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Original Research

Allergen immunotherapy for allergic asthma: The future seems bright

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ABSTRACT

Allergen specific immunotherapy (AIT) is the only causal therapeutic option for allergic airway diseases including asthma and allergic rhinitis. AIT has been shown to restore the allergen immune tolerance, can modify both the early and late-onset allergen-specific airway hyperreactivity, helps to achieve disease control/remission and prevents new sensitisations. Recent real life data on long-term effectiveness of house dust mite (HDM) AIT in a large group of patients with HDM-driven asthma further underscored its unique therapeutic potential as well as confirmed previous data with pollen AIT. More widespread use of this causal treatment in select patient populations should further move this promising therapeutic field. In this mini-review, we discuss updates on new insights based on real world patient data.

1. Introduction

The principle of allergen specific immunotherapy (AIT or ASIT) is based on repeated administration of specific (causal) allergens either subcutaneously (SCIT) or sublingually (SLIT) to allergic individuals, inducing immunological tolerance and thus offering protection against symptomatic IgE-mediated allergic responses caused by these allergens [1].

When Leonard Noon published his findings in the *Lancet* in 1911, demonstrating that subcutaneous application of aqueous grass pollen extract reduced seasonal symptoms of pollinosis and asthma [2], Roald Amundsen's expedition just reached the South Pole to demonstrate how far mankind can get. In the same year, London's last horse-drawn omnibus accomplished its final ride and the first non-stop London-Paris flight successfully landed. Comparing the fast advancements in travel technologies over the same time frame, not much has really changed within the field of AIT. Obviously, some indications have been added (e.g., tree and ragweed pollen, house dust mites (HDM) and Hymenoptera venom allergies), the sublingual route (SLIT) has been introduced, vaccine manufacturing became well-standardized and dose-range finding studies have been effectuated. And although the vaccines and dosing regimen currently applied for allergen shots have become safer, the main concept has not dramatically changed for more than 100 years.

More recently, new insights into the mechanisms underlying allergic diseases helped to move the development of new vaccines as well as new routes of AIT administration. From the clinical perspective, recent evidence of long-term safety and effectiveness across allergic diseases

Abbreviations: AIT, allergen immunotherapy; ASIT, allergen specific immunotherapy; HDM, house dust mite; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; ILC2, innate lymphoid cell (2); TH2, T helper 2 cell; GINA, global initiative for asthma; Treg, T regulatory cell; REACT, real world effectiveness in allergy immunotherapy; FEV1, forced expiratory flow volume in 1 second; AR, allergic rhinitis; PAMPs, pathogen associated molecular patterns; APC, allergen presenting cell; LNIT, local nasal immunotherapy; RCT, randomized controlled trial.

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should help to promote a more wide-spread application of this causal therapy in target populations and stimulate new innovations within this field [3].

2. Mechanisms underlying allergic airway responses in a nutshell

In the past three decades, disease models combined with targeted interventions and molecular immunology substantially improved our understanding of allergic diseases including bronchial asthma and allergic rhinitis [4–7]. In most cases, combined genetic and environmental factors produce an exaggerated immune response to relevant allergens with a predominant role of T helper (Th)2 lymphocytes and type 2 innate lymphoid cells (ILC2) releasing type 2-cytokines interleukin (IL)-4, IL-5, and IL-13 [8]. This switch to the so-called type 2 response is primed by bronchial epithelial cytokines like thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, collectively referred to as alarmins [9]. The effect of bronchial epithelium-derived cytokines on type 2 polarization is mediated via ILC2s as well as by dendritic cells presenting processed allergens to Th0 lymphocytes which differentiate into TH_2 subsets. Type 2 cytokines, IL-4 and IL-13, induce the B-cell isotype switch to production of IgE which binds to Fc-epsilon receptors on mast cells and basophils [10]. Exposure to allergens which bind to membrane-bound IgE, causes degranulation of these cells with subsequent release of multiple pro-inflammatory mediators including histamine responsible for immediate allergic response and cysteinyl leukotrienes inducing local inflammation and potent bronchoconstriction [11,12]. Ongoing allergic inflammation increases (non-specific) airway hyperresponsiveness and promotes structural changes within the airways [13]. IL-5 produced by both Th2 lymphocytes and ILC2 cells regulates proliferation, maturation and priming/activation of eosinophils which dominate in later phases of allergic inflammation. In healthy subjects, inflammatory response is effectively downregulated by regulatory T cells (T_{regs}) which are present in much lower numbers in the mucosa of allergic individuals [14].

