular IgG4 antibodies with inhibitory activity.
AIT, allergen immunotherapy; IFN, interferon; Ig, immunoglobulin; IL, interleukin; iTreg, inducible Treg; Th, T-helper lymphocyte; Treg, regulatory T-cells; SCIT, subcutaneous AIT; SLIT, sublingual AIT

paraphenomena of AIT, often not directly correlated with clinical outcome. Also local cytokines indicate a skew towards a more Th1 response; however only a very limited number of studies are available to support these findings [Kirmaz *et al.* 2011; Scadding *et al.* 2015]. Recent data also demonstrate that AIT inhibits the seasonal increase of type 2 innate lymphoid cells [Lao-Araya *et al.* 2014].

A key mechanism in tolerance induction following AIT is the upregulation of peripheral and local allergen-specific Tregs [Bohle *et al.* 2007; Radulovic *et al.* 2008; O'Hehir *et al.* 2009; Rolland *et al.* 2010; Scadding *et al.* 2010; Akdis and Akdis, 2014]. Treg cells can be grouped into two subsets, Foxp3+ Tregs and inducible Tregs (iTregs) that produce regulatory cytokines such as IL-10, TGF-β and IL-35 [Bohle *et al.* 2007; Shamji *et al.* 2012, 2013]. Several studies have suggested that there is an overlap between these subsets of Treg cells in immunomodulating properties [Akdis and Akdis, 2015]. The early induction of Tregs during AIT has been associated with delayed immune deviation from Th2-type response to Th1-type response, mainly because of increased IL-10 production. Also, the association of increased numbers of Tregs in the nasal mucosa

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after immunotherapy with positive clinical outcome, as well as the suppression of seasonal allergic inflammation, support a central role for Treg cells in the induction of allergen-specific tolerance [Radulovic *et al.* 2008; Scadding *et al.* 2010]. Recently, epigenetic changes of memory Treg cells during dual house dust mite (HDM) and grass pollen SLIT indicated that methylation of the FOXP3 locus might be involved in the mechanism of allergy tolerance after AIT [Mitra *et al.* 2012].

During AIT, B-cells show a shift from producing the allergenic IgE to the more 'protective' IgG4. Although symptoms decrease from the start of AIT, a transient increase in sIgE is observed in serum. Eventually there is a gradual decrease of sIgE in serum over years of treatment [Van Der Neut Kolfschoten *et al.* 2007]. Specific IgG4 shows a relatively early and rapid increase and continues to increase during AIT. After discontinuation of treatment, sIgG4 decreases again; however it still remains elevated compared with baseline levels [Shamji *et al.* 2011, 2012].

Apart from antibody production, B-cells also contribute to immune responses through antigen presentation to T-cells and secretion of cytokines. For the production of antibodies B-cells differentiate to plasma cells which can reside for many years in in the bone marrow; even independent of exposure to antigens they can produce antibodies. The upregulated IL-10 suppresses antigen presentation by antigen presenting cells as well Th2 production of IL-4 which leads to a lower IgE production by plasma cells. At the B-cell level, IL-10 enhances the survival, proliferation, differentiation and isotype switching of human B-cells resulting in IgA and IgG4 production.

DCs are specialized antigen-presenting cells and can initiate and sustain allergic inflammation, or support tolerance induction. A recent AIT study demonstrated a significant decrease in the number of DCs and an upregulation of regulatory DCs (DCreg) after SLIT in grass pollen-allergic patients [Zimmer *et al.* 2012]. Changes in the DCreg/DC2 balance occur after 4 months of SLIT. Changes in DCs were only identified in those patients with a significant decrease in rhinoconjunctivitis symptoms [Zimmer *et al.* 2012]. After 1 year of SLIT, low production of IL-12 and an increased IL-10 secretion as well as a decreased capacity to mature was observed in HDM-allergic children [Angelini *et al.* 2011].

Basophils consist of 1% of leucocytes in peripheral blood and contain cytoplasmic secretory granules that have an important role in systemic allergic responses [Ishizaka *et al.* 1972; Falcone *et al.* 2011]. Allergen cross-linking of sIgE on basophils initiates degranulation and subsequent release of histamine, leukotrienes, and other mediators of the allergic inflammatory response [Schroeder *et al.* 1995; Macglashan, 2010]. It has been shown that after AIT, basophil activation is inhibited by preventing allergen IgE interaction or the interaction with FcγRIIb by competitive allergen-specific IgG antibodies, including IgG4 [Van Neerven *et al.* 1999; Kepley *et al.* 2000; Wachholz *et al.* 2003].

