

Monoallergen Sublingual Immunotherapy Versus Multiallergen Subcutaneous Immunotherapy for Allergic Respiratory Diseases: A Debate During the AAAAI 2013 Annual Meeting in San Antonio, Texas

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At the AAAAI 2013 Annual Meeting in San Antonio, Texas, we debated the following issue: “Multiallergen subcutaneous allergen immunotherapy (SCIT) [defended by Linda S. Cox] is better than monoallergen sublingual allergen immunotherapy (SLIT) [defended by Moises A. Calderon].” After a brief introduction to the subject, we respectively consider clinical efficacy, indications, safety, immunology and regulatory and health economic issues for these 2 allergen immunotherapy (AIT) modalities, as embodied by our AAAAI 2013 debate. The present article is an account of a debate and does not constitute a systematic review of the literature. The reader is free to make up his or her mind on the basis of the opposing evidence presented by 2 experienced clinicians in San Antonio.

Ever since the scientific reports of Noon¹ and Freeman² on clinically efficacious allergen immunotherapy (AIT) for grass-pollen–induced allergic rhinoconjunctivitis were published in *The Lancet*, physicians worldwide have administered a variety of AIT formulations to patients with one or more allergic conditions (notably allergic rhinitis [AR] and allergic asthma [AA]) induced by aeroallergens such as pollen and house dust mite (HDM) components.³ Although the efficacy of both SLIT and SCIT has been demonstrated in well-powered, double-blind placebo-controlled (DBPC) clinical trials and meta-analyses of

these data,^{4–7} debate continues as to the most efficacious allergen formulation, administration route, and treatment regimen.⁸

One key issue is how AIT can be best used to treat individuals who are polyallergic.^{9,10} If, for example, a patient is allergic to both grass pollen and HDM, then what type of guidelines-approved AIT should be prescribed? In essence, there are 2 schools of thought, which (for historical reasons) tend to coincide with geographic areas.¹¹ In Europe, the predominant view is that polyallergy does not always constitute a clinical problem and so the most troublesome allergy should be treated with the corresponding monoallergen AIT. In contrast, the predominant view in the United States is that one should treat as many as possible of the patient’s allergies by administering all the relevant allergens (either as a mixture or as separate extracts). However, the monoallergen SLIT versus multiallergen SLIT debate is complicated by the fact that, in the United States, there are no US Food and Drug Administration (FDA) approved SLIT formulations and no billing codes for prescription of this modality.^{12,13} In contrast, the regulatory and reimbursement frameworks in many European countries and other regions of the world enable physicians to prescribe SLIT formulations.

By their very nature, multiallergen SCIT and monoallergen SLIT differ in terms of their treatment frequency, up-dosing schedules, maintenance doses of allergen, and cumulative doses of allergen. But, regardless of the treatment regimen and route, the clinical efficacy of AIT in clinical trials and routine clinical practice is usually measured in the same way, by assessing either subjective disease parameters (such as patient- and/or physician-reported symptom scores or medication scores) or more objective disease parameters (such as functional respiratory measurements; skin prick wheal diameters; and reactions to nasal, conjunctival and/or bronchial allergen challenge tests, generally recommended as secondary efficacy criteria). The currently recommended primary outcome by regulatory authorities in the United States and Europe is a combined symptom-medication score. Although the choice of efficacy criteria for allergic respiratory diseases (whether treated with AIT or with symptomatic medications) is a debate in its own right, it should be possible to broadly compare a multiallergen SCIT study with a monoallergen SLIT study if both are based on similar patient-reported symptom and/or medication scores.

The multiallergen debate is further complicated by the fact that several allergens can be administered either (i) at a single body site after prior mixing of extracts (eg, a single injection of SCIT with a mixture of allergens), (ii) at a single body site and from different vials but at different time points (eg, grass pollen SLIT in the morning and HDM SLIT in the evening), and (iii)

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Abbreviations used

AA- Allergic asthma
AIT- Allergen immunotherapy
AR- Allergic rhinitis
DBPC- Double-blind, placebo-controlled
FDA- US Food and Drug Administration
HDM- House dust mite
IR- Index of reactivity
RCT- Randomized clinical trial
SCIT- Subcutaneous allergen immunotherapy
SLIT- Sublingual allergen immunotherapy
SMD- Standardized mean difference

at different body sites at the same time or at different times (SCIT with different extracts in the left and right arms). The clinical and immunologic characteristics of these multiallergen approaches are likely to differ and should be investigated. A subanalysis of these approaches was not performed in San Antonio and is beyond the scope of the present article. However, given the lack of head-to-head, prospective randomized clinical trials (RCT) that compared multiallergen SCIT with monoallergen SLIT, we also had to turn to some indirect published evidence (ie, mono-SLIT vs mono-SCIT and mono-SLIT vs multi-SLIT).

