

Allergen-specific immunotherapy for respiratory allergies: From meta-analysis to registration and beyond

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Allergen-specific immunotherapy (SIT) is an etiology-based treatment for respiratory and *Hymenoptera*-allergic diseases. Although introduced a century ago, SIT was not widely accepted for many years until its efficacy in the treatment of both allergic rhinoconjunctivitis and allergic asthma was demonstrated in appropriate double-blind, placebo-controlled trials and its mechanism of action was better understood. The indications for allergen-specific immunotherapy have been specified in consensus reports. Allergen-specific immunotherapy is primarily targeted to benefit patients with *Hymenoptera* allergy or severe upper and mild to moderate lower allergic respiratory diseases that are poorly controlled by pharmacologic treatments or who are unable or unwilling to use the latter. Several recent developments have helped to reinforce the position of SIT in the overall therapeutic management of respiratory allergies: (1) improvement in the quality of allergen extracts as a result of standardization, (2) better understanding of SIT's mechanism of action, (3) the introduction of sublingual tablets and their rigorous registration as pharmaceutical therapies by regulatory agencies, and (4) rationalization of prescribing patterns. There is a requirement for additional well designed, well executed, randomized trials in adults and children with allergic rhinitis and asthma, with a special focus on optimal patient selection, dosage, and treatment duration.

In this review, the authors put into perspective current international expert recommendations on the use of SIT (in relation to levels of clinical evidence) and analyze what is needed for the future. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Specific immunotherapy, allergic rhinitis, allergic asthma, allergens

Allergic diseases are now considered to result from a breakdown, probably T-regulated, in the immune tolerance we normally have to natural exposure to allergens. Specific immunotherapy (SIT) consists of repeatedly administering doses of an allergen to a subject with allergy to induce specific clinical and immunologic tolerance.¹ This will cause a clinical improvement in the symptoms and can alter the natural history of the disease.

The mechanisms of action of SIT are becoming better understood. Subcutaneous allergen immunotherapy (SCIT) reduces allergen-specific IgE production and increases the production of specific IgG (which acts as a "blocking" antibody).² Additional studies have indicated that the predominant mechanism depends on modification of the phenotype of allergen-specific T_H cells.³ The effect of SIT on these cells involves (1) immunologic deviation (stimulation of T_H0/T_H1 lymphocytes, with increased IFN- γ and IL-2 production), (2) specific T-lymphocyte anergy (a decrease in T_H2/T_H0 lymphocyte counts), or (3) induction of regulatory T-lymphocytes, which produce cytokines such as IL-10 and TGF- β . SCIT also reduces allergen-specific inflammation by decreasing inflammatory cell recruitment, activation, and mediator release (histamine, prostaglandin D₂, and eosinophil cationic protein).² All these effects contribute to immune tolerance and the long-lasting changes in the immune system even after treatment is discontinued. In sublingual specific allergen immunotherapy (SLIT), the mechanisms of action are not fully understood but seem to be similar to those of SCIT, with the particular involvement of mucosal dendritic cells.⁴

Since the inception of allergen therapy for treating seasonal allergic rhinitis to grass pollen ("hay fever") by Noon and Freeman⁵ in 1911 in Europe and Lowdermilk⁶ in 1914 in the United States, SIT has remained the only etiology-based treatment for allergic diseases. Its use worldwide is mainly based on evidence of its clinical efficacy. However, the clinical evaluation of SIT must take into account specific critical issues regarding the high heterogeneity among studies.

In the current review, we put into perspective current international expert recommendations on the use of SIT for allergic rhinoconjunctivitis and asthma (in relation to the stated levels of

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Abbreviations used

EMA: European Medicines Agency
 IR: Index of reactivity
 SCIT: Subcutaneous immunotherapy
 SIT: Specific immunotherapy
 SLIT: Sublingual immunotherapy
 SQ-T: Standardized quality tablet
 WHO: World Health Organization

clinical evidence) and offer suggestions on what is needed for the future.

