



Current insights in allergen immunotherapy



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Key Messages

- Allergen immunotherapy (AIT) has been effective for over 100 years and continues to be a disease modifying therapy for many patients.
- Classic subcutaneous AIT (SCIT) has been augmented with the development and use of sublingual AIT (SLIT) worldwide.
- The use of AIT in the treatment of asthma, once considered a contraindication, has now been shown to be safe and effective given as either SCIT or SLIT.
- Challenges for assessing effectiveness of SCIT and SLIT modalities for individual patients remain as there is no recognized “class effect” for the various modalities.
- Each must be individually considered in terms of physical form, dosage and duration of therapy.

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ABSTRACT

Objective: Allergen-specific immunotherapy (AIT) in its subcutaneous and sublingual forms is currently a well-established and experimentally supported treatment for respiratory allergy and hymenoptera venom allergy. There have been advances in its use linked strictly to the advancement in the knowledge of the molecular mechanisms of allergy, the production of well-characterized extracts, and diagnostic techniques. The use of AIT in asthma and the application of new approaches are expanding. We briefly review the advances and concerns in the use of AIT.

Data Sources: PubMed and Scopus.

Study Selections: The most recent and clinically relevant literature was selected and reviewed.

Results: The introduction of high-quality products supported by large dose-finding trials has yielded better defined indications, contraindications, and modalities of use. Some specific products in tablet form have recently been approved in the United States. Sublingual immunotherapy has been found to be effective in asthma, which until recently had been a matter of debate. Another promising therapy is oral and sublingual desensitization for food allergy, for which encouraging results have recently been reported. In the near future, other options will be available, including new routes of administration (intralymphatic and epicutaneous), allergoids, engineered allergens, and peptides. The use of component-resolved diagnosis techniques will further refine and target AIT prescriptions.

Conclusion: This condensed and updated review shows that AIT remains a viable treatment option, especially after the introduction of standardized tablets for some allergens. Food allergy and new administration routes represent a promising expansion.

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Introduction

Allergen-specific immunotherapy (AIT) is currently the object of renewed and growing interest, especially for respiratory and food allergy. This is due mainly to an increase in the knowledge of the mechanisms of allergic reactions and, in parallel, to the increased

availability of advanced laboratory and diagnostic techniques. However, several aspects of AIT remain controversial. First, the use of AIT in asthma remains a matter of discussion because of safety aspects, uncertain efficacy, and lack of robust experimental proofs. Second, the use of sublingual immunotherapy (SLIT) is not universally accepted, despite the availability of numerous clinical trials. Third, the use of oral desensitization for food allergy still shows uncertain or undefined aspects. In addition, new routes of administration are currently being explored, some of which have shown encouraging results, and the availability of modified, engineered, and adjuvant extracts is expanding application. A general regulatory policy is currently ongoing, at least in Europe, to market only well-standardized and experimentally supported products in the context of a “precision medicine.”

Sublingual Immunotherapy

The use of SLIT was first described in a randomized clinical trial in 1986,¹ and the first use of SLIT in tablet form was reported in 2001.² After those early approaches, SLIT rapidly gained scientific credibility and was accepted as the only viable alternative to the traditional subcutaneous administration of AIT for respiratory allergy.³ Currently, there are more than 80 randomized and controlled clinical trials of SLIT, which confirm its efficacy at least as a “class effect.”⁴ Of note, clinical efficacy was demonstrated for all relevant allergens, such as mite, birch, *Parietaria* species, grass, and ragweed. In recent years, many clinical trials involving hundreds of patients were performed (so-called large trials).⁵ Many of these trials were conducted with a dose-finding design and therefore allowed definition of the relevant allergen sources (and specific products) and the optimal maintenance dose for major allergen content (Table 1). At least for SLIT in tablet form, a dose-related clinical efficacy also was clearly demonstrated. The clinical results reported in the literature of regulatory-oriented trials allowed the registration of some specific products as formally defined pharmaceutical medications. After approval from the European Medicine Agency, the US Food and Drug Administration approved the use of SLIT in tablet form for ragweed, mite, and grass in the United States.⁶ There is no more debate on the efficacy of SLIT, at least for well-defined and experimentally supported products,⁷ and an equivalent efficacy of SLIT and subcutaneous AIT was demonstrated.⁸ Nonetheless, some points remain to be clarified. First, the optimal regimen of administration for seasonal allergens seems to be a pre-co-seasonal protocol.⁹ Second, it is clear that a strict and regular evaluation would be the best approach to improve adherence to self-administered therapy.¹⁰ Third, the efficacy of AIT, when correctly prescribed, is independent of the presence of poly-sensitizations.^{11,12} The use of AIT is advisable even in elderly people when the allergic sensitization is correctly ascertained. In addition, a prolonged effect after discontinuation of treatment can be observed.^{13–15}

