Allergen Immunotherapy

History and Future Developments

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KEYWORDS

• Subcutaneous immunotherapy • Sublingual immunotherapy • Indications
• Allergen immunotherapy • Efficacy • Safety • History • Molecular diagnosis

KEY POINTS

- Allergen immunotherapy (AIT) is a cornerstone in the management of respiratory allergic diseases because it is allergen-specific and immunomodulating and may affect disease progression.
- Sublingual immunotherapy (SLIT) represents a significant advance, offering patients an excellent safety and acceptance profile.
- From a historical viewpoint, in the past three decades there has been an impressive development in this form of treatment, which has lasted more than 100 years.
- The most promising fields are the use of AIT in food allergy, preventative effects, and improvement of routes of administration and standardization of extracts and protocols.

THE HISTORICAL PERSPECTIVE

AIT was introduced into clinical practice more than a century ago by Leonard Noon,[1] with the aim of "vaccinating" against hypothetical "aerogenic toxins" (Fig. 1). Despite the wrong rationale, the subcutaneous immunotherapy (SCIT) of pollen extracts was effective in reducing hay fever symptoms. Subsequently, the use of SCIT gradually increased and was progressively extended to other allergens. SCIT remained the only mode of administration for more than 70 years, and its use remained totally empirical until 1965 when IgE was discovered.[2] The first randomized controlled study on AIT was published in 1954 by Frankland and Augustin,[3] and a few years later, Johnstone and Dutton[4] suggested that AIT could modify the natural history of respiratory allergy, but this fact was not considered for another 40 years. In 1978, the first randomized, double-blinded, placebo-controlled (RDBPC) trial with AIT for hymenoptera venom allergy appeared,[5] showing the superiority of purified venoms over whole-body extracts. This was followed by numerous other trials substantially confirming the efficacy

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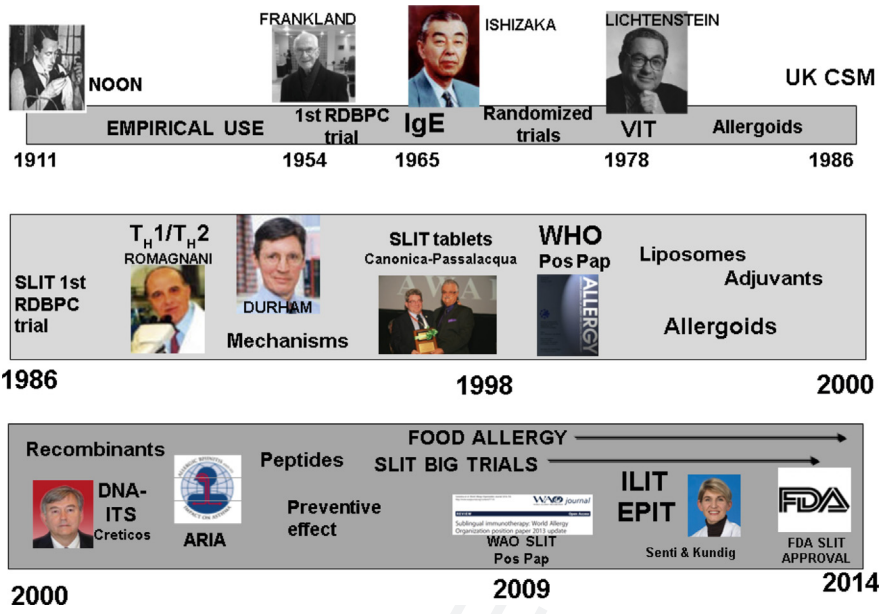

Fig. 1. The history of AIT.

and safety of venom immunotherapy (VIT),[6] now widely used and well standardized in procedures.