Recently, a reverse staining technique for basophil activation was used in which phycoerythrin-conjugated diamine oxidase (DAO) binding histamine within the cell was reduced after degranulation of basophils [Ebo *et al.* 2012].

The results obtained with basophil activation during AIT in placebo-controlled studies are conflicting. Some authors describe reduction in basophil activation following AIT possibly due to serological factors [Ceuppens *et al.* 2009; Aasbjerg *et al.* 2014; Ozdemira *et al.* 2014; Schmid *et al.* 2014]. Van Overtvelt and Gomez failed to demonstrate the effects of AIT on basophil activation following AIT [Van Overtvelt *et al.* 2011; Gomez *et al.* 2015].

The suppression of basophil activation after discontinuation of AIT has been demonstrated 12–24 months following discontinuation of treatment [Nopp *et al.* 2009; Lalek *et al.* 2010; Gokmen *et al.* 2012; Shamji *et al.* 2015; Zidarn *et al.* 2015].

Humoral changes

The gold standard for allergy diagnosis and starting AIT is a serum-elevated sIgE in the context of symptoms in exposure to the relevant allergen [Cox *et al.* 2011; Burks *et al.* 2013; Calderon *et al.* 2013]. Many pollen AIT studies demonstrated transient increases of sIgE levels followed by blunting of the seasonal increases. So far, no functional relevance or severe allergic reactions have been associated with this transient increase. In AIT studies with a long duration, the levels of sIgE levels were shown to decrease over time [Nouri-Aria *et al.* 2004; Pilette *et al.* 2007]. For total IgE response during AIT the results are

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contradictory. Many studies have reported no change while others have reported an increase or decrease in the levels of IgE.

In the mid-1930s, Cooke reported on the induction of serum inhibitory antibody activity following AIT which later proved to be serum inhibitory activity for IgE [Cooke *et al.* 1935]. It is assumed that mainly antibodies in the IgA and IgG fraction of the serum cause this effect [Lichtenstein *et al.* 1968; Platts-Mills *et al.* 1976]. As a result of AIT, increases in the range of 10–100 fold in the concentrations of IgG1 and particularly of IgG4 are observed [Jutel *et al.* 2005; Reisinger *et al.* 2005]. Some studies were even able to demonstrate, a correlation between allergen sIgG4 and clinical outcomes [Gehlhar *et al.* 1999; Moverare *et al.* 2002; Nelson *et al.* 2011; Gomez *et al.* 2015]. After the initial induction of sIgG4 the levels decrease after discontinuation of treatment, although are still elevated compared with baseline levels. It is thought that IgG4 competes with allergen-binding to the IgE on the Fcε receptors of mast cells and basophils, and thus acts as a blocking antibody that prevents the activation and degranulation of effector cells [Van Neerven *et al.* 1999; Wurtzen *et al.* 2008]. In addition, some other features of IgG4 suggest that it could have an anti-inflammatory role. IgG4 antibodies are dynamic molecules that exchange Fab (facilitating antigen binding) arms by swapping heavy-light chain pairs between IgG4 molecules with different specificities and immune complex formation; whereas they retain their inhibitory activity by competing with IgE for allergens, thereby inhibiting IgE-allergen complex formation [Rispens *et al.* 2011]. This process results in the production of bi-specific antibodies with a substantially decreased capacity for cross-linking [Aalberse and Schuurman, 2002]. In addition, serum 'blocking' IgG4 antibodies have the capacity to suppress both allergen-triggered basophil histamine release and the binding of IgE-allergen complexes to B-cells.

Also, in nasal secretions, IgG levels in allergic individuals are also elevated [Platts-Mills *et al.* 1976]. More recently, sIgG4 antibodies with inhibitory activity for IgE-facilitated antigen binding (IgE-FAB) were measured in the nasal fluid of SLIT patients [Saleem *et al.* 2013; Shamji *et al.* 2013]. It was demonstrated that sIgG4 levels were increased in AIT and that the inhibitory effect was significantly increased compared with untreated patients. An interesting observation was that the magnitude of the suppression was higher in the local antibodies compared with peripheral antibodies [Saleem *et al.* 2013; Shamji *et al.* 2013]. Furthermore, the ratio of IgE/sIgG4 was demonstrated to decrease in several SLIT studies and was correlated with a decrease in late-phase skin reaction [Troise *et al.* 1995; La Rosa *et al.* 1999; Lima *et al.* 2002; Bahceciler *et al.* 2005]; however, this was not a consistent finding [Rolinck-Werninghaus *et al.* 2005]. One study with genetically modified allergens showed IgG1 and IgG4 in mucosal fluids after AIT. The increase of IgG4 levels was significantly associated with a reduction in nasal sensitivity [Reisinger *et al.* 2005].

