Update review

Allergic Rhinitis and its Impact on Asthma update: Allergen immunotherapy

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The Allergic Rhinitis and its Impact on Asthma document was first published in 2001. Since then, new data on specific immunotherapy have appeared. This review is intended as an update to the original document. MedLine (2001 to June 2006) was searched with appropriate key words, and panelists were asked to identify further relevant articles. Randomized controlled trials were considered for the evaluation of efficacy. For the evaluation of safety and additional effects, studies with lower grades of evidence were included. The clinical efficacy of injection immunotherapy in rhinitis and asthma was confirmed, as well as the safety, provided that recommendations are followed. Studies have demonstrated the long-term efficacy and the preventive effect of immunotherapy in reducing the onset of new sensitizations. One randomized open trial demonstrated that in children with allergic rhinitis, injection immunotherapy may reduce the risk of developing asthma. There is strong evidence that sublingual immunotherapy is effective in allergic rhinitis in adults. Recent meta-analyses demonstrated its efficacy in allergic rhinitis in children and in asthma, although more definitive trials are required. Current data indicate that sublingual immunotherapy is safe and the rate of adverse reactions is not greater below 5 years of age. One randomized open trial showed that in children with allergic rhinitis, sublingual immunotherapy reduced the onset of asthma. Further studies are needed to identify the optimal maintenance dose and to elucidate the mechanism of action. Novel approaches for immunotherapy are currently under evaluation, including the use of adjuvants, peptides, and DNA-conjugated and recombinant allergens.
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Key words: *Injection immunotherapy, sublingual immunotherapy, efficacy, safety, mechanisms*

The management of allergic rhinitis involves patient education, allergen (and pollutant) avoidance, pharmacotherapy and, when appropriate, allergen-specific immunotherapy.[1] The recommendations of the Allergic Rhinitis and its Impact on Asthma (ARIA) panel for the pharmacologic and immunotherapy treatment of allergic rhinitis are evidence-based and step-wise and relate to the severity and duration of symptoms. The recommendations for the use of various forms of immunotherapy in allergic rhinitis were established in an evidence-based fashion. The first ARIA workshop was held in December 1999, and the outcome was published in 2001.[2] Since then, new information on the clinical use and mechanisms of action of various forms of immunotherapy in allergic rhinitis and allergic asthma has been published. The panelists felt that an update was necessary.

Abbreviations used
ARIA: Allergic Rhinitis and its Impact on Asthma
DBPC: Double-blind, placebo-controlled
MPL: Monophosphoryl lipid
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy

OBJECTIVES AND METHODS

Experimental evidence on subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for allergic rhinitis and allergic asthma, published between January 2000 and April 2006, is reported to update the 2001 ARIA recommendations. Pharmacologic treatments, allergen avoidance strategies, and complementary/alternative medicine for rhinitis and asthma are discussed separately in other ARIA documents.[3-5] Studies were selected for review according to the following strategy:

- Studies were sought from MEDLINE (January 2000 to June 2006) and, in addition, the ARIA Committee members were asked to identify further relevant articles.
- Key words were (allergen) immunotherapy [OR] sublingual immunotherapy [AND] rhinitis [OR] conjunctivitis [OR] asthma. The search was also refined to identify randomized, placebo-controlled trials, meta-analyses, and reviews.
- Only randomized, double-blind, placebo-controlled (DBPC) clinical trials were selected for the

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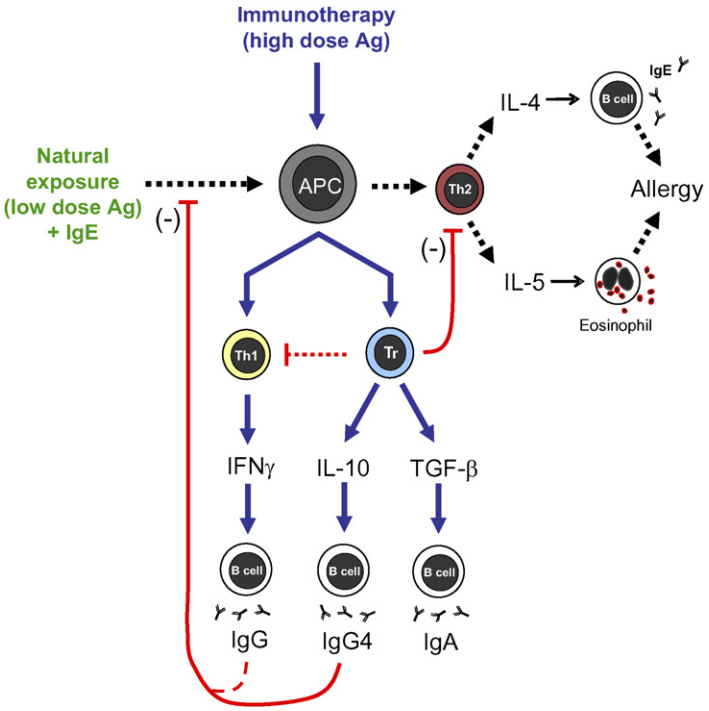