AIT and Asthma

According to US surveys, asthma is considered a contraindication and a major risk factor for the use of AIT.¹⁶ When considering risk factors, it must be remembered that the modality of AIT significantly differs between the United States and European countries. In the United States (and other parts of the world), different allergens are mixed together in a single dose, thus increasing the overall allergen load, whereas in Europe only a few allergens (maximum 3) are given separately with subcutaneous AIT or SLIT.^{17,18} In addition, until 2010, very few clinical trials specifically designed for asthma were conducted. In fact, most data concerning AIT and asthma were derived from studies designed for rhinitis in which some patients also had asthma,^{19,20} and the clinically relevant aspects (eg, intake of inhaled steroids, rate of exacerbation, and pulmonary function) were not always assessed. The most recent literature reviews reported that only uncontrolled and symptomatic asthma remains the only absolute contraindication to the prescription of AIT.^{21,22} In addition, some recent studies specifically designed for asthma found that AIT can decrease the use of inhaled corticosteroids and, more importantly, that AIT can lower the rate of asthma exacerbations. This was clearly shown in some regulatory-oriented studies involving hundreds of patients in which the add-on SLIT achieved a significant decrease in the use of inhaled corticosteroids and/or a significant decrease in asthma exacerbation rate.^{23–25} This is a very novel finding, because the use of AIT in asthma remained a matter of debate owing to the lack of trials designed to investigate AIT in asthma. In addition, SLIT in tablet form caused no increase in the risk of asthma exacerbation or increase of systemic adverse events according to the available literature.²⁵ The description and severity of adverse events with SLIT, which are mainly local and spontaneously resolving, have been summarized elsewhere^{26–28} and proper recommendations have been made in official documents.⁴ Of note, the most recent Global Initiative for Asthma Management document included, for the first time, SLIT as a possible add-on therapeutic option in asthma treatment.²⁹

New Perspectives

Knowledge of AIT is currently and progressively expanding in parallel with the improving quality of extracts and proposed new administration modalities. The intralymphatic and epicutaneous routes remain promising options.^{30,31} It is clear that the patch-mediated administration would be optimal in pediatric patients, especially for food allergies. Also, the direct intralymphatic administration would allow the immediate presentation of the antigen to the competent cells. In addition, latex allergy remains a potential clinical application for AIT, especially in the SLIT form.³² There is still room for improvement in the use and prescription of AIT. Certainly, the use of AIT as a desensitizing approach for food allergy remains a mainstay in clinical research when considering the possible risks (including eosinophilic esophagitis).³³ It is clear that

Table 1
Main Dose-Finding Studies of Sublingual Immunotherapy According to Allergen, With Optimal Dose Identified

Author, year	Optimal dose identified	Allergen source	Patients (A/P)	Reference
Durham, 2006	Phl p 5 25 µg/d (tablet)	Grass	569/150	<i>J Allergy Clin Immunol.</i> 2006;117:802–809
Didier, 2007	grass group 5 25 µg/d (tablet)	Grass	470/156	<i>J Allergy Clin Immunol.</i> 1997;120:1341–1360
Creticos, 2013	Amb a 1 12 µg/d (tablet)	Ragweed	596/198	<i>J Allergy Clin Immunol.</i> 2013;131:1342–1350
Bergmann, 2014	Der p 1/Der f 1 28/120 µg/d	Mite	339/170	<i>J Allergy Clin Immunol.</i> 2014;133:1608–1614
Mosbech, 2014	6 SQ/d (70 µg/d)	Mite	461/143	<i>J Allergy Clin Immunol.</i> 2014;134:568–575
Nolte, 2015	12 DU/d (equivalent 6 SQ/d)	Mite	83/41	<i>J Allergy Clin Immunol.</i> 2016;138:1631–1638
Virchow, 2016	6 SQ/d	Mite	455/287	<i>JAMA.</i> 2016;315:11715–11728

Abbreviations: A/P, active/placebo; SQ, subcutaneous.

desensitization or tolerance can be induced for food allergy,³⁴ but the question remains whether a permanent tolerance is induced in selected patients or whether regular food intake is required to maintain a previously achieved tolerance. Chemically modified allergens (allergoids), engineered allergens, and peptides derived from allergens are other promising modalities for the development of AIT, especially from the viewpoint of safety.³⁵

Another, and only recently emerged, interesting aspect is the use of “artificial” exposure to allergens (eg, a challenge chamber or specific nasal and conjunctival provocation tests) to evaluate the clinical efficacy of AIT. Ideally, this approach would avoid the intrinsic variability of natural exposure and allow a clear definition of the direct effect of the allergen. In this model, symptoms (sneezing, itching, obstruction, and rhinorrhea) can be directly and exactly quantified compared with what usually happens in clinical trials based on natural exposure, in which symptoms can be only self-reported. Some of the more recent trials have provided new and more specific insights into the time and dose dependence of AIT,^{36–38} substantially confirming previous results obtained with the natural exposure model. Of note, the most recent randomized trial reported that a 3-year course of grass SLIT was necessary to obtain a long-lasting effect, whereas a 2-year course seemed to be insufficient.³⁷ Moreover, the component-resolved or molecular diagnosis has become a powerful instrument to better define the etiologic diagnosis, which is essential for a correct and targeted prescription of AIT, especially in patients with poly-sensitization.^{39,40}

Conclusion

The use of AIT in any reasonable application (eg, when the pathogenic mechanism is well known) has made surprising advancements in the past decade. The use of the component-resolved diagnosis model, bioengineering techniques, and especially the enterprise of large population-based (often with a dose-finding design) trials has allowed a better definition of the indications and limitations of this therapeutic approach. This continues to be true particularly for SLIT, which remains the most investigated route of administration, and for the tablet formulation. The use of SLIT, or “oral desensitization,” in its various forms and procedures also remains an intriguing field of research for food allergy. It must be highlighted that it is currently not possible, and not scientifically correct, to consider the clinical effects of AIT as a general “class effect,” but the efficacy needs to be clearly demonstrated and documented for each product with a well-defined dose.⁷

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