

Specific immunotherapy, one century later

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Introduction

One hundred years have elapsed since Leonard Noon first described the ‘vaccination’ against hay-fever. In its original article, he hypothesized that the subcutaneous injection of an extract of grass pollen could generate an active immunization [1], as happens for many infectious diseases. Although the mechanisms of allergy were totally unknown at that time, and the supposed rationale was partially incorrect, the procedure proved clinically effective in reducing symptoms, as testified by the decrease in responsiveness to the conjunctival challenge with grass pollen. In addition, we presently know that the hypothesis of an active immunization was not completely wrong, since specific immunotherapy (SIT) induces the generation of allergen-specific IgG4 antibodies, which block the IgE facilitated antigen presentation.

From an historical perspective, since its first description by Noon until the middle 1980s, the development of SIT had very few important novelties, with the exceptions of the discovery of IgE [2], of the adoption of randomized controlled trials and of the introduction of modified extracts (allergoids). Starting from the 1980s, there was an impressive acceleration in the evolution of SIT, which included the introduction of the sublingual route (SLIT), the discovery of the Th1/Th2 paradigm and T regulatory cells [3], the availability of recombinant molecules and peptides, until the very recent proposal of an intralymphatic and epicutaneous administration route.

Clinical developments

One of the most important recent cornerstones in the history of SIT is certainly the World Allergy Organization position paper, published in 1998 [4]. It represented the first attempt to provide documented, although non strictly evidence based, guidelines on indications, contraindications, and practical aspects of SIT. New official documents have been published later on but the WHO position paper still represents the general basis of the

current guidelines, and it remains overall valid. So far, subcutaneous SIT (SCIT) is still the reference modality of vaccination, and it is sufficiently standardized worldwide. Subcutaneous SIT, in addition, represents the only modality of immunization for hymenoptera venom allergy [5]. Another milestone was the acceptance of SLIT, first proposed in 1986 [6] as a viable alternative to the traditional subcutaneous route, which became substantially official in the first version of the ARIA guidelines [7]. In recent years, several ‘registrative trials’, including hundreds of patients, have been carried out with SLIT [8], and those trials provided the unique opportunity to identify for grass pollen the optimal maintenance dose, as previously done for SCIT [9]. Of note, SLIT is currently not approved for clinical use in the USA, but recently some trials with positive results have been for the first time published by US authors [10–12]. This auspices a more large use of SLIT, with a consequent improvement in our clinical knowledge. Interestingly, the good safety profile of SLIT opened the way to new and intriguing clinical developments. A good example is the possibility of using SLIT in children below 5 years of age (relative contraindication for SCIT), as confirmed by several postmarketing surveys [13,14]. The opportunity to use SLIT in early ages is expected to provide a special advantage in terms of secondary prevention [15,16], although more structured and robust data are needed on this aspect. Another possible clinical development is the use of SLIT in food allergy. As food allergy is sustained by a ‘pure’ IgE mediated reaction, SIT is expected to be highly effective, as in the case of venom allergy. Nevertheless, the earliest attempts with SCIT for peanut allergy [17] resulted in an intolerably high rate of side effects. Nowadays, the preliminary clinical trials with SLIT have shown a good efficacy [18–20] with a satisfactory safety profile. The same considerations remain valid for latex allergy [21], where SLIT is clinically utilized, although not officially approved [8].

The expected aim of SIT is to make the allergen reach some antigen presenting site, namely lymph-nodes. We do this either by giving the extract subcutaneously or sublingually. Thus, it has been suggested that the allergen extract could be injected directly into lymph-nodes. The intralymphatic immunotherapy was tested in a phase III study: its efficacy in only three injections was similar to that of a regular course of SCIT [22]. On the basis of the same rationale, and considering that the skin

is an efficient antigen presenting organ, the epicutaneous administration has been also recently proposed, with provisional positive clinical results [23].