3. Protective mechanisms induced by AIT – *current evidence and future promises*

The (potential) clinical and immunological effects of AIT have been visualized in Fig. 1. Despite the development and widespread availability of many effective anti-allergic treatment modalities, so far, disease-modifying effects can be only attributed to AIT [1]. AIT can restore the allergen immune tolerance by attenuation and/or inhibition of the early- and late-onset allergen-specific hyperreactivity and, consequently, helps to achieve disease control and may prevent further sensitisation. During the past few decades, the mode of action of AIT has been identified and forthcoming immunological effects have been summarized in Table 1. Mechanisms of AIT are mainly based on the induction of regulatory T cells (T_{regs}) which downregulate allergic inflammation by the production of cytokines IL-10 and TGF-beta. Furthermore, AIT seems to suppress type 2 responses and related IgE production by switching IgG_4 and IgA production together with upregulation of antagonistic type 1 responses with the release of IFN-gamma [15]. Finally, AIT probably also affects memory T and B cells since clinical effects persist for several years after termination of treatment [16]. These AIT effects induce disease remission and/or modification in selected patients and hence, successful AIT positively contributes to cost-effectiveness [17,18]. According to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines, AIT is now recommended in patients with moderate to severe allergic rhinitis with confirmed causal allergies who remain symptomatic despite