FIG 1. A summary of the putative mechanisms of action of SCIT. Reprinted with permission from Robinson DS, Larche ML, Durham SR. Tregs and allergic disease. J Clin Invest 2004;114:1389-97. *Ag,* Antigen; *APC,* antigen-presenting cell; *Tr,* T regulatory.

evaluation of efficacy. When randomized, DBPC trials were not available (eg, for the evaluations of safety and preventive effects), studies with a lower grade of evidence were included. References on treatment mechanisms were also included to provide background data.

- Abstracts from meetings were not considered.
- All studies meeting the search strategy were examined by 2 of the experts, reviewed by the chair of the group, and discussed during plenary sessions of the ARIA Scientific Committee.
- Studies were excluded when (1) the methodology made the assessment of efficacy and/or safety impossible, (2) the text of the article was not in English, or (3) the methodology was not clearly stated.

MECHANISMS OF SCIT AND SLIT

SCIT

Subcutaneous immunotherapy is an allergen-specific therapy that is clinically effective and induces long-term remission of allergic rhinitis and allergic asthma, as shown in randomized, double-blind controlled studies.[6,7] In contrast with symptomatic treatment with pharmacologic agents, it may also prevent the onset of new sensitizations[8,9] and reduce the progression of the disease from allergic rhinitis to allergic asthma.[10] Such responses involve immunologic memory and therefore direct and/or indirect effects on T and/or B lymphocytes (Fig 1).

Antibody responses. SCIT has been shown to be associated with a transient increase in allergen-specific IgE followed by blunting of seasonal increases in IgE. These effects are accompanied by an increase in allergen-specific IgG antibodies, particularly in the IgG_4 subclass.[11-14] Studies have confirmed and extended these observations to include measurements of the biological effects of IgG. These effects include the IgG-dependent ability of postimmunotherapy serum to inhibit the binding of allergen-IgE complexes to B cells, the blocking of subsequent IgE-facilitated allergen presentation and activation of allergen-specific T lymphocytes, and the prevention of allergen-IgE–dependent activation of peripheral basophils.[15-17] This last effect of allergen-specific IgG may be explained either by competition for IgE-allergen binding or by an effect mediated via the inhibitory IgG receptor FcγRIII, which is coexpressed with FcεRI on basophils and inhibits post-IgE receptor signaling pathways after allergen binding.[18,19] The biologic relevance of increases in immunoreactive serum IgG and IgG_4 after SCIT has been questioned because there is a poor correlation with improvement in clinical symptoms. Whether these additional functional measures of IgG are surrogate and/or predictive of the clinical response to immunotherapy remains to be determined.

Effector cells. SCIT is accompanied by an inhibition of the recruitment and/or activation of effector cells, including mast cells and eosinophils, at the site of the allergic reaction. Studies before and after SCIT have confirmed a reduction in the number of nasal mucosal eosinophils, basophils, and

mast cells during the pollen season.[20-24] As in previous studies, a reduction in the mucosal expression of vascular adhesion molecule 4 was observed[25] and was accompanied by a decrease in IL-4 and IL-13, cytokines that are known to upregulate vascular adhesion molecule 4 expression. One study showed that immunotherapy did not reduce $CD1a^+$, IgE^+, and $Fc\varepsilon RI^+$ cells in the nose during the birch pollen season, whereas nasal corticosteroids did.[26]