It became clear that SCIT with respiratory allergens involved a certain risk of severe or even fatal adverse events,[7] as established by the UK Committee on Safety of Medicines in 1986.[8] Many AIT adverse events are due to human errors, but some adverse events are unpredictable and unavoidable.[9,10] This fact prompted the search for safer routes of administration of AIT. Among the proposed routes, SLIT rapidly established scientific credibility and soon remained the most viable alternative to SCIT. Other routes of administration had been proposed: the local bronchial during the 1950s, the local nasal during the 1970s, and the oral at the beginning of the 1980s (for review see Canonica and Passalacqua[11]). The results of clinical trials demonstrated that the efficacy of oral and bronchial routes is unproved and the risk/benefit ratio is unfavorable; thus, these routes of administration were abandoned, although there is currently a renewed interest for the oral route in the desensitization for food allergy. The local nasal immunotherapy proved effective for allergic rhinitis but because of the impractical administration technique, its clinical use rapidly declined.

The first randomized, double-blind, placebo-controlled trial with SLIT appeared in 1986,[12] and it was followed by numerous other trials which, although conducted in small samples, substantially confirmed the efficacy of this route. SLIT was first mentioned as a possible alternative to SCIT in a World Health Organization position paper[13] in 1998, and its role in clinical practice was confirmed in the subsequent official documents.[14,15]

In the meanwhile, other relevant advances about AIT appeared. Among the most important were the discovery of the helper T cell (T_H1/T_H2) system,[16] the re-evaluation of the role of IgG4 as blocking antibodies,[17] and the description of the regulatory T cells.[18,19] The improved knowledge of the mechanisms of action[20] allowed for the introduction of new approaches, such as the use of adjuvants (currently some

products are commercialized) and the use of antigenic peptides and the recombinant allergens. In parallel, other specific aspects began to be investigated, namely the preventive effect on the development of asthma, that was demonstrated for both SCIT and SLIT, although in open trials and with relatively small populations.[21–23]

In the past decade, the efficacy of SLIT was clearly confirmed in the so-called big trials, which included hundreds (usually from 250 to more than 800) of patients. Some of those trials involved a dose-ranging design[24–29] and therefore allowed identification of the optimal maintenance dose for each of the tested products, at least for the relevant allergens (grass, mite, and ragweed). There is 1 single dose-ranging large trial performed with SCIT.[30] The introduction of fast-dissolving tablets for SLIT further improved the convenience. The official acceptance of SLIT culminated in 2009 with the publication of a first position paper prepared by the World Allergy Organization,[31] including 60 RDBPC trials, followed by an updated version with 77 trials.[32] Approximately 1 year ago, the Food and Drug Q14 Administration (FDA), approved 3 SLIT tablet products to be marketed in the United States.[33]

THE PRESENT SITUATION

Practical Aspects

To date, the practice of AIT is standardized, and numerous official position papers and practice parameters are available worldwide (Table 1). In particular, hymenoptera VIT, although there are different extracts available, is well standardized and its practice is uniform.

Table 1
The main position papers and guidelines on allergen immunotherapy Q27

Year	Organization	Type of Allergen Immunotherapy	Reference
1998	World Health Organization	SCIT/SLIT	Ann Allergy Asthma Immunol 1998;81(5 Pt 1):401–5.
1998	European Academy of Allergy and Clinical Immunology	Non injection routes	Allergy 1998;53:933–44.
2001	Allergic Rhinitis and its Impact on Asthma	SCIT/SLIT	J Allergy Clin Immunol 2001;108(5 Suppl):S147–334.
2005	European Academy of Allergy and Clinical Immunology	VIT	Allergy 2005;60:1459–70.
2007	American Academy of Allergy, Asthma & Immunology/ American College of Allergy, Asthma & Immunology	SCIT	J Allergy Clin Immunol 2007;120(Suppl):S25–85, IV.
2008	Allergic Rhinitis and its Impact on Asthma	SCIT/SLIT	Allergy 2008;63(Suppl 86):8–160.
2009	World Allergy Organization	SLIT	Allergy 2009;64(Suppl 91):1–59.
2011	American Academy of Allergy, Asthma & Immunology/ American College of Allergy, Asthma & Immunology	SCIT	J Allergy Clin Immunol 2011;127(1 Suppl):S1–55.
2011	British Society for Allergy and Clinical Immunology	VIT	Clin Exp Allergy 2011;41:1201–20.
2013	World Allergy Organization	SLIT	World Allergy Organ J 2014;7(1):6.