CLINICAL EVIDENCE OF SHORT-TERM, LONG-TERM, AND SUSTAINED EFFICACY IN ADULTS AND IN CHILDREN

In favor of monoallergen SLIT: Moises A. Calderon

The clinical development of SLIT coincided with the broad adoption of the RCT as the criterion standard for evaluating clinical efficacy. Historically, Scadding and Brostoff,¹⁴ in 1986, reported on what is widely acknowledged to be the first DBPC cross-over RCT of HDM SLIT. Over the following 25 years, a flurry of SLIT trial results were published, which, in 2005, enabled performance of the first meta-analysis of SLIT for AR.¹⁵ This provided Level 1 evidence of efficacy (according to the Centre for Evidence Based Medicine's system [<http://www.cebm.net/?o=1025>]), despite significant interstudy heterogeneity in design and outcomes. Meta-analyses of SLIT trials (mainly single allergen) and position statements from medical organizations and academic institutions around the world have concluded to the efficacy and safety of SLIT.^{6,7,16,17} Furthermore, most of the well-powered DBPC RCTs of AIT performed in the past 10 years have featured monoallergen SLIT (Table 1).¹⁸⁻³⁶ Importantly, studies of tablet formulations of a *Phleum pratense* extract, a 5-grass extract and a ragweed pollen extract have yielded highly concordant results for single-season efficacy in both adults and children. The *P pratense* and 5-grass formulations have also yielded similar results for multiseason efficacy and posttreatment efficacy in adults.

The initial studies of the monoallergen grass SLIT tablets were performed in Europe as multicenter DBPC RCTs. Durham et al¹⁸ tested 3 dose levels (2500, 25,000, or 75,000 standardized quality tablet units) of a *P pratense* extract SLIT tablet. A total of 855 participants (ages 18-65 years old) were included through 55 investigating centers in 8 countries. In patients who completed the recommended preseasonal treatment of at least 8 weeks (followed by coseasonal treatment) of the 75,000 standardized

quality tablet dose (which corresponded to 15 µg of Phl p 5 major allergen), the average daily rhinoconjunctivitis symptom score over the whole pollen seasons was 21% lower in the active AIT group than in the placebo group ($P = .002$), and the rescue medication score was 29% lower ($P = .012$). In the study population as a whole, these symptom score and medication score differences were 16% and 28%, respectively. The active AIT tablet also was associated with a significantly greater number of "well days" ($P = .041$) and higher disease-specific quality of life scores ($P = .006$) versus placebo. The 75,000 standardized quality tablet was selected for use in further studies, including a 5-year extended study (completed by 238 patients) with 3 years of daily treatment and 2 years of follow-up.²⁰⁻²² The symptom scores in the 5 pollen seasons were 25% to 36% lower in the SLIT group than in the placebo group ($P < .004$), and the rescue scores were 20% to 45% lower ($P < .022$ for the 3 treatment seasons and the first post-treatment season; $P = .114$ for the second post-treatment season).²² These results were confirmed in North American adult and pediatric populations.^{25,33,36}

In a single-season, dose-ranging study with a different (5-grass extract) SLIT tablet, Didier et al²³ found that a pre- and coseasonal daily regimen with a 300 index of reactivity (IR) dose (which corresponded to 25 µg of group 5 major allergens) was associated with a significantly lower mean $\pm$ SD average rhinoconjunctivitis total symptom score (3.58 ± 3.0) than in the placebo group (4.93 ± 3.2 ; a 27% difference; $P = .0001$). The results for the lowest dose (100 IR) did not differ significantly with respect to the placebo, and the highest dose (500 IR) gave similar results to the 300 IR dose. The efficacy of the 300 IR formulation was subsequently confirmed in (i) a long-term European study with posttreatment follow-up seasons, and (ii) a single-season study in North American adults.^{24,27}

Importantly, the results for monoallergen SLIT formulations were obtained in study populations that comprised a majority of patients who were polysensitized; *post hoc* analyses found that polysensitization was not a covariate for efficacy in these studies,^{35,36} which suggests that monoallergen SLIT formulations are just as effective with patients who were polysensitized as with patients who were monosensitized. However, participants sensitized to allergens other than grass pollen were only included in these studies if they were unlikely to experience potentially confounding symptoms during the grass pollen season. Unfortunately, at present there are no equivalent data on sensitization status from "big trials" of multiallergen AIT.