WHERE ARE WE NOW?**International recommendations**

Over the past few years, guidelines on the use of SIT in allergic respiratory diseases have been published by the European Academy of Allergy and Clinical Immunology,⁷ the International Consensus Report on Asthma,⁸ the International Consensus Report on Rhinitis,⁹ the Global Strategy for Treatment and Prevention of Asthma,¹⁰ Allergic Rhinitis and its Impact on Asthma,¹¹ the World Health Organization (WHO),¹ the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology,¹² the World Allergy Organization,^{13,14} and the British Society for Allergy and Clinical Immunology.¹⁵

These guidelines are based on the published literature and have primarily focused on the efficacy and safety of SIT in allergic rhinitis and allergic asthma. Eight meta-analyses have included all of the publications published over the last 20 years: 2 for SCIT^{16,17} and 6 for SLIT.^{18–23} The Allergic Rhinitis and its Impact on Asthma document, which is in collaboration with WHO,²⁴ gave SIT the highest level of evidence according to the grading system of Shekelle et al²⁵ (ie, level Ia). However, the various studies suffer from large clinical and methodologic heterogeneities,²⁶ including diverse sources and types of allergenic extracts, treatment durations, doses, outcome measures, symptom and outcome scoring systems, rhinitis and/or asthma of different severities, and population ages (ie, adults vs children). Most importantly, the population sizes in these studies were generally small. This is identified in recent reviews.^{27,28} We consider that because of this high heterogeneity among studies, the results from meta-analyses should be viewed with caution.

Registration of SIT products

In 2010, only 3 SIT products have been registered as pharmaceutical treatments by the European Medicines Agency (EMA): 2 SLIT and 1 SCIT grass pollen products for allergic rhinitis. There are other products registered at national levels (eg, in Germany). All other formulations worldwide are used as named-patient products.²⁹ In contrast to the situation in Europe, more than 95% of the final allergen extracts used in the United States are prepared in the physician's office.³⁰ In the United States, allergen extracts are regulated by the Food and Drug Administration's Center for Biologics Evaluation and Research but are not registered.²⁹ At the end of 2008, the EMA published a specific guideline on SIT therapeutic trials that are designed for product registration³¹ (Table I).

Standardization of allergens

High-quality allergen extracts are essential for both the diagnosis and treatment of respiratory allergic diseases.¹ Most of the common extracts used in the clinic are now available in standardized forms or are in the process of being standardized.

Allergenic extracts are labeled in biological units on the basis of skin tests.²⁹ A major difference in standardization between Europe and the United States is the use of skin prick tests and wheals (Europe) and intradermal skin tests and flare (United States). There are multiple allergen specific units and concentrations resulting in a variety of unrelated unit names among marketed products. These units are not comparable and extracts may have different potencies because of (1) differences between extracts, (2) differences in the sensitivity of the patient population chosen, (3) the relatively small number of patients tested, or (4) methodologic differences.^{29,32,33}

In Europe, potency determination is based on comparison with in-house (manufacturer-specific) reference standards.³² As a consequence, each manufacturer defines its own specific units and concentrations. In the European Pharmacopoeia,³⁴ the allergen preparations for SIT may be (1) unmodified extracts (natural extracts), (2) chemically modified extracts, (3) extracts modified by adsorption (depot extracts), (4) modified and adsorbed extracts (allergoids), or (5) recombinant allergens (though none of the last are yet on the market). In the United States, potency determination is centralized and based on comparison with Center for Biologics Evaluation and Research reference samples.²⁹ The allergen extract types available are natural and alum-precipitated depot extracts.

The biological activity, composition, and stability of some allergen extracts have been documented. Composition can be categorized as follows²⁴: (1) extracts originating from a single raw material, (2) extracts containing mixtures of similar cross-reacting allergens (such grass pollens, tree pollens, ragweed pollens, or house dust mites) and (3) extracts containing mixtures of unrelated allergens (as long as data for stability and clinical efficacy are available). There are significant differences between Europe and the United States regarding the number of allergens that are used together in a named-patient preparation for SIT. In Europe, most formulations are single-allergen extracts, whereas most of the preparations in the United States contain an average of 8 different components.³⁰

Subcutaneous immunotherapy

Efficacy. The clinical efficacy of SCIT in allergic rhinitis and asthma is well established, and Cochrane meta-analyses of the efficacy of this therapy in allergic rhinitis¹⁷ and asthma¹⁶ are available (Table II). However, dose-response issues complicate the position of SCIT. At a low dose, SCIT is ineffective. However, high doses of allergen extracts can give rise to an unacceptably high level of systemic reactions. Efforts have been made to define the "optimal monthly dose" (defined as the dose inducing an adequate clinical effect in the majority of patients without provoking undesirable side-effects) in biological units or as the weight of major allergen content. For most allergen extracts, this value corresponds to between 5 and 20 µg of major allergen per injection.¹