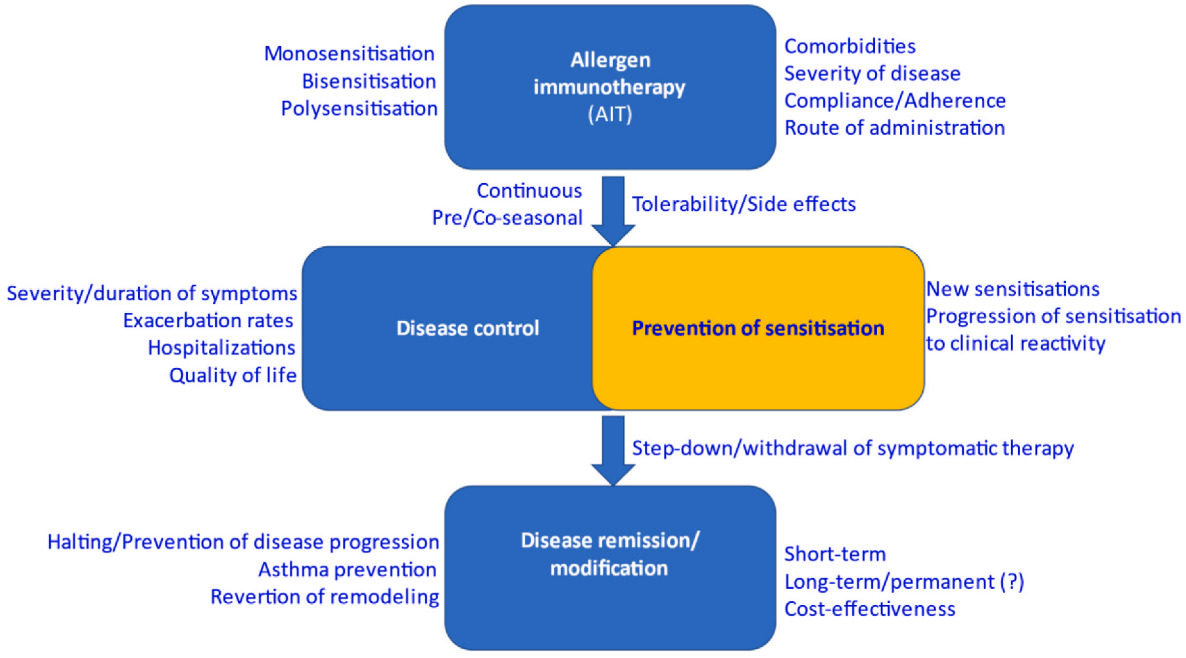

Fig. 1. Clinical Effects of Allergen Immunotherapy.
Legend to figure: Allergen immunotherapy (AIT) is the only anti-allergic treatment with disease-modifying effect. AIT may be initiated in allergic patients with proved causal allergy regardless of the type of sensitisation (mono-/bi-/polysensitisation) since safety and effectiveness have been confirmed in all these patient populations. Selection of the route of AIT application depends on patient phenotype, availability of particular allergens, anticipated patient's compliance/adherence, severity of disease and associated comorbidities. The clinical effect of AIT and its persistence depend on the tolerability and side effects and the application scheme (continuous vs. pre-/co-seasonal). The preferred scheme consists of a 3-years continuous application of AIT. AIT may achieve and maintain disease control, suppress symptoms and improve quality of life. Its uniqueness includes the prevention of asthma development and stop disease progression. Prevention of new sensitisations or prevention of clinical manifestation of latent sensitisations, is another positive AIT effect, however with only moderate evidence. Whether AIT can revert airway remodeling should be addressed in future studies. Another challenge is the persistence of the clinical effectiveness of AIT which is supposed to last as long as possible (permanently?) after cessation of the treatment.

Table 1
Summary of the most important mechanisms of AIT treatment in allergic diseases [7,23, 67–70].

Cells	Effect of AIT
Innate (non-specific) immunity	
Mast cells and basophils	• Early desensitisation → ↑ threshold of activation → ↓ response to allergens • ↓ number of basophils (← cell deletion) • ↑ H_2R on basophils • ↓ spontaneous and induced degranulation • ↓ infiltration in tissues
Eosinophils	• ↓ activity and numbers in blood and tissues • ↓ ECP concentration
Neutrophils	• ↓ activation → ↓ antigen-presentation
NK cells	• ↑ NK regulatory cells → ↑ IL-10
Macrophages	• Conversion of M2a cells into M2b-like regulatory macrophages
Innate lymphoid cells	• ↓ number and activity of IL-5-producing $CRTH2^+CD127^+$ ILC2 (+↓ expression of *CRTH2* and *CD127* genes) • Normalization of ILC2:ILC1 proportion similar to healthy subjects • ↑ ILC3 → ↑ IL-22 with regulatory functions • ↑ regulatory ILC → ↑ IL-10
Dendritic cells	• ↑ tolerogenic phenotype • Induction of regulatory dendritic cells • ↑ FcεRI expression
Adaptive (specific) immunity	
T cells	• Tolerance induction • Deletion of allergen-specific T_H2 clones • Switch from T_H2 to T_H1 phenotype • ↓ circulating T follicular helper cells • ↓ T_H2A cells • ↓ T cell proliferation • Facilitation of T cell exhaustion • ↑ allergen-specific T_{regs} $CD4^+CD25^+$ (nT_{reg}, iT_{reg}) • ↓ of dysfunctional subtype of $ILT3^+$ T regulatory cells • Differentiation of T follicular regulatory cells $CXCR5^+Foxp3^+$ • ↑ expression of selected genes (CTLA-4, CD25) • Epigenetic changes (e.g. demethylation of *FOXP3* → ↑ T_{reg}; methylation of promotor *IL4* region → ↓ T_H2 response)
B cells and immunoglobulins	• ↓ specific IgE production (with possible transient ↑ after AIT initiation) • ↑ neutralizing/blocking IgG_4 • ↑ B regulatory cells (B_{regs}) → production of IL-10, IL-35, TGF-β • ↑ allergen specific IgG_1 and IgA → inhibitory effect on allergen binding and complex formation • ↓ expression of CD23 (FcεRII)

pharmacotherapy - while the American Academy of Allergy, Asthma, and Immunology (AAAAI) released almost similar recommendations [19–21]. Clearly, there is an urgent need for long-term real-life studies of AIT to further explore durability of clinical effectiveness (including prevention, disease remission and modification) as well as cost-effectiveness in real-life settings.

4. Predictive biomarkers of AIT effectiveness

So far, no specific biomarkers can reliably predict AIT clinical effectiveness nor its persistence in individual patients. Nevertheless, clinical efficacy is usually accompanied by several immunological changes involving the decrease in effector cells (e.g. eosinophils) and their activity (expressed by the decrease in type 2 inflammatory mediators) as well as several other immunological changes indicative of a T_H1 (type 1) switch and the induction of T_{reg} cells with a subsequently reduced T_H2 response as outlined in the previous chapter and summarized in Table 1. Moreover, changes in the expression of a broad-spectrum of immune-related genes have been observed during both SCIT and SLIT treatment [22,23].

