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Benefit of SLIT and SCIT for Allergic Rhinitis and Asthma

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Abstract Allergen immunotherapy (AIT) has been in use since more than one century, when Leonard Noon experimentally proved its efficacy in hayfever (Noon, in Lancet 1:1572–3, 1911). Since then, AIT was administered only as subcutaneous injections (SCIT) until the sublingual route (SLIT) was proposed in 1986. The use of SLIT was proposed following several surveys from the USA and UK that repeatedly reported fatalities due to SCIT (Lockey et al. in J Allergy Clin Immunol 75(1): 166, 1985; Lockey et al. in J Allergy Clin Immunol 660–77, 1985; Committee on the safety of medicines. CSM update. Desensitizing vaccines. Br Med J, 293: 948, 1986). These reports raised serious concerns about the safety and the risk/benefit ratio of AIT. Many cases of life-threatening events with SCIT were due to avoidable human errors in administration, but a relevant fraction of them remained unexplained and unpredictable (Aaronson and Gandhi in J Allergy Clin Immunol 113: 1117–21, 2014). Subsequently, in a few years, SLIT gained credibility and was included in the official documents and guidelines (Table 1) (Bousquet et al. in J Allergy Clin Immunol 108(5 Supp):S146–S150, 2001; Canonica et al. in Allergy 64 (Supp 91):1–59, 2009) as a viable alternative to traditional SCIT. Of note, the local bronchial (aerosol) and the intranasal route of administration were attempted after the 1970s as alternatives to SCIT: the bronchial route was soon abandoned due to the poor efficacy and/or side effects, and the local nasal route, although effective and safe, was judged substantially impractical (Canonica and Passalacqua in J Allergy Clin Immunol 111: 437–48, 2003). In contrast to SCIT, SLIT was tested in very large clinical trials (need references), including hundreds of patients and with dose-ranging experimental designs, so that some products (tablets) for grass, mite, and ragweed were officially approved as commercial drugs by regulatory agencies such as the Food and Drug Administration and the European Medicines Agency and the optimal content for the maintenance dose was identified for selected allergens. In parallel, the knowledge on the mechanisms of action of AIT was rapidly refined, leading to further improvements, such as the chemically modified extracts and the use of adjuvants to enhance efficacy and safety. In addition, in the last 10 years, there has been an increasing scientific and clinical interest in AIT applied to food allergies, in particular in children, with the use of orally administered extracts (Albin and Nowak-Węgrzyn in Immunol Allergy Clin North Am 35: 77–100, 2015). The results are so far encouraging, at least for cow's milk, egg, and peanut, although the use of treatment is still restricted to clinical trials or within specialized centers. Finally, the introduction of molecular- or component-resolved diagnosis has allowed detailing the prescription of AIT, by better delineating true sensitization versus cross-reactivity (Canonica et al. in World Allergy Organ J 6(1):17, 2013). This latter point is also in strict relation to the use of recombinant, engineered or highly purified molecules, instead of raw extracts, for the desensitization process.

Keywords Subcutaneous immunotherapy · Sublingual immunotherapy · Allergic rhinitis · Allergic asthma

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An Overview on the Mechanisms of Action of AIT

Allergen immunotherapy (AIT) is not a receptor antagonist or a mediator-blocking agent. It acts by deeply affecting the immunologic allergen-oriented response at various levels [1]. The main mechanism previously investigated for subcutaneous injections (SCIT) involve (a) the immune deviation towards a Th1-oriented response (and a reduction of the Th2 response); (b) the production of allergen-specific IgG4, which inhibit the IgE-facilitated antigen presentation; and (c) the emergence of T regulatory cells, which secrete cytokines like IL-10 able to downregulate the allergen-mediated response [2, 3]. The immunologic mechanisms of the action of sublingual route (SLIT) do not substantially differ from those of SCIT. The mechanistic aspect of SLIT includes a relevant role for dendritic cells that are particularly abundant in the mouth and that, through specific cytokine and signaling networks, perform an efficient antigen presentation [4, 5].