In allergic rhinitis, clinical efficacy (in terms of a reduction in symptoms and/or the need for additional medication) has been shown for grass, birch, ragweed and *Parietaria* pollens, house

TABLE I. EMA recommendations for future registration of SIT products

- Conventional phase I trials in healthy subjects are generally not possible. Patients with allergy should be included at this early stage of development.
- Pharmacokinetic and pharmacodynamic studies are not possible either because of the nature of the products, which are undetectable in serum. Specific biological tests (IgG response, T-lymphocyte response) may be carried out during the course of the trials. However, because they do not always correlate with the clinical response, they cannot replace a clinical evaluation of the treatment effect.
- Phase II studies are certainly applicable, and a dose effect should be investigated/demonstrated.
- Because of variability in the level of allergens from one year to the next and from one site to another and a bias in patients' recall of previous symptoms, the investigation of the baseline level of symptoms in previous seasons is not relevant. Only a prospective evaluation of the severity of symptoms before randomization is possible, but this also has its limitations.
- For the same reasons (combined with interindividual variability in the clinical response), noninferiority studies are not possible: only randomized, double-blind superiority studies vs placebo (or another comparator) are acceptable. If possible, the placebo should contain histamine to maintain the double-blind nature.
- Levels of pollen for seasonal allergens should be documented as close as possible to the patients. The season (the period during which symptoms will be evaluated) should be defined as accurately as possible.
- Treatment effects should always be investigated in the long term (for a minimum of 1 pollen season or symptomatic period). Evaluation of potentially long-term carry-over effects (on symptoms or on prevention of the development of asthma or polysensitization) after stopping SIT is best performed in separate studies, without intermediate analyses.
- The score used should take into account symptoms and rescue medication because use of the latter clearly affects symptom severity. A validated combined score does not exist and is required.

Created from data from EMEA. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. London, 20 November 2008. Doc. Ref. CHMP/EWP/18504/2006. <http://www.emea.europa.eu/pdfs/human/ewp/1850406enfin.pdf>.

dust mite and cat dander. Only few studies clearly demonstrated that the clinical effect was dose-dependent.³⁵⁻³⁷ SCIT studies have also shown improvement in patients' quality of life.^{35,38} In allergic asthma, the clinical efficacy of SCIT was demonstrated by a Cochrane meta-analysis.¹⁶ The duration of SCIT needed to guarantee long-term efficacy after stopping the treatment is generally agreed to be 3 years.³⁹⁻⁴¹

Only 2 published studies have found that extracts containing recombinant allergens were effective in reducing the symptoms of allergic rhinitis.^{42,43} New forms of SCIT using the adjuvant monophosphoryl lipid⁴⁴ and adjuvanted allergen extracts using oligodeoxyribonucleotide immunostimulatory sequence of DNA containing a CpG motif as immunostimulants^{45,46} have been evaluated.

Safety. SCIT is associated with a risk of systemic side effects and anaphylaxis. Side effects may occur with all allergen preparations, whether they are standardized extracts, allergoids, or recombinant allergens. The risk is greater in subjects with asthma^{1,47} and with accelerated dosing schedules. Using the European Academy of Allergy and Clinical Immunology classification for adverse events,⁸ a Cochrane meta-analysis of SCIT for seasonal allergic rhinitis¹⁷ found that 8% and 7% of patients in the treated groups experienced grade II and grade III systemic reactions, respectively. A small number of patients (0.72%; 3 in the treated group vs 1 in the placebo group) experienced grade IV reactions. Adrenaline/epinephrine was used in 0.13% of injections. Some patients had systemic side effects with injections containing 5 to 20 µg major allergens,³⁵ considered to be the "optimal dose" for most allergen extracts.¹ Pretreatment with oral H₁-antihistamines during the induction phase reduces the frequency and severity of systemic side effects.⁴⁸ Recent international efforts have aimed at standardizing the reporting and rapid treatment of postinjection adverse events.⁴⁹

Indications. International guidelines suggest the use of SCIT in pollinosis when (1) the condition is severe and/or prolonged, (2) it is poorly controlled by adequate pharmacological treatment, or (3) pharmacologic treatment is refused by the patient or leads to significant side effects. Furthermore, SCIT is

particularly indicated when perennial allergic rhinitis is associated with mild or moderate asthma. The indications and contraindications for SIT are the same for children >5 years of age and for adults (Table III).