At variance with SCIT, which is standardized in regimens and protocols, SLIT is affected by numerous variables. It can be administered as drops, monodose vials, or tablets and with variable timings and doses. In particular, the maintenance dose is strictly dependent on the method of standardization, which varies from one manufacturer to another. It is also true that all the products that are officially approved (eg, by the FDA or European Medicines Agency) display the content in micrograms of major allergen(s) per dose. At present, tablets that were first introduced in 1998 as monomeric allergoids[34] seem to represent the preferred SLIT formulation because of ease of use. Also, the time interval between each maintenance dose varies from one producer to another (daily, on alternate days, or twice weekly), but the current attitude is to prefer once-a-day administration.[35] For pollen allergies, the pre-coseasonal protocol is the most largely used, because its efficacy does not differ from that of the continuous (all-year-long) administration.[36,37]

Another important and unresolved debate concerns the use of mixtures of allergens. The European view is that AIT is given for no more than 3 allergens in the same patient,[38] and the dose of each allergen is given separately. In the United States, the usual practice is multiple allergens mixed together in a single preparation with attention to not mixing allergens that can degradate other proteins.[39] This dichotomy has cultural and historical reasons and is attributable to different concentrations of allergen solutions, which are usually higher in the United States products.[40] There are few well designed studies that have evaluated and demonstrated the efficacy of allergen mixtures.[41] On the contrary, it is now accepted that AIT with a single allergen is effective in polysensitized patients, provided the allergen chosen is responsible for the disease.[42] In this regard, the molecular-based diagnosis (molecular allergy) has become a useful tool to refine the prescription of AIT (discussed later).

Other current fields of research in AIT are pharmacoeconomic aspects and adherence. Looking at the published studies, it seems that in the long term both SCIT and SLIT produce economic savings for both patients and health providers.[43] This is a result of a combination of reduced drug consumption and health care utilization (direct costs) as well as improvement of the quality of life (indirect costs). In contrast, adherence is a major problem, particularly for SLIT, which is self-administered: although structured studies provided overall favorable results in terms of adherence,[44] real-life adherence is reported to be poor,[45] although more frequent follow-up of patients seems to increase compliance.[46]

The Role of Molecular Diagnosis

The IgE response is not generically directed toward an allergenic source but rather to specific proteins (or epitopes) that are contained into the raw material. For instance, the IgE response to "grasses" is directed to a few proteins (Phl p 1, Phl p 5, an Phl p 6), and the IgE response to mite is specific for the proteins Der p 1, Der p 2, Der f 1, Der f 2, and so forth.[47] Such molecules are considered the genuine sensitizers. On the other hand, there are also highly conserved, are present in different species (eg, profilins, lipid transfer proteins, and storage proteins). They are called pan-allergens or cross-reacting proteins[47] and are often responsible for multiple positivities on the standard diagnostic tests. The relevant implications of pan-allergen sensistization may be particularly pertinent in AIT. The molecular diagnosis allows distinction of genuine sensitizations from the positivities due to cross-reacting proteins, thereby refining the choice of the allergen to be used for AIT.[48] Several studies have shown that molecular diagnosis significantly modifies the prescription of AIT in polysensitized patients.[49,50] Many recombinant or purified molecular components for skin testing and immunoassay are available in multiplexed

systems that allow detecting in a single analysis specific IgE toward approximately 130 allergenic molecules.[51]

Regulatory Aspects

Despite the amount of clinical and mechanistic data on AIT and its consolidated use, the regulatory aspects (pharmacologic classification of products, marketing authorization, national and supranational approval, and deputy regulatory authorities) remain vague and largely differ among countries. Although in the United States and in the European Community (EC), there are well-defined regulatory authorities (FDA, European Medicines Agency, and Paul Ehrlich Institute), in other countries, such as those in Latin America, there is no uniform regulation.[52]

In Europe, numerous official regulatory documents have been released (for review, see Kaul and colleagues[53] and Bonini[54]), mainly concerning Good Manufacturing Practice. Those documents impose on all members of the EC specific standards for the production of allergen extracts. Within the EC, apart from a few exceptions, allergen extracts are considered named patient products (NPPs), prepared individually according to a physician's prescription, but almost all extracts are manufactured by industrial procedures. There is a general effort to abolish NPPs, with exceptions of rare allergens or special sensitization profiles, whereas a single preparation should contain in the near future only allergens from homologous groups (trees, grasses, mites, and so forth).[53] In addition, for each new product, a registration dossier (from phase I to III) is required for the marketing authorization.