Indeed, the purported rationale of a rapid mucosal absorption with SLIT was incorrect [6], but the role of local antigen presentation in the oral mucosa was soon recognized as a main mechanism of action [7].

Efficacy and Safety: SCIT and SLIT

The demonstration of the efficacy of AIT in reducing symptoms and symptomatic drug intake in allergic rhinitis and asthma relies on numerous randomized trials, as reported in the official documents (of which agencies) reported in 37 [8, 9, 10, 11] (Table 1). In particular, the updated version of the World Allergy Organization document on SLIT included 77 trials [10]. Looking at the literature at a glance, the class effect of AIT is well demonstrated in both rhinitis and asthma, for the most relevant allergens, and this observation was confirmed by several meta-analyses [12–17]. Whereas for SCIT, there has been only one dose-ranging study [18]; several dose-finding studies were conducted with standardized extracts for SLIT, leading to identify the optimal maintenance dose for some products (Table 2).

SCIT is quite well standardized in regimens and protocols [8, 11], while SLIT can still be administered as drops, monodose vials or tablets, and with variable timings and doses. At present, tablets which were firstly introduced in 1998 as monomeric allergoid [19], and that are now well standardized, seem to represent the preferred option [20] either as pre-co-seasonal or continuous administration.

One of the most important methodological problems in studying AIT is the definition of outcomes and measurements. This is considered simple when pollen allergy is taken into account, since the allergen exposure can be easily measured and rhinitis symptoms are easy to quantify subjectively. In the case of asthma, only a few studies were powered for asthma symptoms, with a concomitant measurement of objective variables (such as pulmonary function) as what [21, 22]? More recently, some large clinical trials specifically designed for house dust mite-induced asthma were performed using SLIT, and all confirmed the reduction in asthma symptoms, asthma exacerbations, and a significant reduction in the use of inhaled corticosteroids [23–25].

The safety of AIT is well demonstrated. With SCIT, there were in the past some reports of fatalities, mainly coming from the USA [26, 27, 28, 29, 30], where highly concentrated extracts are used and multiple allergens are mixed for administration [31]. This information cannot be extrapolated to other countries (e.g., Europe) where AIT is given only for a limited number of allergens and where

Table 1 Position papers and guidelines on AIT

Year	Organization	Type of AIT	Reference
1998	World Health Organization (WHO)	SCIT/SLIT	Ann Allergy Asthma Immunol. 1998; 81(5 Pt 1): 401–5
1998	European Academy of Allergy and Clinical Immunology (EAACI)	Non injection routes	Allergy. 1998; 53: 933–44.
2001	Allergic Rhinitis and its Impact on Asthma (ARIA)	SCIT/SLIT	J Allergy Clin Immunol 2001; 108 (5 Suppl):S147–S334.
2007	American Academy of Allergy Asthma and Immunology/American College of Allergy Asthma and Immunology (AAAAI/ACAAI)	SCIT	J Allergy Clin Immunol 2007; 120 (suppl): S25–85, IV.
2008	Allergic Rhinitis and its Impact on Asthma (ARIA)	SCIT/SLIT	Allergy. 2008; 63 Suppl 86: 8–160
2009	World Allergy Organization (WAO)	SLIT	Allergy. 2009;64 Suppl 91: 1–59
2011	American Academy of Allergy Asthma and Immunology/American College of Allergy Asthma and Immunology (AAAAI/ACAAI)	SCIT	J Allergy Clin Immunol. 2011; 127 (1 Suppl):S1–55
2013	World Allergy Organization (WAO)	SLIT	World Allergy Organ J. 2014 Mar 28; 7(1): 6

Table 2 Optimal doses identified in SLIT studies

Author, Year	Allergen	Dose
Duham, 2006	Grass Tablets	15 mcg Phl p 5/day
Didier, 2007	Grass Tablets (five grass)	25 mcg group 5/day
Creticos, 2013	Ragweed	12 mcg Amb a 1/day
Bergmann, 2014	Mite	28/128 mcg Der p 1/Der f 1/day
Mosbech, 2014	Mite	6 SQ/day (70 mcg/day)
Nolte, 2015	Mite	22 DU/day (70 mcg/day)

severe adverse events have been reported only anecdotally [32]. With SLIT, it is well recognized that side effects are mainly local, transient, and self-resolving [10, 33, 34]. Specifically, for both SLIT and SCIT, uncontrolled (symptomatic) asthma remains the main absolute contraindication, in addition to active autoimmune diseases or malignancies [35].