The clinical success of SCIT can be optimized if the patient fulfills a number of specific conditions assessed by the prescribing physician before SIT initiation (Table IV). Doctors, nurses, and health care personnel in general should be trained particularly in the surveillance and emergency treatment of anaphylactic reactions. A supply of adrenaline should be readily available in health care facilities in which SCIT is administered.

Impact of SCIT on the natural history of allergic disease. Small size studies show that the efficacy of SCIT persists for some years after treatment is withdrawn.^{39,40} SCIT may prevent the development of new sensitizations in house dust mite monosensitized children⁵⁰ and the appearance of allergic asthma in patients with grass and/or birch pollen induced-allergic rhinitis.⁴¹

Economic evaluation of SCIT. The health economics of SCIT versus pharmacologic treatment for pollen and mite allergic rhinitis have been modeled for Germany,⁵¹ France,⁵² and the United States.⁵³ SCIT was found to be cost-effective on the basis of on this modeling.

Sublingual immunotherapy

Sublingual immunotherapy is commercially available in several countries worldwide. The most recent SLIT extracts are standardized by using biological or immunologic methods, and the major allergen content is indicated in micrograms (using in-house manufacturer-specific assays and reference standards). Extracts can be administered as drops or fast-dissolving tablets.

Efficacy. In allergic rhinitis, the efficacy of SLIT has been shown in 4 meta-analyses^{18,19,22,23} (Table II). These meta-analyses have shown moderate to high heterogeneity in study designs; therefore, conclusions should be drawn with caution.²⁶⁻²⁸ However, recent data from large phase III studies of SLIT tablets in grass pollen allergic rhinitis has enabled the assessment of

TABLE II. Summary of meta-analyses for SCIT and SLIT

Disease	Authors (y)	RCTs included (No. of participants)	Symptom scores SMD (95% CI) I ² (heterogeneity) No. of studies	Medication scores SMD (95% CI) I ² (heterogeneity) No. of studies	Cochrane Review
SCIT					
Asthma	Abramson et al (2003) ¹⁶	75 (3506) Adults and children	−0.72 (−0.99, −0.44) I ² = 74.1% 28 Studies	−0.80 (−1.13, −0.48) I ² = 65.5% 15 Studies	Yes
Rhinitis	Calderon et al (2007) ¹⁷	51 (2871) Adults	−0.73 (−0.97, −0.50) I ² = 63.2% 15 Studies	−0.57 (−0.82, −0.33) I ² = 64.0% 13 Studies	Yes
SLIT					
	Calamita et al (2006) ²⁰	25 (1706) Adults and children	−0.38 (−0.79, 0.03)* I ² = 63.9% 9 Studies	−0.91 (−1.94, 0.12)* I ² = 91.8% 6 Studies	No
	Penagos et al (2008) ²¹	9 (441) Children	−1.14 (−2.10, −0.18) I ² = 94.4% 9 Studies	−1.63 (−2.83, −0.44) I ² = 95.4% 7 Studies	No
Asthma	Olaguibel et al (2005) ²²	5 (193) Children	−1.42 (−2.51, −0.34) I ² = NR 6 Studies	NR 7 Studies	No
	Compalati et al (2009) ²³ (only HDM)	9 Adults and children	−0.95 (−1.74, −0.15) I ² = 93% 9 Studies (476 participants)	−1.48 (−2.70, −0.26) I ² = 96% 7 Studies (397 participants)	No
Rhinitis	Wilson et al (2005) ¹⁸	22 (979) Adults and children	−0.42 (−0.69, −0.15) I ² = 73.5% 21 Studies	−0.43 (−0.63, −0.23) I ² = 43.8% 17 Studies	Yes
	Penagos et al (2006) ¹⁹	10 (484) Children	−0.56 (−1.01, −0.10) I ² = 81.1% 10 Studies	−0.76 (−1.46, −0.06) I ² = 85.5% 7 Studies	No
	Olaguibel et al (2005) ²²	6 (232) Children	−0.44 (−1.22, 0.35) I ² = NR 6 Studies	NR 7 Studies	No
	Compalati et al (2009) ²³ (only HDM)	8 Adults and children	−0.95 (−1.77, −0.14) I ² = 92% 8 Studies (382 participants)	−1.88 (−3.65, −0.12) I ² = 95% 4 Studies (175 participants)	No

HDM, House dust mite; I², I squared (for heterogeneity); NR, not reported; RCT, randomized controlled trial; SMD, standardized mean difference.