T-cell responses. The cardinal features of allergic inflammation are tissue eosinophilia and IgE synthesis, events regulated by T_H2 lymphocytes that produce a distinct profile of cytokines. Studies over the period of the past decade have confirmed the blunting of allergen-driven T_H2 responses, including reductions in IL-4, IL-13, IL-5, and IL-9 in the periphery and/or within the target organs.[13,24,27-32] These changes are associated with (1) immune deviation in favor of T_H1 responses with an overproduction of IFN-γ and/or (2) the emergence of a population of regulatory T lymphocytes that produce the inhibitory cytokines IL-10 and/or TGF-β.[33-35] It is hypothesized that these regulatory T cells act directly to suppress allergen-specific T_H2 responses. Alternatively, IL-10 is a known switch factor for IgG_4 production,[36] whereas TGF-β favors IgA,[37] and both of these antibody classes are increased in peripheral blood after SCIT.[33]

SLIT

Sublingual immunotherapy is associated with certain qualitatively but not quantitatively similar events known to occur during SCIT, including modest increases in IgG, a transient increase in IgE, and the suppression of eosinophil recruitment and activation in target organs.[38-42] On the contrary, other studies have failed to demonstrate changes in either systemic T-cell or cytokine responses[43,44] or local changes in T cells or effector cells within the sublingual mucosa.[38] Some studies have reported an increase in IL-10 production,[45,46] and 1 showed the suppression of allergen-specific T-cell responses after 12 months of grass immunotherapy.[47] Another *in vitro* study demonstrated that SLIT reduced the expression of IL-5 and enhanced the expression of IL-10 in PBMCs stimulated with the allergen.[48] Further studies are needed to determine whether the same or alternative mechanisms are important for the effects of SLIT.

Implications

The modification of allergen-specific T-lymphocyte responses after any form of immunotherapy is pivotal to the downstream events on antibody synthesis and to the activation/recruitment of inflammatory cells. This is at least in part supported by the documented effect of specific immunotherapy (SIT) on the late-phase reaction after challenge. These novel insights have important implications for future research, namely the potential to develop bioassays to predict the clinical response to immunotherapy, when to stop such therapy, and how to preempt relapse by reintroducing therapy after withdrawal. Second, they highlight the need to develop novel strategies to facilitate immune deviation and/or the promotion of regulatory T-cell populations and the use of alternative routes or adjuvants to enhance efficacy while reducing the risk of IgE-dependent systemic side effects.

SCIT

Subcutaneous immunotherapy is currently marketed in Europe and the United States and is generally available in most countries. Many extracts are standardized either biologically or immunologically, although this frequently involves the use of in-house standards, which makes comparison of the allergen content of extracts from different sources difficult or impossible. For some preparations, the microgram content of the major allergens is also available.

Efficacy

The clinical efficacy of SCIT is now well established. Meta-analyses of the efficacy of SCIT for both allergic asthma[49] and rhinitis[50] are available. Since 2000, many studies (Table I) have confirmed these findings. Clinical efficacy (reduction of symptoms and/or need for medications) has been confirmed with grass,[51-56] birch,[51,57,58] *Parietaria*,[59,60] mites,[61-66] and ragweed.[67] Two clinical studies, 1 evaluating symptoms on exposure[54] and 1 evaluating the response to a nasal provocation test,[68] demonstrated the dose-dependency of SCIT for clinical efficacy.

Safety

Winther et al,[69] in a randomized DBPC study with grass and birch vaccines, found that systemic reactions with SCIT occurred in 3.3% of the injections with grass and in 0.7% of the injections with birch. All the reactions were mild, but no specific predictor for systemic reactions was identified. A postmarketing surveillance study[70] reported that systemic reactions occurred with 0.9% of the total doses given and in 3.7% of patients. All reactions were mild or moderate. Another survey on grass pollen SCIT reported an occurrence of systemic reactions in 2% of patients,[71] with no life-threatening side effects. Nettis et al,[72] in a survey including more than 500 subjects, reported an occurrence of severe reactions in 5.2% of patients and 0.1% of doses. A retrospective study[73] of 65 patients receiving multiple vaccines and rush immunotherapy reported a 38% rate of systemic reactions with 1 severe episode. An e-mail survey of more than 17,000 physicians[74] reported a high rate of errors in administration (wrong patient or wrong dose). These data may explain, at least in part, the occurrence of reactions[75] and confirm the importance of a careful administration of SCIT as recommended in current guidelines.[76,77]