In contrast, a recent review concluded that there is a need for additional studies of multiallergen AIT trials (especially SLIT)³⁷ because the majority of reviewed studies had the absence of a placebo group, poorly defined inclusion-exclusion criteria, and/or the lack of separately reported results for patients on mono- and multi-AIT. Although some of these trials showed that multi-allergen SCIT was superior to placebo, a key question was raised: to what extent does each allergen in a mixture actually relieve symptoms of a patient who is polyallergic? Lastly, Dretzke et al⁸ performed a review of the clinical effectiveness of both SCIT and SLIT versus placebo and concluded that "superiority of one mode of administration over the other could not be consistently demonstrated through indirect comparison". More robust data are required on the efficacy of multiallergen SCIT; although clinical efficacy is clearly dose-dependent in grass pollen monoallergen SLIT tablet formulations,^{19,23} we lack dose-ranging studies for multiallergen SLIT and multiallergen SCIT formulations.

TABLE I. Well-powered DBPC RCTs in AIT with symptom and medication scores as efficacy criteria

Study	No. of patients	AIT	Allergen	% Efficacy, active vs placebo difference in symptom score*	% Efficacy, active vs placebo difference in medication score*
With adults					
Durham et al, ¹⁸ 2006	855	SLIT	<i>P pratense</i>	−16	−28
Frew et al, ¹⁹ 2006	410	SCIT	<i>P pratense</i>	−29	−32
Dahl et al, ²⁰ 2006	407	SLIT	<i>P pratense</i>	−31	−39
Didier et al, ²³ 2007	628	SLIT	5 Grasses	−27	−35
Nelson et al, ²⁵ 2011	439	SLIT	<i>P pratense</i>	−18	−26
DuBuske et al, ²⁶ 2011	1028	SCIT	Modified pollen allergens from 13 grasses	−13	13†
Cox et al, ²⁷ 2012	473	SLIT	5 Grasses	−23	−46
Nolte et al, ²⁸ 2012	784	SLIT	<i>Ambrosia</i>	−1	−36
Creticos et al, ²⁹ 2012	565	SLIT	<i>Ambrosia</i>	−17	−45
With children					
Röder et al, ³⁰ 2007	168	SLIT	5 Grasses	+9	+7
Bufe et al, ³¹ 2009	253	SLIT	<i>P pratense</i>	−28	−65
Wahn et al, ³² 2009	266	SLIT	5 Grasses	−28	−24
Blaiss et al, ³³ 2011	340	SLIT	<i>P pratense</i>	−28	−41
De Bot et al, ³⁴ 2012	251	SLIT	<i>Dermatophagoides pteronyssinus</i>	+11	n.r.

n.r., Not reported.

*The mean AIT versus placebo difference in the average daily symptom score or medication score across the whole of the treatment season, defined as (placebo score − active score)/(placebo score). For example, in the study by Frew et al,¹⁹ the mean symptom score during the season was 4.39 in the placebo group and 3.13 in the 100,000 standardized quality units AIT group, which corresponds to a 29% difference.

†Combined symptom and medication score.

In favor of multiallergen SCIT: Linda S. Cox

Multiallergen SCIT (whether with mixed allergens or with the separate administration of several allergen extracts) has long been acknowledged as an effective and potentially disease-modifying therapy for allergic respiratory disease and has been successfully tested in DBPC trials since the mid-1960s.³⁸ A 1968 prospective, controlled, long-term study of children touched on many elements of “modern” AIT³⁹: (i) the link between AR and the subsequent development of asthma; (ii) SCIT’s preventive effect on asthma, and (iii) the putative relationship between the allergen dose and the rate of loss of asthma. More recent DBPCs have emphasized the efficacy of multiallergen SCIT. Hedlin et al⁴⁰ investigated SCIT with several, separately administered allergens in children with polyallergy. The subjects were allergic to a seasonal allergen (birch pollen or timothy pollen) and a perennial allergen (cat or HDM). All the subjects received SCIT for birch or timothy pollen but were randomized to additionally receive either cat-HDM SCIT or a placebo extract. After 3 years of treatment, the researchers found a significantly greater improvement in perennial-allergen–induced bronchial hyper-responsiveness (as assessed by the provocative concentration of allergen causing a 20% fall in the forced expired volume in one second) in patients who received the seasonal and perennial allergens than in patients who received seasonal allergens alone. Alvarez-Cuesta et al⁴¹ compared orchard grass and olive pollen SCIT with placebo in patients with AR and AA and found significantly better symptom, medication, and quality-of-life scores in the SCIT group.