*P value = not significant.

efficacy and safety with more confidence^{54–59} (Table V). The quality of life of patients treated with SLIT is improved.^{56,60} The size of these studies has allowed subgroup analyses showing, for example, that the beneficial effect does not vary according to the presence or absence of asthma and is similar in monosensitized and polysensitized patients.⁶¹ It is interesting to note that low doses (25,000 standardized quality tablet [SQ-T] and 100 index of reactivity [IR], equivalent to 5–7 µg allergen Phl p 5 per day, according to the manufacturers) are ineffective and that a daily dose of around 15 to 25 µg is required to obtain a statistically significant clinical improvement in symptom scores. One study showed that a higher dose (33–40 µg major allergen Phl p 5 per day) was no more effective than 15 to 25 µg.⁵⁶

In allergic asthma, 4 meta-analyses with small number of studies have shown significant reduction on asthma symptoms and asthma medication use^{20–23} (Table II). Here again, there was significant interstudy heterogeneity, so the results of ongoing large studies of allergic asthma with SLIT products are keenly awaited.

Safety. SLIT is well tolerated by adults and children in many different clinical trials using drops and tablets. In clinical trials, local side effects (notably mild itching and mild swelling of the

lips and floor of the mouth) are typically observed in 60% to 85% of patients. These symptoms appear within minutes or hours after taking SLIT and are usually of short duration (less than 14 days). They do not require medical treatment or dose adjustment and often disappear during the course of treatment. Side effects are not necessarily more frequent in patients taking high doses.^{55,56} The high incidence of local side effects had led to some concern about the inability to blind SLIT trials adequately.⁶²

Systemic reactions such as urticaria, angioedema, and asthma occur during dose escalation and maintenance phases. These reactions may be dose-dependent and allergen-dependent. Six clinical cases of anaphylaxis to SLIT have been published.^{63–67} These events have stressed the indication that the first dose of SLIT should be taken in a doctor's office with an observation period of at least 30 minutes; this advice is now clearly stated in the labeling of the SLIT tablet.

As SLIT is administered to patients in their home, the following precautions are recommended: (1) give the patient (or the parents, in the case of a child) clear and simple written instructions on the steps to take if an adverse event occurs, and (2) store the allergen tablets or drops in a secure place, out of the reach of children.²⁷

TABLE III. Indications for specific immunotherapy^{1,7,24}

High-dose SCIT is indicated in the following cases:

- Patients presenting with symptoms induced by exposure to allergens
- Patients exposed to a prolonged season or presenting with symptoms induced by successive pollen seasons
- Patients with allergic rhinitis and lower respiratory disease during peak exposure to the allergen
- Patients in whom H₁-antihistamines and moderate doses of topical glucocorticoids do not control symptoms sufficiently
- Patients who do not wish to undertake constant or prolonged pharmacotherapy
- Patients in whom pharmacotherapy causes side effects

High-dose SLIT may be indicated in the following cases:

- Clearly selected patients with rhinitis, conjunctivitis, and/or asthma caused by allergy to pollens or house dust mites
- Patients who are inadequately controlled with conventional pharmacotherapy
- Patients who have had systemic reactions during specific immunotherapy by injection
- Patients who have compliance problems with or refuse immunotherapy by injection

Indications. When nationally registered, SLIT is indicated in allergic rhinitis and asthma induced by pollens (birch, cypress, grasses, olive tree, *Parietaria*) or house dust mites as summarized in Table III.