Concerning the preparation of extracts, the availability of purified/recombinant allergenic components has suggested the possibility of a 'tailored' immunotherapy, by administering only the immunologically relevant molecules. The vaccination with single molecules has been proven effective [24,25], although the advantage of such therapy versus the whole extracts remains to be clarified. On the contrary, the association of the allergen with adjuvants seems to be promising, as the adjuvant allows reducing the amount of allergen needed to provide effective desensitization. Monophosphoryl lipid A (a toll-like receptor 4 agonist) has been already commercialized, whereas the use of prokaryotic DNA oligodeoxynucleotides (toll-like receptor 9 agonists) is still under investigation, with very positive preliminary results [26]. Finally, there are interesting reports on the use of allergenic peptides. The aim of this approach is to maintain, by giving fragments of allergenic proteins, the immunological effects, without the capacity of evoking an IgE-mediated reaction [27].

Immunological developments

Allergy-specific immunotherapy has a number of immunological and end-organ changes which may be involved in its beneficial effects. Reduced sensitivity to conjunctival, nasal, and bronchial allergen challenge, along with reductions in immediate and late-phase skin responses have been observed [28]. Although a complete understanding of underlying mechanisms is yet to be determined, important advances in the immunological changes accompanying allergen-specific immunotherapy have appeared and continue to evolve.

In 1935, Cooke *et al.* [29] coined the term 'blocking antibody' for the serum factor induced by immunotherapy that reduced a cutaneous reaction at a passive cutaneous transfer site to antigen challenge. Lichtenstein *et al.* [30] and Pruzansky and Patterson [31] during the 1960s showed that decreased histamine-release by peripheral blood basophils was associated with clinical improvement with immunotherapy. Further studies in the 1980s showed that allergen-specific suppressor cells were generated during immunotherapy that would inhibit allergen specific IgE production and lymphocyte proliferation [32]. Since then, new immunological techniques have enhanced our knowledge. Jutel and Akdis [33] have provided an excellent recent review. Antibody isotypes switching to IgG₄ from IgE by interleukin-10 (IL-10), the increase of allergen-specific suppressive capacity of immunotherapy-induced subsets of CD4⁺ CD25⁺ forkhead box (FOX) P3⁺ regulatory

T-cells, and induction of IL-10 secreting type 1 regulatory T-cells play critical roles. The changes induced by immunotherapy also result in suppression of eosinophil, basophil, and mast cell activities [33]. Even after immunotherapy is discontinued, the inhibitory bioactivity of allergen-specific IgG antibodies against IgE-allergen complexes binding to B-cells persists for several years [34].

The emergence of SLIT as a viable alternative to subcutaneous immunotherapy has resulted in additional mechanistic studies of its mode of action. A recent review [35] brings focus to the importance of mucosal antigen presenting cells, particularly dendritic cells, which induce protolerogenic mechanisms. Among these are upregulation of B7H1 and B7H3 co-inhibitory molecule expression and release of IL-10. Understanding of these basic mechanisms can lead to more effective and safer approaches to immunotherapy.

Unmet needs

Medicine is progressively passing from an 'opinion-based' to an 'evidence-based' era. The evidence based approach has the aim of optimizing the effectiveness of treatments, also taking into account patients' preferences, costs, safety, and regulatory aspects [36]. SIT is not an exception within this scenario. We are realizing now that the scientific evidence on SIT is far from being optimal [37]. In fact, we have available several meta-analyses on the efficacy of SLIT and SCIT, but the large heterogeneity of trials, especially for SLIT, limits the reliability of the analysis itself [38]. Another problem is the poor reporting on SIT trials, almost never following the CONSolidated Standard Of Reporting Trials guidelines and, therefore, difficult to compare each other [39]. A significant discrepancy remains between the European and the US approach, mainly concerning the use of allergen mixtures. The practice of mixing allergens is common in the USA, and usually not adopted in Europe [40]. The literature is so far of little help concerning this aspect [41]. Another problem with SIT that we should afford in the next years is the standardization of extracts, which is largely variable, especially in Europe [42], and does not allow a proper comparison among clinical trials.

In summary, SIT rapidly developed during the last 25 years and, although there is room for improvement, we do believe that allergen-specific immunotherapy plays an important role in the treatment of allergic diseases. Ongoing efforts to improve the safety, effectiveness, and ease of administration of this approach to treatment will continue to benefit patients who suffer from allergic disorders.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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