Additional properties

In some of the DBPC studies, SCIT reduced nonspecific bronchial hyperresponsiveness[61,65] to methacholine, whereas other studies found no change in the methacholine provocation dose[62] but only an improvement in AMP-induced hyperreactivity.[57] Two DBPC studies with grass pollen SCIT showed marked improvements in the quality of life of patients with seasonal allergic rhinitis.[54,55] A long-lasting effect, previously reported in

TABLE I. DBPC trials on the efficacy of SCIT published since the year 2000

Author, year	Reference	Age range (y)	No. of patients*	Allergen	Duration	Dose	Disease
Winther et al, 2000†	51	3-56	26/26	Grass/birch	3 y	Median cumulative/y: 72 μg Bet v 1 120 mcg Phl p5	R
Grembiale et al, 2000	61	10-38	22/22	Mite	2 y	9600 BU/y	A
Walker et al, 2001	55	22-64	20/17	Grass	2 y	20 μg Phl p 5/mo	R
Leynadier et al, 2001	52	18-44	15/12	Grass	1 y	7 μg Phl p 5/100 IR	R
Rak et al, 2001‡	57	18-45	20/30	Birch	6 mo	Cumulative 120 μg Bet v 1	R/A
Drachenberg et al, 2001	130	18-56	81/60	Grass (MPL-adjuvanted)	4-8 wk	Cumulative 60 μg group 1	R
Bodtger et al, 2002	58	19-46	17/18	Birch	6 mo	100,000 SQU/injection	R
Basomba et al, 2002	127	14-50	25/25	Mite (liposomes)	1 y	Cumulative 37.8 μg Der p 1	R/A
Varney et al, 2003	62	19-55	15/13	Mite	1 y	Cumulative 88 μg Der p 1	R/A
Polosa et al, 2003	59	20-54	15/15	Parietaria (wall pellitory)	36 mo		
Maestrelli et al, 2004	63	6-43	31/41	Mite	3 y	84 μg Der p 1/y	A
Mirone et al, 2004	67	23-60	16/16	Ragweed	1 y	Cumulative 176 μg Amb a 1	R
Corrigan et al, 2005	53	18-60	77/77	Grass	2 y	6000 TU/injection	R
Álvarez-Cuesta et al, 2005	64	17-58	25/28	Grass + olive depigmented	2 y	Cumulative: 1.48 mg grass; 1.66 mg olive	R
Ameal et al, 2005	65	14-48	29/26	Mite depigmented	1 y	Cumulative: 350 μg	A
Jutel et al, 2005	141	21-30	29/28	Grass (recombinant)	20 mo	Cumulative 490 μg total protein	R/A
Ferrer et al, 2005	60	16-60	20/21	*Parietaria*	20 mo	1.5 μg Par j 1	R/A
Frew et al, 2006	54	18-60	203/104/103	Grass	8 mo	20 μg Phl p 5/2 μg Phl p 5/0 μg/mo	R
Roberts et al, 2006	56	3-16	18/17	Grass	2 y	20 μg Phl p 5/mo	A
Wang et al, 2006	66	9-35	64/65	Mite	1 y	9.8 μg Der p 1/mo	A

BU, Biological units; *IR*, index of reactivity; *SQU*, standardized quality units; *TU*, therapeutic units; *R*, rhinitis; *A*, asthma.
*Active/placebo.
†Double-blind with 2 active treatments.
‡Double-blind with nasal steroid.

clinical trials, was confirmed in 23 children who were followed-up for 6 years after the discontinuation of grass SCIT.[7] The same children were evaluated again after 12 years, and persistence of a moderate beneficial effect was identified.[78] A long-lasting effect on the magnitude of skin positivity was reported in 82 subjects 8 to 16 years after participating in a randomized double-blind trial with various allergens.[79] In 2 large retrospective studies,[8,9] SCIT appeared to prevent the onset of new atopic sensitizations as determined by skin prick testing. In a large randomized, controlled, but not blind study of SCIT (the Preventative Allergy Treatment study), pollen immunotherapy reduced the risk of the onset of asthma in children who had allergic rhinitis and no asthma.[10] This preventive effect was observed to persist in the same patients for 2 years after the termination of SCIT.[80] A randomized, controlled trial of rhinoconjunctivitis and oral allergy syndrome provided evidence that SCIT administered for birch pollen allergy may possibly reduce oral symptoms caused by eating apples.[81] The protective effect of birch immunotherapy on apple-induced oral allergy syndrome was reported to be long-lasting.[82]