Unbiased, head-to-head comparisons of SCIT versus SLIT are difficult to design but have been performed. Although Khinchi et al⁴² failed to see a lack of a significant difference between SCIT and SLIT in a DBPC double-dummy trial of birch AIT in patients with AR, they admitted that their sample size was small and, therefore, did not necessarily indicate equivalent efficacy.

In a double-blind dummy-controlled trial of an HDM extract in patients with AA, Keles⁴³ found that SCIT and SCIT plus SLIT were both associated with a decrease in asthma attacks and the use of corticosteroids at 4, 12, and 18 months but that SLIT alone was associated with a decrease at 12 months only. In a DBPC double-dummy trial in patients with AR and AA, Yukselen et al⁴⁴ observed significantly lower symptom and medication scores with SCIT and SLIT (vs placebo) but found that SCIT had a greater treatment effect than did SLIT. Lastly, Chelladurai et al⁴⁵ examined 8 “SCIT versus SLIT” trials and concluded, “Our review provides low-grade evidence to support that SCIT is superior to SLIT for reduction in asthma symptoms and moderate-grade evidence for reduction of allergic rhino-conjunctivitis. Additional studies are required to strengthen this evidence base for clinical decision making.”⁴⁵

A meta-analysis—based comparison between SCIT and SLIT by Di Bona et al⁴⁶ (based on the results of 36 DBPC RCTs) showed that the overall effect size (expressed as the standardized mean difference [SMD] [95% CI]) for the symptom score was significantly higher for SCIT (SMD, −0.92 [95% CI, −1.26 to −0.58]) than for SLIT drops (SMD, −0.25 [95% CI, −0.45 to −0.05]) and SLIT tablets (SMD, −0.40 [95% CI, −0.54 to −0.27]). Similar findings were reported for the medication score. Di Bona et al⁴⁶ concluded that their results provided “indirect but solid evidence that SCIT is more effective than SLIT” in controlling symptoms and medication use in seasonal AR. On the basis of symptom score data, Di Bona et al⁴⁶ also analyzed SLIT versus SCIT differences with respect to the number of pollens included in the pharmaceutical preparations. Use of more than one pollen allergen was associated with a lower effect size for symptom scores for both SLIT and SCIT (single-allergen SCIT; median SMD, −0.52; multiallergen SCIT; median SMD, −0.85; single-allergen SLIT; median SMD, −0.22; multiallergen SLIT; median SMD, −0.43).⁴⁶ In other meta-analyses of AIT in AR, the SMDs

for symptom scores and medication scores are higher for SCIT than for SLIT.^{4,6}

For SLIT, few trials have addressed the monoallergen vs multiallergen question. Amar et al⁴⁷ compared monoallergen SLIT (timothy pollen) with multiallergen SLIT (timothy pollen plus 9 additional pollen extracts) in a DBPC RCT with patients with a history of seasonal grass pollen AR and did not find a significant difference in symptom or medication scores between the 2 groups or relative to placebo. Amar et al⁴⁷ suggested that this lack of difference was due to record low grass pollen counts (and thus low disease levels) in the Denver area during the study season. However, most of the objective study criteria (titrated nasal challenge, titrated skin prick tests, serum timothy-specific IgG4 levels and IFN- γ levels differed significantly when comparing the timothy-only group with placebo. The only improved objective criterion in the timothy plus multiallergen group (vs placebo) was skin test reactivity, albeit to a lesser extent than in the timothy-only group.⁴⁷

Most recently, a DBPC phase I study of timothy pollen SLIT and HDM SLIT (in separate vials; ie, administered sequentially) showed that, after 12 months, the 2-allergen SLIT group had significantly higher allergen-specific IgG4 levels and lower symptom and medication scores, skin prick test scores, basophil activation, and allergen-specific IgE levels than in the placebo group.⁴⁸ Although there was no single-allergen SLIT group, these results suggest that, as with multiallergen SCIT, multiallergen SLIT is effective in patients who are polysensitized.