THE NEAR FUTURE: PERSPECTIVES

After the introduction of SLI and recent mechanistic studies, there was an impressive advancement in the clinical research on AIT, and new opportunities rapidly appeared (**Table 2**).

The current indication for AIT is allergic rhinoconjunctvitis with/without allergic asthma and hymenoptera venom allergy,[13,38,39] but for the SLIT tablets approved in the United States, asthma is not an indication. In recent years, many clinical trials have suggested that the indications of AIT can be expanded. In terms of amount of clinical data, the most promising application is food allergy. As discussed elsewhere, there are many clinical trials proving the efficacy of desensitization for cow's milk, peanut, egg, and some other allergenic foods (for review, see Albin and Nowak-Węgrzyn[55] and Jones and colleagues[56]). Whether administration of gradually increasing amounts of an offending food represents a true AIT or, better, a simple oral induction of tolerance is still not clear. Latex allergy is not an official indication for AIT, although SLIT products are available and commercialized, based on the results of clinical trials.[57] The same is true for atopic dermatitis, for which both SLIT and SCIT were demonstrated partially effective, especially if a sensitization to dust mite is present.[58,59]

According to current knowledge, the goal of AIT is to take the allergen into contact with antigen-presenting cells to develop an immunologic desensitization. This can be made, in addition to the subcutaneous or sublingual route, by administering an allergen directly into lymph nodes. An innovative clinical trial[60] supports this rationale, showing that the intralymphatic immunotherapy (ILIT) requires much lower doses of allergen and fewer injections than the traditional SCIT modality, while maintaining the same efficacy.[61] Also, skin is a suitable site for presenting antigens. Epicutaneous immunotherapy (EPIT) has been tested with good results for both aeroallergens and food allergens.[62] This route seems particularly suitable in children.

Table 2
The future developments of allergen immunotherapy Q28

Advancement	Description	Comments
Route of administration	ILIT Epicutaneous Intradermal	The ILIT allows short courses of administration with lower doses of antigens. EPIT is totally noninvasive and, therefore, particularly suitable for children.
Formulation	Nanoparticles Slow release/mucoadhesive	At early experimental stage, with positive results in animal models
Extract + adjuvants	Bacteria-derived adjuvants DNA-derived adjuvants	Bacterial adjuvants already are commercially available for SCIT. Low number of injections. DNA-adjuvants are under experimental investigation, with a single human trial.
Peptides	Long or short peptides	Under investigation, mainly with Fel d 1 allergen
Molecules	Recombinant/highly purified sensitizing molecules	Some trials available in humans. The single molecules seem not to perform better than the crude extracts.
New indications	Food allergy Atopic dermatitis Latex allergy Nickel allergy?	Despite the existence of numerous trials with positive results, none of these indications is currently approved for clinical practice. Latex SLIT products are commercialized and used.

The products commonly used for AIT are crude extracts, derived from allergenic sources (eg, grasses, ragweed, and mite) and, therefore, contain allergenic and nonallergenic proteins and carbohydrates or lipids. They can be improved by adding adjuvants, which provide an additional enhancement of the T_H1 response. An organic adjuvant usually stimulates the Toll-like receptors of the innate immunity, which in turn favor the T_H1-oriented response.[63] Monophosphoryl lipid A, derived from the cell wall of *Salmonella minnesota*, is proved safe, effective, and capable of reducing the number of injections and the dose of allergen and is currently commercialized. Many other trials with adjuvants are ongoing.[64] Also prochariote-derived oligodenucleotides (CpG Q24 sequences) are good adjuvants, because they stimulate the Toll-like receptor 9, with a consequent increase in the T_H1 response. Early trials using this approach provided encouraging results,[65,66] but the clinical research remains at the initial stage. Another possible manipulation is to give only allergenic fragments, instead of the whole allergenic proteins, because antigen-presenting cells recognize linear sequences; this is called peptide-based immunotherapy. There are so far some promising studies with mixtures of peptides from cat and mite allergens.[67]