Impact of SLIT on the natural history of allergic disease. SLIT may also have an effect on the natural course of the disease. A study published in 2010 demonstrated that 3 years of treatment with SLIT tablets resulted in consistent clinical improvement associated with immunologic changes that were sustained 1 year after treatment cessation.⁶⁸ It has been suggested that SLIT may prevent asthma in treated patients with allergic rhinitis⁶⁹ and may reduce the development of additional allergen sensitivities.⁷⁰ Additional data are needed to confirm these observations.

Economic evaluation of SLIT. The health economics of SLIT versus pharmacologic treatment for pollen and mite allergic rhinitis in children and adults have been modeled in Europe.^{52,71,72} These analyses suggest that SLIT is cost-effective.

Comparison of sublingual and subcutaneous immunotherapies

The comparative efficacy of SLIT and SCIT in patients with allergic respiratory diseases has been evaluated in several underpowered trials.⁷³⁻⁷⁶ Allergic rhinoconjunctivitis was evaluated in all studies; in addition, 2 studies included mild-to-moderate allergic asthma.^{73,75} Different allergens were evaluated, such as mixed grass pollens, birch pollen, house dust mite, and multiple allergen extracts. The published data show little or no statistical difference between SCIT and SLIT with respect to symptom scores and medication scores. The lack of significant difference between the 2 treatments does not indicate equivalent efficacy. To detect minor differences, larger groups are necessary. Moreover, we must consider that not all the studies had a double-blind double-dummy randomized design: some were open-label, whereas others were placebo-controlled and randomized. These differences limit interpretation of the data.

WHERE ARE WE GOING?

International recommendations

After reviewing published guidelines, we advocate a single international consensus statement based on large, well designed phase III studies with registered products. This guideline could then be adapted at regional and/or national levels. The role of an

international organization is pivotal as it is conformed by panels of clinical and research experts who will reflect the regional needs, influenced by cultural, economic, environmental, and genetic differences.

Clinical trial reporting

When researchers embark on a clinical trial, they make a commitment to perform the work and report the findings in accordance with basic ethical and study conduct principles, as outlined in the International Congress of Harmonization (ICH) guideline.⁷⁷ This should include maintaining the accuracy of the results and making both positive and negative findings publicly available. Unfortunately, a significant proportion of health care research remains unpublished or is published only in part. Selective reporting (for whatever reason) leads to an incomplete and potentially biased view of a trial and its results; this also explains why few “negative” studies are available for systematic review and meta-analysis.^{26,28}

We still consider that meta-analyses of SIT based on well performed systematic reviews represent the highest level of evidence (Table III). However, at this stage of evidence-based medicine, it is mandatory to report all negative and positive studies. In addition, studies included in meta-analyses should be carefully scrutinized for adequate design (including appropriate and well characterized subject populations, use of validated and standardized outcomes, and vigorous recording of concomitant and rescue medications). Finally, because of large discrepancies in the methodology followed by small and middle-sized studies, it is crucial to evaluate well powered, large clinical studies in both children and adults in SIT. Recommendations should be carried out by unbiased methodologists with the input of clinicians.

We support the recently developed Consolidated Standards of Reporting Trials statement for SIT,⁷⁸ which proposed a checklist in the context of performing and reporting trials in allergen SIT. Only randomized, blind (with respect to participants, care providers, and outcome assessors), placebo-controlled, phase III studies with explicit description of participant inclusion and exclusion criteria and identification of primary, secondary, and exploratory outcomes, involving standardized allergens and reporting adverse events in an ICH guidelines-based fashion, should be evaluated.^{77,78} In this way, the discrepancy of data reported and published in peer-reviewed journals and data reported in regulatory agencies (see Table V) should eventually be eliminated.

TABLE IV. Considerations for the initiation of immunotherapy^{1,7,24}

1. Presence of a diagnosed IgE-mediated disease:
 - a positive skin test and/or the presence of specific serum IgE
2. Demonstration of the role of specific sensitization in the symptoms:
 - exposure to allergens (determined by allergy tests) is associated with the appearance of symptoms
 - If necessary, perform a challenge test with the allergens in question
3. Characterization of other triggering factors that could be involved in the symptoms
4. The severity and duration of symptoms
 - Subjective symptoms
 - Objective parameters, eg, absenteeism from work or school
 - Respiratory function (essential in patients with asthma): exclusion of patients with severe asthma
 - Monitoring of respiratory function
5. Response of symptoms to pharmacotherapy
6. Availability of standardized or good quality vaccines
7. Contraindications:
 - Treatment with β -blockers
 - Other immune diseases
 - Observation impossible (injections or surveillance for 30 min after each injection)
 - Initiation of immunotherapy with aeroallergens during known pregnancy
8. Socioeconomic factors:
 - Cost
 - The patient's occupation
9. Objective proof of efficacy of immunotherapy to the selected allergen (availability of controlled, randomized studies)

Safety

Safety of any treatment is fundamental. Evidence is required throughout the entire spectrum of the treatment life cycle, from the premarketing phase to the postmarketing phase.