CLINICAL CRITERIA FOR SELECTING THE AIT MODALITY

In favor of monoallergen SLIT: Moises A. Calderon

The monoallergen AIT approach is based on the choice of the most clinically relevant allergen for a given patient who is polysensitized and/or polyallergic (ie, administration of the allergen that causes the longest-lasting and/or most-severe symptoms, which have the greatest impact on quality of life and/or which are more difficult to avoid).⁴⁹ As mentioned above, the data from well-powered trials of grass-pollen tablets show that polysensitization is not a covariate for the efficacy of monoallergen SLIT in AR in this context. For safety and comfort reasons, SLIT is often preferred to SCIT in the treatment of young children with AR.^{50,51} Young children may not be able to recognize the signs of a systemic, allergen-driven serious adverse event (or at least not as rapidly as an adult might).

In favor of multiallergen SCIT: Linda S. Cox

The indication for AIT is clinically confirmed allergy, and multiallergen AIT is indicated in cases of clinically confirmed polyallergy. Although polysensitization is not a direct proxy for polyallergy, physicians will use this parameter as a guide when screening for polyallergy. By definition, patients have to be polysensitized to be polyallergic, whereas they are not necessarily polyallergic if they are polysensitized. Polysensitization is a global phenomenon observed in all clinical settings. The US National Health and Nutrition Examination Survey of the general population from 1988 through 1994 found that 38.8% of 10,508 subjects tested against 10 allergens were polysensitized.⁵² The European Community Respiratory Health Survey yielded similar findings.⁵³ Many (or even most) patients in AIT studies are polysensitized.^{35,36} Polysensitization develops over time in patients with AR and/or AA.^{54,55} In the particular indication of

pollen-induced AR and/or AA in children and adolescents, multiallergen SCIT shows evidence of efficacy.^{39,56}

SAFETY

In favor of monoallergen SLIT: Moises A. Calderon

Sublingual AIT has a better safety profile in terms of systemic adverse reactions than does SCIT.^{57,58} This necessarily means that monoallergen SLIT is preferable to multiallergen SCIT. With monoallergen SLIT, adverse reactions are generally mild, local, and transient.¹⁶ In a recent review, it was calculated that, worldwide, approximately 1 billion doses of SLIT had been administered between 2000 and 2010; during that time, only 11 cases of anaphylaxis (all nonfatal) were reported in the scientific literature.⁵⁹ Furthermore, all these 11 cases corresponded to nonstandard practice (over-rapid up-dosing, SLIT in a patient having already reacted badly to SCIT, etc). Critically, the interpretation of adverse reactions in multiallergen AIT (whether SCIT or SLIT) is challenging. Lessons can be learned from the field of microbial vaccines. The AAAAI and American College of Allergy, Asthma & Immunology (ACAAI) Task Force Report on adverse reactions to vaccines states that "all suspected anaphylactic reactions to vaccines should ideally be evaluated in an attempt to determine the culprit allergen".⁶⁰ When AIT preparations contain an average of 8 distinct extracts,¹¹ how can the physician tell which allergen is causally linked to an adverse reaction? If the problem allergen cannot be determined, then how can use of the multiallergen AIT be safely reinitiated?

In favor of multiallergen SCIT: Linda S. Cox

When administered in an appropriate setting, modern SCIT formulations are safe and well tolerated.⁶¹ We should focus on safety data from the past decades rather than the 1960s. Epstein et al⁶² surveyed AAAAI and/or ACAAI members in 2008 to 2011 and reported that there were no fatalities attributable to SCIT in approximately 18.9 million injections. Ninety-six percent of systemic adverse events were grade 1 or 2, and the overall systemic reaction rate was 0.1% of injections.

IMMUNOLOGIC ASPECTS

In favor of monoallergen SLIT: Moises A. Calderon

By means of an introduction to this subtopic, it must be borne in mind that type I allergies are complex conditions that are characterized by inappropriate T-helper-2–type cell responses and allergen-specific IgE secretion. The reduction in sensitivity induced by AIT involves relatively characteristic changes in immune cell populations and Ig levels and the long-term appearance of antigen-specific T-helper 1 responses.^{17,63–65} Within hours of the administration of allergen, the intensity of mast cell and basophil degranulation decreases. After several months of AIT, the tissue density of mast cells and eosinophils starts to fall steadily. In terms of immunoglobulins, serum specific IgE levels first rise after the initiation of AIT (perhaps as a marker of allergen exposure) and then progressively fall after several months or years. In parallel, levels of inhibitory allergen-specific IgG (particularly IgG1 and IgG4) increase over time. Nevertheless, these effects have not been observed in all AIT studies and a specific universal proxy biomarker of clinical efficacy has not yet been identified.