As discussed previously, it is now possible to synthesize (or highly purify) the most relevant single sensitizer proteins. Thus, if identifying for each subject the allergenic components toward which IgE are directed, it would be possible to vaccinate only with those molecules (tailored immunotherapy). Nonetheless, it seems that the use of single genuine sensitizers does not perform better than the raw extracts.[68] In addition, the sensitization profile, dissected by molecular diagnosis, is largely variable in each subject.[69] Finally, the regulatory authorities require a registration trial for each single allergen product. All those considerations, despite the intriguing immunologic rationale, make this approach so far unfeasible.

UNMET NEEDS AND CONCLUDING REMARKS

The body of evidence for SCIT, SLIT, and VIT is robust, as a result of an abundance of clinical and mechanistic trials. Nonetheless, some points to be clarified, and debated aspects are still present (Table 3). For instance, there is a large variability in administration schedules, dosages, and duration of SLIT, which is marketed in numerous countries as NPPs. Only a few products represent exceptions—Oralair (Stallergenes, Antony Cedex, France), Grazax or Grastek (ALK-Abelló, Copenhagen, Denmark), and Ragwitek (Merck, Whitehouse Station, New Jersey)—because they are registered and marketed as pharmaceutical products.[70] Another critical point is the standardization. Almost all AIT vaccines commercialized are standardized either biologically or immunologically, based on in-house references. Thus, extracts are labeled in units that differ from one manufacturer to another, and comparison among trials and products is only rarely possible.

Again, there is no experimental demonstration that the regimens used are the most appropriate and cost effective, that the pre-coseasonal regimen for pollen allergens is better, or that for perennial allergens a continuous treatment is needed. There is no rigorous study on the optimal duration of an AIT treatment; thus, the current suggestions are only empirical or based on sparse clinical data.[71,72] The same is partly true for the preventative effect, demonstration of which is based on only 3 controlled open trials.[73] Finally, there is great heterogeneity in clinical trials, which affects the robustness of meta analyses, and the reporting of trials is unsatisfactory.[74,75]

AIT is a cornerstone in the management of respiratory allergic diseases because it is allergen-specific and immunomodulating and may affect disease progression. SLIT has represented a significant advance, offering patients an excellent safety and acceptance profile. From a historical viewpoint, in the past 3 decades there has been an impressive development of this form of treatment, which has lasted more

Table 3
Main unmet needs in allergen immunotherapy

Problem	Comments
Optimal maintenance dose	Currently fixed only for grass, ragweed, and mite (soluble tablets, single products). The optimal maintenance dose remains to be clearly defined for the remaining relevant allergens.
Optimal maintenance regimen	Is it needed to give an all-year treatment of perennial allergens? Is the pre-coseasonal (coseasonal regimen) more convenient than the continuous one?
Use of multiple allergens	Few studies are available. The efficacy of multiple allergens, even mixed, is poorly defined.
Adherence	Data about adherence with AIT differ among controlled and real-life studies.
Standardization of extracts	The use of in-house references and of different units make the clinical studies not comparable. The potency of the extracts is still yet not well defined.
Standardization of studies	Large heterogeneity among clinical trials (design, patients' selection, dose, duration, and analysis). Reporting is still poor.
Duration and long-lasting effect	The optimal duration of an AIT course is not experimentally defined. The demonstration of long-lasting and preventive effects relies on a small number of clinical trials

than 100 years. The most promising fields are the use of AIT in food allergy, the preventative effects, and the improvement of the routes of administration and standardization of extracts and protocols.

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