Possibly, more sophisticated techniques combining several biomarkers at different levels (e.g. omics) may help to identify responders to AIT treatment and thus help to move precision medicine in this high-potential treatment area [24,25].

5. Recent insights into long-term AIT effectiveness in asthma and related diseases

Until recently, only scarce data exist on effectiveness of AIT in asthma based on a handful of (mainly) randomized controlled trials over a limited time span only [26,27]. Despite a recent GINA recommendation on HDM-SLIT for patients with HDM-driven asthma issued in 2021, for long, a certain restraint existed to apply AIT in asthma [28]. This was mainly driven by several misconceptions including presumed safety concerns (based on observations in uncontrolled asthma and/or in patients with a compromised lung function), doubts on effectiveness of a therapeutic option requiring a long treatment time (3–5 years), adherence issues as well as the relatively high costs with often no or only partial reimbursement [29,30].

The recent paper by Fritzsching and colleagues presented data of a large retrospective cohort study REACT (Real world effectiveness in allergy immunotherapy) aimed to assess long-term effectiveness of AIT in allergic rhinitis and particularly in bronchial asthma [3]. So far, this is the largest AIT study with a cohort of 46,024 subjects on AIT therapy and comprehensively matched 1:1 controls. Drug prescriptions, asthma exacerbations, respiratory infection rates and changes in asthma treatment steps were evaluated over a 10 years period. Apart from the ability to step-down asthma treatment, AIT-treated asthma patients experienced significantly less severe exacerbations as well as less respiratory infections and hospitalizations compared to controls. This study provides high-quality real-world evidence of long-term effectiveness of AIT while strongly supporting current clinical guidelines [[19–21,26,28]]. Another more recent nationwide epidemiological study conducted in Denmark, comprising of 2688 adult asthma patients (18–44 years) with seasonal or perennial allergy, showed sustained effectiveness of AIT in terms of a reduced risk of exacerbations and lower respiratory tract infections during 3 years post-AIT follow-up period [31].

In addition to the studies confirming sustained clinical effectiveness of HDM-AIT in asthma, evidence also exists for clinically relevant benefits of AIT with pollen allergens: i.e., both for asthma treatment and prevention [18+refs therein]. In several studies, AIT with pollen allergens reduced asthma symptoms (occurrence and severity) and the use of anti-asthma therapy (relievers and controllers), while also improved several lung physiology parameters (e.g. forced expiratory volume in 1 s (FEV1) and both non-specific and allergen-induced bronchial hyperresponsiveness [18,32]. Some of the listed clinical effects were confirmed for both SCIT and SLIT, although some studies showed differences between both administration routes and varying clinical benefits have been observed across different allergens and study populations [18,33–35]. Obviously, there is still room for improvement requiring more research and real-life studies including large numbers of patients.

Apart from disease remission/modification, another clinically relevant observation is the capability of AIT with pollen extracts to prevent the development of bronchial asthma both in children and in adults with allergic rhinitis [36–41]. Interestingly, the evidence for asthma prevention is more powerful for AIT with pollens compared to HDM [23,42, 43].

The required duration of AIT treatment should be at least 3 years [44]. The first two years are required to achieve a maximum reduction in symptom severity and/or medication use, while the third year is needed to achieve long-term effectiveness and maintain the immune tolerance. However, many clinical studies of AIT in asthma treatment suffer several limitations: e.g., mild-to-moderate asthmatics. In analogy with AR, it could be hypothesized that ‘more severe’ patients with allergen-driven asthma may actually more benefit from AIT [45]. Again, this is subject to further research.

Absolute contra-indications of AIT include uncontrolled (severe) asthma while several relative contra-indications apply in which case the benefits of AIT should be weighed against individual risks or disadvantages [46].

6. Allergen products and administration routes

Although the currently available allergen extracts and dosing regimens are both effective and safe, there is a high need to improve patient adherence, which is often negatively affected by various factors such as cost, inconvenience, side effects, doubts on the effectiveness and the long duration of treatment [47,48]. In this context, there are currently several lines of research aiming to improve adherence e.g., through education and regular follow-up visits [49–51] while eHealth tools may also provide additional support [52]. In addition, innovative and modified AIT products may also help better adherence [1].