The SIT safety and effectiveness also need to be assessed in the real world, where outcomes differ from those in controlled clinical trials, which provide premarket test results. Postmarketing safety surveillance is required for all marketed treatments including drugs, vaccines, and biologicals to evaluate a new treatment safety code. It usually relies on spontaneous adverse drug reaction reports and represents an important tool in monitoring the safety and in providing information on any required revision of the prescribing information. The classification and reporting methods should be standardized around the world. Although reporting is mandatory in many countries, underreporting exists primarily because of the general burden of reporting (time required to report, questions of privacy, confidentiality, liability, and so forth). Also, these reports can be limited by quality problems including incomplete data and difficulty in demonstrating a causal relationship between exposure and adverse events.

A universal terminology and grading system for SIT-related adverse events should be implemented by an independent multidisciplinary group of experts and promoted by international and local medical organizations.⁴⁹ However, currently, the Medical Dictionary for Regulatory Activities is the only internationally recognized system for the classification of adverse reactions in all studies, from phase I to postpharmacologic surveillance. The public should have access to the information on all SIT-related adverse reactions.

Registration of SIT products

All the most relevant allergen extracts (in terms of public health issues in a particular country or region) should be registered. Such measures would directly benefit the health of the population affected and, in the long term, would be advantageous for the

local or regional economy. We acknowledge that manufacturers cannot afford to execute the requisite registration procedures for the other allergen extracts they are producing. The less relevant allergen extracts could still be sold on a named-patient basis. There is also a need for standardizing and validating surrogate outcomes that could possibly replace the need for seasonal trials (exposure chambers, allergen challenges, and so forth).

Standardization of allergens

Because allergen extracts are usually prepared from natural biological sources, standardization procedures are of crucial importance. No progress will occur if each manufacturer is using its own in-house standard. Currently, no standards for the measurement of allergen content are universally accepted. To address this issue, internationally standardized measurement of major allergens is a realistic and justifiable aim,²⁴ but other alternatives should be considered. To achieve this, the input of experts worldwide is needed. Allergen manufacturers should indicate the content of representative major allergens in their products in units of mass ($\mu\text{g/mL}$), even though direct comparisons between the various manufacturers would still be prevented by differences in the assays and analytical methods used.^{24,33} Therefore, the use of standardized assays (provided by WHO), which can be used in an identical fashion, should be implemented. For allergen mixtures, the proportion of each component should be specified.

Economic evaluation of SIT

Although few studies have compared the cost-effectiveness of SIT with that of standard pharmaceutical treatment, these 2 approaches are very difficult to compare in view of differing national health insurances, variable epidemiologic data, and the different prescription habits and outcome measures used.⁷⁹ Moreover, because these studies were based on modeling, it is important that prospective, randomized, cost-effectiveness trials are

TABLE V. Large randomized controlled studies on grass pollen SLIT tablets for seasonal allergic rhinitis

No. of patients	Daily	Age (y),		Symptom scores,*			Symptom scores,*			Medication scores,*			Medication			References	
		SLIT/placebo	dose	mean	SLIT	Placebo	adjusted mean	SLIT	Placebo	median	SLIT	Placebo	adjusted mean	SLIT	Placebo		Reduction†
Adults																	
153/150	75,000	36	36	2.47	2.94	−16	2.13§	2.53§	−16§	1.46	2.05	−28	0.35§	1.24§	−72§	55	
316/318	75,000	33.3	34.5	2.85‡	4.14‡	−31‡	2.1§	3.2§	−34‡	1.65‡	2.68‡	−39‡	1.7§	0.8§	−53§	54	
155/156	300 IR	28.7	29.1	3.58	4.93	−27§	2.91	4.62	−37	0.28	0.43	−35	0.10§	0.27§	−63‡	56,59	
Children																	
126/127	75,000	10.1	10.1	3.36	4.29	−28	2.71	3.75	−28	2.68	3.53	−65	0.64	1.83	−65	57	
131/135	300 IR	10.5	11.5	3.25	4.51	−28	2.48§	4.08§	−39	0.60§	0.79§	−24§	0.39§	0.76§	−49	58	

*The definition of pollen season varies from one study to another. Here we show the symptoms for all studies during the pollen season defined as >30 grains/m³ air.