SLIT

Sublingual immunotherapy is currently marketed in several European countries and is also available in other countries (eg, Argentina, Brazil, the Gulf States, and South Africa). Extracts may be standardized either biologically or immunologically,[83] and for some preparations, the microgram content of the major allergens is also available.

Efficacy

After publication of the ARIA document and since the year 2000, many DBPC randomized trials on SLIT have been published[38,39,84-104] (Table II), although with largely variable doses of allergens. Several trials have confirmed the clinical efficacy of SLIT in allergic rhinitis caused by grasses, trees, ragweed, *Parietaria*, and mites, whereas other studies with mites[84] and grasses[38] have failed to demonstrate a significant difference between active and placebo groups. In the study by Bufe et al,[39] a significant effect was reported only in a subset of patients with more severe disease. One DBPC study demonstrated the clinical efficacy of SLIT in isolated allergic conjunctivitis caused

TABLE II. DBPC trials on the efficacy of SLIT published since the year 2000

Author, year	Reference	Age range (y)	No. of patients*	Allergen	Duration	Dose	Disease
Pajno et al, 2000	85	8-15	12/12	Mite	2 y	360 μg Der p1	A
Guez et al, 2000	84	6-51	24/18	Mite	2 y	90,000 IR 2.2 mg Der p 1	R
Caffarelli et al, 2000	86	4-14	24/20	Grass (monoid)	3 mo	37,000 AU	R/A
Ariano et al, 2001	87	19-50	10/10	Cypress	8 mo	250,000 RU	R/A
Bahcecilier et al, 2001	88	7-15	8/7	Mite	6 mo	7000 IR 0.56 mg Der p1	R/A
Voltolini et al, 2001	89	15-52	24/13	Tree	24 mo	Cumulative 250,000 BU	R
Lima et al, 2002	38	16-48	24/22	Grass	18 mo	0.9 mg Phl p 5 per mo	R
Mortemousque et al, 2003	90	6-60	26/19	Mite	24 mo	Cumulative: 90,000 IR = 2.2 mg Der p 1	C
Andrè et al, 2003	91	6-55	48/51	Ragweed	7 mo	Variable	R
Ippoliti et al, 2003	92	5-12	47/39	Mite	6 mo	Cumulative: 57 μg Der p1	R/A
Pajno et al, 2003	93	8-14	15/15	*Parietaria*	13 mo	23 μg Par j1	R/A/C
Wuthrich et al, 2003	94	6-13	11/11	Grass	2 y	138 μg group 5 allergens per year	R/A
Tonnel et al, 2004	95	7-45	15/17	Mite	2 y	1.28 mg Der p1	R
Bufe et al, 2004	39	6-13	68/74	Grass	3 y	Cumulative: 2,650,000 AU = 9.6 mg Phl p5	R/A
Smith et al, 2004	96	18-60	45 1 y, 46 2 y 46 placebo	Grass	1 y 2 y	6.2 mg Lol p 1, 3.6 mg Dac g 1 per year	R
Rolinck-Werninghaus et al, 2004	97	3-14	39/38	Grass	3 y	Cumulative: 188 μg group 5 allergens	R
Bowen et al, 2004	98	6-52	36/40	Ragweed	4 mo	Cumulative: 10 to 30 mg Amb a 1	R
Dahl et al, 2006	99	18-64	61/32	Grass	6 mo	Cumulative: 2.7 mg Phl p 5	RC
Niu et al, 2006	101	6-12	49/48	Mite	6 mo	Cumulative: 1.7 mg Der p and 3 mg Der f	A
Passalacqua et al, 2006	100	56	28/28	Mite	2 y	Cumulative: 104,000 AU (Allergoid)	R
Durham et al, 2006	102	18-60	815	Grass (3 doses)	5 mo	2,500 SQ 0.06 mg Phl p 5/4 mo; 25,000 SQ 0.6 mg Phl p 5/4 mo; 75,000 SQ 1.8 mg Phl p 5/4 mo	R
Valovirta et al, 2006	103	6-14	88	Mixture of hazelnut, birch, elm (2 doses)	18 mo	Weekly dose of Bet v1, Cor a 1, Aln g 1: Group 1: 3.6 μg Group 2: 30 μg	RC
Dahl et al, 2006	104	23-35	274/272	Grass	7 mo	15 μg Phl p 5/d	RC