SCIT is well standardized, whereas SLIT maintains a certain variability in protocols and procedures of administration. Nonetheless, the available literature suggests that the once a day administration and the pre-co-seasonal protocol should be preferred [36–38].

Finally, it must to be considered that, due to the particular mechanism of action, AIT display an effect that persists for years after it is discontinued. In addition, some studies consistently showed that AIT can prevent the onset of asthma in children with rhinitis, thus intervening in the evolution of the allergic march [39].

SCIT and SLIT: a Critical Appraisal

The comparison of SCIT vs. SLIT has been a matter of discussion since the introduction of SLIT in clinical practice[8]. Presently, this aspect seems to be of secondary relevance. Both routes of administration have a clearly demonstrated efficacy that is certainly of better methodological quality for SLIT. The direct comparison studies [41–44] failed to show a difference in clinical efficacy between the two routes [45], and this was confirmed in recent reviews [46, 47], where SLIT resulted to be even superior to SCIT [46], at least in the use of symptomatic medications for rhinitis. (For rhinitis alone? For asthma too?)

Despite the demonstration of clinical efficacy is considered robust enough as “class effect” for AIT in general, there are still so far some unmet needs. For instance, almost all AIT vaccines currently commercialized are standardized either biologically or immunologically, but the standardization methods are based on in-house references. Thus, extracts are labeled in units that differ from one manufacturer to another, although the content in micrograms of the major allergen(s) is usually available for the EMA and FDA officially approved products [48]. There is no controlled study on the optimal duration of an AIT treatment; thus, the current suggestions remain empirical. An open controlled 15-year follow-up of subjects treated with SLIT for 3, 4, or 5 years suggested that a 4-year course would be the best option [49], and another controlled trial in children showed that a 3-year is equivalent to a 5-year course [50]. AIT is currently being tested in conditions different from respiratory allergy, e.g., food allergy and extrinsic atopic dermatitis, where favorable results were reported [51, 20, 52, 53]. Of note, the pioneering studies, previously performed with peanut SCIT, provided overall positive results, but with an unacceptable occurrence of severe adverse events. In this sense, the favorable safety profile of oral or sublingual administration for food AIT encourages its experimental use to clearly define indications and contraindications.

The clinical efficacy of AIT (SCIT and SLIT) is well documented by clinical trials and meta-analyses in rhinitis and asthma. Nevertheless, several questions still need to be addressed: (a) the standardization of extracts and the optimal dose of allergen at maintenance, for all the relevant allergens and products [54]; (b) the real existence of a long-term benefit from AIT, such as persistent relief of symptoms following discontinuation, or prevention of disease progression; (c) combination therapy with multiple allergens has not been sufficiently evaluated for both efficacy and safety, although repeatedly suggested [55, 56], whereas the efficacy of SLIT for a single allergen in polysensitized patients was demonstrated [57]; (d) adherence remains a main problem [58] that can be partly resolved with a strict surveillance [58]; and (e) the available meta-analyses pooled the results of clinical trials performed with different extracts and different allergens, thus enhancing the heterogeneity of results that remain not generalizable.

In conclusion, AIT is one of the cornerstones in the management of respiratory allergic diseases since it is allergen specific, immunomodulating, and may affect disease progression. SLIT represents a significant clinical advance, offering an excellent safety and acceptance profile. The tablet-formulated AIT is an additional step-up, since its robustly based demonstration of efficacy and safety, and its recognition as a pharmaceutical product (for grass and mite in Europe, plus ragweed in the USA) is the best example of the rapid evolution in this field [59].

Compliance with Ethical Standards

Conflict of Interest Drs. Passalacqua, Canonica, and Bagnasco declare no conflicts of interest relevant to this manuscript.

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