In the large trials of timothy pollen SLIT tablets in patients with AR, significant AIT versus placebo differences in specific

IgE and IgG4 levels have been observed. In a 5-year study in Europe, IgG4 and blocking IgE levels rose concomitantly and progressively in the active AIT group but not in the placebo group during the 3 years of treatment.²¹ The intergroup difference was smaller but nevertheless marked in the first year after treatment. Similarly, a single-season study by Blaiss et al³³ of the same SLIT tablet in North American children and adolescents found that peak-season Phl p 5-specific IgG4 levels were significantly greater in the active AIT group than in the placebo group. Lastly, Nelson et al²⁵ observed very similar changes after a year of treatment with the timothy SLIT tablet in North American adults; the mean log₁₀ end-of-season IgG4 level at the end of the season was -0.29 in the active AIT group and -0.72 in the placebo group ($P < .001$), and the corresponding values for IgE-blocking factor were -0.11 and -0.05 ($P < .001$).

These active versus placebo differences in levels of key immune effectors indicate that single-allergen SLIT is immunologically effective in grass-pollen-induced AR and thus support the observed clinical benefits. Although levels of immunologic markers are rarely studied in multiallergen trials, they provide indirect evidence to suggest that several concomitantly delivered allergens can interfere with each other. In a placebo-controlled SLIT study, Amar et al⁴⁷ compared a timothy-only pollen extract with a multiallergen formulation that contained the same dose of timothy extract. Firstly, significant levels of serum timothy-specific IgG4 were only observed in the timothy-only SLIT group. Despite the absence of clinical differences between the study groups (possibly due to very low grass pollen counts in the 2008 season in Denver, Colo), participants in the timothy-only SLIT group became less sensitive to a nasal challenge with timothy allergen than did participants in the multiallergen SLIT group.

In favor of multiallergen SCIT: Linda S. Cox

A single allergen is composed of multiple allergenic proteins capable of inducing an immune response. Each of these allergenic proteins has several T-cell epitopes.⁶⁶ Many different T-cell clones may be involved in the immune response to AIT. The immune system does not limit itself to responding to epitopes from a single allergenic protein. As mentioned above, a DBPC phase I study by Swamy et al⁴⁸ showed that 12 months of treatment with timothy pollen and HDM SLIT in separate vials had clinical efficacy. Concomitantly, the rise in allergen-specific IgG4 levels, the decline in allergen-specific IgE levels, and the presence of epigenetic changes in memory regulatory T cells were consistent with disease modification.

REGULATORY AND HEALTH ECONOMICS ISSUES

In favor of monoallergen SLIT: Moises A. Calderon

Multiallergen AIT involves the preparation of a mixture of allergens extracts some time before administration or immediately before administration. The European Medicines Agency "Guideline on Allergen Products: Production and Quality Issues"⁶⁷ refers to "homologous groups" of allergens, defined as a those having a similar biochemical composition and homology and/or cross-reactivity. The European Medicines Agency guideline states that, "If the finished product consists of a mixture of allergen extracts not belonging to the same homologous group, stability studies have to be performed for the mixture considering each individual active substance."⁶⁷ This requirement constitutes an obstacle to the use of preprepared multiallergen formulations.

According to the European Medicines Agency guidelines, (i) allergens with proteolytic activities should not be used in mixtures, (ii) perennial and seasonal allergens should not be mixed, (iii) Hymenoptera venoms should not be mixed with any other allergens, and (iv) venoms from different genera should not be mixed together. It is not possible to extrapolate from one pollen allergen (eg, grass) to another pollen allergen (eg, ragweed) if they are from different homologous groups. Mixing multiple allergens in a single vaccine dilutes the final allergen content, which, in many cases, will be subtherapeutic.