BU, Biological units; *IR*, index of reactivity; *SQU*, standardized quality units; *AU*, allergenic units; *RU*, RAST units; *R*, rhinitis; *A*, asthma; *C*, conjunctivitis.
*Active/placebo.

by mite allergy.[90] Compared with inhaled fluticasone propionate, SLIT produced no additional benefit in allergic asthma but improved nonbronchial symptoms.[93] In 2 recent large trials of sublingual immunotherapy for grass pollen–induced seasonal rhinitis, the magnitude of the effect, defined as the reduction in diary symptoms and rescue medication scores compared with placebo, was reported as 16% and 28%[102] and as 30% and 38%,[104] respectively. A 2-year course of SLIT significantly reduced the severity of bronchial hyperresponsiveness in children with *Parietaria*-induced asthma.[105] A double-blind, double-dummy, placebo-controlled study compared SCIT and SLIT in birch pollinosis.[106] Symptoms and drug intake were reduced by about 1/3 in the SLIT group and by 1/2 in the SCIT group, with no significant difference evident between treatments. On the other hand, there were 6 grade 3 and 4 reactions in the SCIT group and none in the SLIT group. A meta-analysis of SLIT for allergic rhinitis that included 22 trials and 979 patients until September 2002 concluded that SLIT had significant efficacy compared with placebo,[107] whereas the studies in allergic asthma were too few to perform a meta-analysis. A meta-analysis in asthma was recently repeated, including 25 trials (either open or blind) and involving more than 1000 adults and children.[108] This meta-analysis demonstrated a significant effect of SLIT for most of the considered outcomes (symptoms + medications, pulmonary function, overall improvement), with the exception of asthma symptoms alone. Another meta-analysis of the treatment of allergic rhinitis with SLIT in pediatric

patients (age 4-18 years), involving 10 trials, showed that SLIT was effective, as assessed by the reduction in symptom scores and rescue medications.[109]

Safety

In all reported DBPC trials, SLIT was well tolerated, the most frequent side effects being local (oral itching or swelling) or gastrointestinal (nausea, vomiting, diarrhea, and ''stomach ache''). These side effects were generally described as either mild and self-limiting or manageable by a temporary dose reduction. On reviewing the DBPC trials, the rate of all adverse events was reported to be 17% to 60% of patients in the SLIT-treated groups and 8% to 14% in the placebo-treated groups. The majority of these events were local, very mild, and self-resolving. Systemic reactions were, respectively, 17% and 12%.[110] According to an extensive review of the literature, 17 serious adverse events (mainly asthma) were reported.[111] Two cases of anaphylaxis were recently reported, 1 with a nonstandardized mixture of 7 allergens[112] and 1 with a rush administration of latex extract.[113] Some postmarketing surveys in children[114-116] and adults[117] are available. On the basis of these large surveys, the overall rate of side effects ranged between 3% and 18% of patients and was invariably less than 1 reaction per 1000 doses. Adverse events were similar in children 5 years or less. No life-threatening or fatal events have been reported in any study.

Additional effects

In an open randomized trial of patients with grass pollen allergy, Novembre et al[118] found that after 3 years of SLIT, 8 of 45 actively treated subjects and 18 of 44 controls developed asthma, with a relative risk for untreated patients of developing asthma of 3.8. In 1 randomized open study,[119] SLIT appeared to prevent the onset of new atopic sensitizations as determined by skin prick testing. In a nonrandomized observational study in 60 children with mite allergy,[120] the clinical effects of SLIT were maintained for as long as 5 years after its discontinuation. More studies on these aspects are required.