In Europe, patients are currently (almost) exclusively treated with crude, i.e., naturally occurring, allergens [53]. Crude allergen extracts contain a mixture of allergenic and non-allergenic components which may interact and thus decrease the immunogenicity of dominant allergens. To overcome drawbacks related to impurity, recombinant allergens have been introduced for *in vitro* diagnostics of allergen-specific IgE. Whether recombinant allergens may help the development of more effective AIT vaccines of consistent quality and allow a more personalized approach for future allergy treatment is currently a matter of debate [53].

Furthermore, immunogenicity of AIT vaccines can be enhanced by adjuvants [54]. In addition to the traditional adjuvants used in AIT (e.g., aluminium hydroxide), new adjuvants are being investigated, e.g., pathogen associated molecular patterns (PAMPs)). While allergens stimulate the adaptive immunity and thus induce an allergen-specific long-term effectiveness, PAMPs stimulate pattern recognition receptors (RRRs) on antigen presenting cells (APCs) resulting in an allergen non-specific short-term effectiveness. A combination of allergens and PAMPs may thus achieve a superior and sustained clinical effectiveness in a shorter time span which may improve adherence and cost-effectiveness. Creticos and colleagues previously showed that such approach may be both effective and prevent progression of allergic diseases if applied at an early stage in life [55]. Alternatively, modulation of immune responses to applied allergen may also be affected by biologic therapy with monoclonal antibodies against IgE, e.g., omalizumab, or with dupilumab [56,57]. Furthermore, the use of allergen loaded liposomes, biodegradable nanoparticles or virus-like particles may represent new delivery vehicles for better administration [58]. Regarding alternative routes of administration, intralymphatic application has been tested with promising results allowing fewer injections (which may improve adherence). Alternatively, the invasiveness of this approach might limit its routine clinical use [59]. Another route of AIT administration is the epicutaneous AIT (EPIT), which has a favorable safety profile and good adherence, showing some perspectives on future routes in the treatment of selected respiratory and food allergies [60–62]. Local nasal immunotherapy (LNIT) represents still another route of allergen application, which reduces the clinical symptoms and anti-allergic medication use [63]. However, it is associated with local side effects requiring nasal premedication limiting its clinical use [64].

7. Future perspectives

Allergen immunotherapy with more than a century of clinical experience remains the only disease modifying and potentially preventive therapy in allergic diseases although there remains still room for improvement requiring further research.

Given the substantial placebo-effect usually found in RCTs [27,65], long-term real-life monitoring of patients is indispensable to establish better insight into the actual effectiveness in terms of disease outcomes, patient reported quality of life as well as health-economics [66].

Despite initial observations of substantial long-term AIT effectiveness in a large real-life cohort, there are still several aspects which need to be addressed. In the first place, real-life effectiveness of HDM-AIT in asthmatic patients should be further extended for other allergen extracts and confirmed in adequately powered large-sized studies aimed to evaluate the duration of post-discontinuation effectiveness including disease control, disease remission, prevention of sensitisation to other allergens and disease modification. Other aspects include proper timing (age, season) for starting AIT as well as adequate selection of most eligible candidates (''good'' responders to AIT, predictive characteristics/biomarkers). For patients with more severe asthma, this may require pretreatment with *anti*-IgE therapy (or other biologics) to achieve adequate asthma control before AIT can be safely installed. This treatment aspect may require more practical guidance for physicians.

In this context, there is also a growing need for effective (and standardized) AIT for different allergies e.g., pet-allergies (including cat allergy, dog allergy, rabbit allergy, etc.), horse allergy and ragweed allergy; the latter presently mainly in East and South-East Europe and in the East and Midwest of the USA, in the future possibly also in West Europe due to climate change.

During the COVID-19 pandemic, a non-negligible number of patients unfortunately discontinued AIT (particularly SCIT requiring outpatient visits). On the other hand, the progress in the development of *anti*-SARS-CoV-2 vaccines globally and the speed of their clinical implementation may inspire future innovations of AIT products (e.g., type of allergen, allergen isolation and preparation, recombinant allergens, adjuvant systems) to be more effective and at least similarly long-lasting after discontinuation of treatment as in the recently presented data by Fritzsching and colleagues [3].

CRediT authorship contribution statement

Zuzana Diamant: Conceptualization, Writing – original draft, Writing – review & editing. **Milos Jesenak:** Writing – review & editing. **Ilja Striz:** Conceptualization, Writing – original draft. **Maurits van Maaren en Antonella Muraro:** both contributed to the manuscript and approved the final version.

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