In allergic individuals, allergen-IgE complexes bind to low-affinity IgE receptor FcεRII (CD23) on the surface of B-cells (IgE-FAB); subsequently activated B-cells would be able to present the allergen to specific T-cell clones. It has been demonstrated in several studies that serum obtained from subjects receiving birch pollen immunotherapy inhibits IgE-facilitated presentation of allergen by B-cells to an allergen-specific T-cell clone [Van Neerven *et al.* 1999; Wurtzen *et al.* 2008]. Furthermore, serum obtained from patients that received grass pollen immunotherapy could inhibit IgE-facilitated allergen presentation to a grass-specific T-cell clone [Wachholz *et al.* 2003]. Specific IgG4 appears to play a key role in this mechanism [Nouri-Aria *et al.* 2004; James *et al.* 2011]. IgE-Fab has been shown to decrease after AIT and is modestly correlated with a clinical response to grass and birch AIT up to 2 years after discontinuation of AIT [Van Neerven *et al.* 1999; Wachholz *et al.* 2003; Durham *et al.* 2012].

Follow up on immunotherapy

Clinical follow up

The efficacy of AIT is evaluated by clinical symptoms and rescue medications scores at the time of natural allergen exposure; however there is no validated and generally accepted method for combining clinical parameters with medication scores. An overview of available methods was presented by Pfaar and colleagues in an European Academy of Allergy and Clinical Immunology (EAACI) task force position paper in 2014 [Pfaar *et al.* 2014]. All advantages and unmet needs of the different methods are listed.

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The task force highlights combined symptom and medication scores (CSMS) as primary endpoints for AIT in allergic rhinoconjunctivitis. For assessing the disease from the patients' perspective, the Visual Analogue Score (VAS) is considered to be a useful, easy and (partially) validated measure, to be included in clinical trials on AIT aimed to provide a quantitative evaluation of disease severity [Pfaar *et al.* 2014; Hellings *et al.* 2015].

Biomarkers

Biomarkers are quantitative measurements that predict clinical and immunological effects of AIT in the target organ. Markers can be cellular (e.g. Tregs), humoral (sIgG4, IgE/IgG4), molecular (interleukins) or functional (IgE-FAB and blocking factor). Biomarkers could assist in patient selection, identification of responders, target intervention of those who will benefit and to exclude those who are less likely to respond to AIT. Furthermore, they could be of assistance in clinical trials for the development of treatment modalities. Although an overview and recommendations for the standardization of clinical outcomes used in AIT is available [Pfaar *et al.* 2014], to date there is no consensus on candidate biomarkers that are predictive of the clinical response to AIT [Food and Drug Administration, 2008]. Table 1 presents an overview of studies with a clinical improvement after AIT presenting data on some biomarkers. At present, raised serum sIgE in the context of a clear history of symptoms on exposure to the relevant allergen is the only generally available biomarker for selection of patients for immunotherapy.

The recent availability of allergen micro-arrays has refined the process to assist in the identification of patients with irrelevant cross-reacting IgE-antibodies to pan allergens. An example is selecting patients for grass immunotherapy on the basis of having IgE-antibodies to Phleum p 1 and/or Phleum p 5, whereas a positive skin test with Phleum extract in the context of a positive Phleum p 12 is likely to represent irrelevant cross-reactivity with the birch profilin Bet v 2.

As mentioned above, many cellular and humoral changes are observed during and after AIT. For example with the increase in sIgG4, some studies were even able to demonstrate a correlation between allergen sIgG4 and clinical outcomes [Gehlhar *et al.* 1999; Moverare *et al.* 2002; Nelson *et al.* 2011; Gomez *et al.* 2015]. Although after the initial induction of sIgG4 the levels decrease after discontinuation of treatment, they are still elevated compared with baseline levels.