†Percentage compared with placebo.

‡These values differ from those given in the publications but have been reviewed by the regulatory authorities in the EMA registration file.

§These data were provided by the manufacturers.

conducted. Evaluation with unified criteria and outcomes carried out by independent investigators is now mandatory, because the use of SIT is encouraged as a result of its long-term clinical benefits and potential to prevent the development of new sensitizations and asthma in severe high-risk populations.

Indications for SIT

The WHO estimates that allergic rhinitis affects 600 million people worldwide, including 200 million with associated asthma.⁸⁰ Half of all adults with asthma and at least two thirds of children with asthma have allergies.¹⁰

Most people with allergic rhinitis have mild symptoms that do not affect their quality of life and/or that are satisfactorily controlled with readily available pharmacologic treatments (eg, antihistamines and nasal corticosteroids).⁸¹ However, around 20% of these patients see little or no improvement with these treatments (because of the severity of their disease), whereas others wish to adopt a more curative approach to their illness. These patients can clearly benefit from SIT⁸² and should therefore be eligible and selected for allergen immunotherapy. Criteria selection of patients with asthma for SIT should be established.

Efforts should be made to (1) evaluate the usefulness of all registered SIT products in polysensitized patients, (2) consider the exact regimen (eg, coseasonal treatment vs year-round treatment), (3) assess treatment duration, and (4) evaluate early use of SIT in children to prevent asthma and reduce the development of additional allergen sensitivities. Preliminary studies are addressing these issues, but further data are required.⁸³⁻⁸⁶

After almost a hundred years of clinical use of SIT for allergic rhinitis and asthma, tremendous progress has been achieved worldwide. In this review, we raise many relevant clinical and research issues that to be addressed need proper funding.

Currently, SCIT represents the most common administration route in allergen immunotherapy, and we believe that (1) large, well designed, randomized, controlled studies are needed for the most common allergens (house dust mite and grasses in both children and adults), (2) further economic evaluations and postmarketing surveillance studies are required, (3) objective evaluations of the effect of SCIT in monosensitized and polysensitized individuals should be established, (4) the use of

multiple-allergen SCIT in polysensitized patients should be objectively evaluated and documented, and (5) SCIT's safety profile in high-risk groups (such as patients with moderate to severe asthma) should be specified and included in the guidelines.

Regarding SLIT, we suggest that (1) the clinical efficacy and safety for perennial allergens (mainly house dust mite) should be established in large, well designed, international clinical trials; (2) the treatment duration and optimal regimen (including data on coseasonal or continuous treatment for seasonal allergens) should be objectively evaluated; (3) the long-term effect after discontinuation should be clinically and immunologically documented; (4) given that SLIT is recommended for home use, the regular assessment and reporting of adverse events by the prescribing physician should be monitored (patients and doctors must be aware of the potential risk of very rare but potentially severe systemic reactions, including anaphylaxis); (5) clinical trials with other relevant pollens (such as tree pollens) should be encouraged; and (6) large, well designed, head-to-head SLIT versus SCIT comparisons are needed.

Finally, a number of future forms of immunotherapy may provide better alternatives to the currently available SCIT or SLIT, including combination of conventional SCIT with anti-IgE, allergen plus anti-IL-4 or Toll-like receptor 4 agonists, CpG (Toll-like receptor 9 agonists) oligonucleotides ± allergen, allergen coupled with viruslike particles, allergen/IgG chimeric proteins (in clinical trials soon), and recombinant allergens/peptides. Ultimately, these newer forms will provide information on the pathogenesis of allergic diseases and ideally will result in decreased symptoms and improved quality of life and profound immunomodulation, will be cost-effective, and will have favorable risk/benefit ratios.

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