Unmet needs

Much evidence is available on the efficacy and safety of SLIT.[121] Important questions about its routine use remain to be answered. SLIT is self-administered by the patient; thus, the degree of compliance represents a concern. There are 2 observational trials of compliance. In 1 trial (126 patients), the compliance was greater than 90% over a 1-year period.[122] In the second (442 patients), the compliance measured at 3 and 6 months was reported to be higher than 75% in 86% of the patients.[123] To date, there are no experimental data on the optimal duration for SLIT. Whether this turns out to be 3 to 5 years for a long-term benefit, as observed for SCIT, remains to be determined. Other aspects of SLIT requiring investigation include the following[111]:

1. The optimal maintenance dose and dosing schedule
2. The mechanism of action of SLIT
3. Criteria for the selection of patients who are likely to obtain most benefit
4. Cost-effectiveness.

CURRENT AND FUTURE DEVELOPMENTS

During the last 10 years, new insights into understanding the basic underlying mechanisms of various forms of allergen immunotherapy have led to the development of novel approaches to improve efficacy and convenience while reducing the risks of side effects. Many of the new and experimental approaches have been developed for SCIT.

Subcutaneous immunotherapy and monoclonal anti-IgE antibodies have complementary modes of action. Additional clinical benefits were demonstrated in patients with grass or birch allergy in both pollen seasons by adding anti-IgE therapy to SCIT.[124] The coseasonal application of omalizumab after preseasonal SCIT decreased ocular and nasal symptom scores and rescue medication use in children with grass pollen allergy.[125] Although this study was underpowered, the combination appeared to be more effective than either treatment alone. This combination might be useful for the treatment of allergic rhinitis, especially for polysensitized patients. Similarly, the combination of anti-IgE with a rush protocol for ragweed SCIT in patients with seasonal allergic rhinitis was effective and reduced the prevalence of systemic reactions by 80%.[126]

The use of liposomes to encapsulate allergens for SCIT has been proposed. There is 1 randomized DBPC study with a liposomal mite vaccine that showed clinical efficacy compared with traditional vaccines as well as a good safety profile.[127] The administration of adjuvants with the allergen is a promising field of research. *In vitro* studies of cultured human PBMCs showed that alum, in contrast with studies in mice, resulted in the downregulation of T_H2 responses,[128] whereas the LPS derivative monophosphoryl lipid (MPL) induced immune deviation in favor of T_H1 responses.[129] A randomized controlled trial of SCIT with a grass pollen extract combined with the adjuvant MPL demonstrated a significant improvement in patients with allergic rhinitis[130] associated with immunologic changes similar to those induced by traditional SCIT.[131] DNA technology has allowed the development of allergens conjugated with oligodeoxynucleotides (immunostimulatory sequences) that are potent T_H1 stimulators.[132,133] The exploratory studies performed on human beings with a DNA-conjugated ragweed allergen[134,135] provided encouraging results, at least from the immunologic point of view. A phase II, DBPC trial with the DNA-conjugated ragweed allergen conducted in 25 adults[136] reported significant clinical benefit that was maintained for 2 pollen seasons.

Allergen fragments (peptides) instead of the whole allergen are being used to modulate favorably the T-cell response to allergen exposure without IgE recognition. Attempts have been made by using short Fel d 1 peptides, but this was associated with delayed side effects.[137] A mixture of overlapping cat allergen peptides[138] resulted

in the suppression of human allergen-induced late skin responses and an enhanced T-regulatory response. Importantly, the preparation was well tolerated, although studies are now required to address clinical efficacy.

The strategy of using recombinant/engineered allergens, possibly modified by site-directed mutagenesis,[139,140] represents an exciting alternative approach that is directed at maintaining the immunogenicity of a vaccine while reducing/avoiding the capacity to bind allergen-specific IgE, thereby reducing the risk of IgE-dependent side effects. Moreover, the use of recombinant allergens will permit an individualized, ''component-resolved'' approach to diagnosis and therapy. One randomized, controlled trial of recombinant birch allergens resulted in reduced skin test responses and in the inhibition of basophil histamine release,[141] whereas a trial of 4 recombinant grass allergens resulted in a decrease in seasonal symptoms and medication requirements compared with placebo treatment.[142]