A promising assay for the follow up of AIT is IgE-FAB, an *in vitro* biofunctional cellular assay that proved to be highly reproducible. It has a within-assay and between-assay reproducibility of 4% and 12% respectively, and can be utilized to detect IgG-associated serum inhibitory activity during as well as after discontinuation of AIT. The assay is highly complex and therefore limited to specialized laboratories. More recently, an alternative and less complex method, an Enzyme-Linked Immunosorbent Facilitated Antigen Binding (ELIFAB) assay, has become available [Shamji *et al.* 2013].

Some studies show a modest correlation with clinical response to grass or birch and IgE-FAB [Van Neerven *et al.* 1999; Wachholz *et al.* 2003]. One study even demonstrated sustained immunological changes of IgE-FAB for 2 years [Durham *et al.* 2012]. Furthermore, an inverse correlation has been found between symptom scores, rescue medication scores and IgE-FAB [Shamji *et al.* 2012; Schmid *et al.* 2014]. Unfortunately to date there are no data available on the possible relationship between IgE-FAB and responders *versus* nonresponders to AIT.

Concluding remarks

AR and asthma are common diseases that often coincide, while AR itself is an independent risk factor in the development of asthma. Disease burden has an impact on the quality of life and work productivity. When allergen avoidance and pharmacotherapy are not sufficient for disease control, AIT is advised under available guidelines. AIT is an effective, antigen-specific immune-modifying treatment that induces longterm tolerance. The mechanisms involved in AIT become clearer. Skewing from a Th2 response towards a more Th1 profile appears to play a key role in the mechanisms of AIT. IL-10 producing Tregs promote the development of sIgG4-producing plasma cells and sIgG4 competes with sIgE in allergen binding. A better understanding in the underlying

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Table 1. An overview of biomarker responses in AIT studies.

Biomarkers	Allergens	Immunologic response	Number of studies	References
sIgG4	Grass	Increased	18	Didier *et al.* [2007]; Dahl *et al.* [2008]; Purohit *et al.* [2008]; Durham *et al.* [2010, 2012]; Scadding *et al.* [2010]; Blaiss *et al.* [2011]; James *et al.* [2011]; Nelson *et al.* [2011]; Klimek *et al.* [2012]; Shamji *et al.* [2012b, 2015]; Aasbjerg *et al.* [2014]; Ozdemira *et al.* [2014]; Keskin *et al.* [2006]; Amar *et al.* [2009]; Cox *et al.* [2012]; Wahn *et al.* [2012]
		Decreased	2	Ariano *et al.* [1999]; Zidarn *et al.* [2015]
		No change	2	Mosges *et al.* [2007]; Ott *et al.* [2009]
	HDM	Increased	8	Bousquet *et al.* [1999]; Lue *et al.* [2006]; Pham-Thi *et al.* [2007]; O'Hehir *et al.* [2009]; Zielen *et al.* [2010]; Keles *et al.* [2011]; Yukselen *et al.* [2012]; Gomez *et al.* [2015]
		No change	3	Cosmi *et al.* [2006]; Yukselen *et al.* [2012]; Wang *et al.* [2013]
IgE-BF	Grass	Increased	8	Dahl *et al.* [2008]; Durham *et al.* [2010]; Blaiss *et al.* [2011]; Nelson *et al.* [2011]; Durham *et al.* [2012]; Shamji *et al.* [2012b]; Aasbjerg *et al.* [2014]; Schmid *et al.* [2014]
	HDM	Increased	1	Corzo *et al.* [2014]
IgE-FAB	Grass	Increased	7	Scadding *et al.* [2010]; James *et al.* [2011]; Durham *et al.* [2012]; Shamji *et al.* [2012b, 2015]; Aasbjerg *et al.* [2014]; Schmid *et al.* [2014]
sIgE/tIgE	Grass	Increased	1	Di Lorenzo *et al.* [2009]
	HDM	Increased	2	Di Lorenzo *et al.* [2009]; Li *et al.* [2014]
		No change	1	Eifan *et al.* [2010]

AIT, allergen immunotherapy; HDM, house dust mite; Ig, immunoglobulin; IgE-BF, IgE blocking factor; IgE-FAB, IgE-facilitated antigen binding to B-cells; sIgE/tIgE, ratio of sIgE over total IgE; sIgG4, allergen specific IgG4.

mechanisms will eventually lead to novel treatment modalities as well as biomarkers for the follow up of AIT.

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