SIT IN LOW-INCOME COUNTRIES

In the first ARIA document, it was proposed that SIT should be contraindicated in low-income countries because the resources allocated to SIT might be better allocated to a wider use of generic drugs such as inhaled corticosteroids. However, 1 study has suggested that SIT may lead to economic savings in the long term.[143] Moreover, the diagnosis of allergy in most developing countries is difficult because allergens in the environment are ill-defined and there is a lack of trained specialists. As a result, appropriate testing cannot be performed. In other low-income countries, where allergens are well defined, high-quality vaccines are available, and allergy can be diagnosed by trained health professionals, SIT can be performed. On the other hand, SIT is not always reimbursed; thus, only the patients who can afford the costs receive SIT without modifying the allocation of resources. Taking all these considerations into account, no precise rule can be applied in general to all countries. If SIT is used, its cost-effectiveness at the individual level should be evaluated depending on the health care priorities, health system, and resources of each country. In low-income countries, it is recommended that physicians working with SIT should receive regular updating in the field. SLIT may be a safer or more convenient option for immunotherapy in patients with rhinitis who are monosensitive to certain allergens and in areas where allergy specialist facilities for SCIT are not available.

CONCLUSION

Immunotherapy is an effective form of treatment for respiratory allergy. The indications for SIT provided in the ARIA and World Health Organization documents[1,2] remain essentially unchanged. Nonetheless, since the 2001 ARIA document, new studies have enhanced the knowledge about this form of therapy. An updated grading of the strength of the experimental evidence[144] for SCIT and SLIT is provided in Table III. The key messages that can be derived from the updated literature are the following:

TABLE III. Experimental evidence for immunotherapy

	SCIT	SLIT
Clinical efficacy: rhinitis	Ib	Ia
Clinical efficacy: asthma	Ia	Ia
Clinical efficacy: children (rhinitis)	Ib	Ia
Prevention of new sensitizations	Ib	IIa
Long-term effect	Ib	IIa
Prevention of asthma	Ib*	Ib*

Ia, Evidence from meta analysis of randomized controlled trials; *Ib*, evidence from at least 1 randomized controlled trial; *IIa*, evidence from at least 1 controlled trial without randomization; *IIb*, evidence from at least 1 other type of quasi-experimental trial; *III*, evidence from nonexperimental descriptive studies (comparative, correlation, case-control); *IV*, evidence from panels of experts or clinical experience or authorities.
*One single randomized open controlled trial. Strength of evidence according to Sheckelle et al.[144]

- SCIT acts by inducing an immune deviation of T-lymphocyte responses in favor of T_H1 responses to allergens and/or by the downregulation of T_H2 responses, probably via regulatory T cells. IgG antibodies are also involved and have functional significance.
- The clinical efficacy of SCIT in allergic rhinitis and allergic asthma has been confirmed for most of the relevant allergens (grasses, trees, weeds, cat, and mites).
- SCIT is safe provided that recommendations to minimize/manage adverse reactions are followed.
- Several studies have demonstrated the long-term efficacy of SCIT and a preventive effect on the onset of sensitization to additional allergens as assessed by skin testing.
- One randomized controlled open trial demonstrates that SCIT in children with pollen-sensitive rhinitis may reduce the risk of progression from allergic rhinitis to asthma.
- There is strong evidence that SLIT is effective in allergic rhinitis in adults. A recent meta-analysis demonstrated efficacy in allergic rhinitis in children and another in asthma, although more large definitive clinical studies are required.
- Current data indicate that SLIT is safe and that the rate of adverse reactions is not greater in children below 5 years of age.
- One randomized, controlled open trial demonstrates that SLIT in children with allergic rhinitis may reduce the risk of progression from allergic rhinitis to asthma.
- Further SLIT studies are needed to identify the optimal maintenance dose and to elucidate the mechanism of action.
- Novel approaches for various other forms of allergen immunotherapy currently under evaluation include the use of adjuvants, peptides, recombinant/engineered allergens, and DNA-conjugated allergens.

There are some practical aspects of immunotherapy for which the experimental evidence is scarce or absent and therefore still need to be defined. These aspects include the appropriate use of SIT in polysensitized patients, the most adequate interval between doses, the optimal duration of SIT to achieve the best long-term effect, and the pharmacoeconomic aspects. In addition, further rigorous studies directly comparing the efficacy, safety, and costs of SLIT and SCIT are needed.

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