In a similar vein, the US practice parameter states that "Once the relevant allergens in a polysensitized patient are identified, a mixture can be formulated but one has to consider allergen cross-reactivity, dose optimization and potential enzymatic degradation."⁶⁰ According to Cox and Jacobsen,¹¹ "allergen extracts or formulations must prove efficacy and safety in appropriately controlled studies before being approved by the FDA." The FDA considers each allergen as a separate development that requires dose-ranging and phase III efficacy and safety studies. Hence, each allergen (grass, ragweed, HDM, etc) requires its own development program. Even though single formulations are controlled, the practice of blending several formulations before administration without the rigor of pharmaceutical control (required for all other drug products!) is surprising.

A very recent systematic review and economic evaluation for the United Kingdom National Health Service found that, when compared with symptomatic treatment, both SCIT and SLIT may become cost effective at a threshold of £20,000-30,000 per quality-adjusted life year from approximately 6 years of use.⁶⁸ In a study of a timothy grass pollen SLIT tablet, Nasser et al⁶⁹ found that patients treated with AIT gained the equivalent of 72 days of perfect health over 9 years. Levels of resource use and productivity loss were lower in the SLIT tablet than in the placebo group. The corresponding cost per quality-adjusted life year gained with the SLIT tablet was £4319, which prompted the researchers to describe this single-allergen AIT formulation as highly cost effective (at least from a societal perspective).⁶⁹

In favor of multiallergen SCIT: Linda S. Cox

The FDA regulates allergen extracts and not the final formulation administered to the patient. In 1972, jurisdiction for nonstandardized allergen extracts was transferred to the FDA's Bureau of Biologics and is now with the Center for Biologics Evaluation and Research. The FDA convened 2 external review panels (in 1974 and 1983) to review safety and efficacy.⁷⁰ Subsequently, 19 standardized extracts were available: venom ($n = 5$), grass ($n = 8$), short ragweed, cat, and HDM.⁷⁰ Before release, standardized extracts are compared with US reference standards (maintained and distributed to manufacturers by the Center for Biologics Evaluation and Research). In 2003, the FDA began reviewing the safety and efficacy of 1269 non-standardized products, of which only 17 had potential safety concerns. Major incompatibilities between allergen extracts are well known, and guidelines have been published that recommend preparing them in separate vials.^{71,72} Preparation in the allergist's office before administration allows more flexibility if there is a need to reduce the dose of any of the components or reduce the number of components in a mixture.¹¹

Most cost-efficacy studies of AIT conclude that mono- and multiallergen SCIT has significant economic advantages over pharmacotherapy alone.⁷³ In a study by Ariano et al,⁷⁴ the net

saving per patient was \$830 per year. Only Petersen et al⁷⁵ reported a poor economic outcome for AIT. Other positive outcomes include the report by Hankin et al,⁷⁶ in which 6 months before AITs were compared with 6 months after AIT discontinuation in the same children; the median 6-month weighted cost savings associated with AIT was \$401. Hankin⁷⁷ also compared 18 months of AIT with 18 months of pharmacotherapy in a matched cohort study. The mean annual benefit for SCIT in children was \$1218 (33%). These cost savings were seen even when the duration of SCIT was not optimal. In a very recent report, a population of adult and pediatric patients with newly diagnosed AR and treated *de novo* with SCIT had significantly lower 18-month health care costs than versus matched control subjects who did not receive SCIT (\$6637 vs \$10,644, respectively, which gave a 38% difference; $P < .0001$).⁷⁸

CONCLUSIONS

Conclusion in favor of monoallergen SLIT: Moises A. Calderon

There is good evidence of efficacy for monoallergen SCIT and very good evidence for monoallergen SLIT. In contrast, there is no evidence for multiallergen SCIT and/or SLIT. Hence, the clinical evidence for monoallergen SLIT outweighs the clinical experience with multiallergen SCIT.

Conclusion in favor of multiallergen SCIT: Linda S. Cox

In the absence of satisfactory head-to-head clinical studies, there is indirect evidence that multiallergen SCIT is effective in both reducing clinical symptom scores and decreasing the costs associated with use of health care resources and medication use (according to large retrospective health economic evaluations). Multiallergen SCIT is safe and well tolerated if administered in an appropriate setting. Patient commitment is a key factor in treatment compliance and thus efficacy. In patients with polyallergy, restriction to several successive or overlapping courses of monoallergen AIT is likely to weaken commitment. Hence, multiallergen SCIT is preferable to monoallergen SLIT.

DISCUSSION: IS IT POSSIBLE TO REACH A CONSENSUS ON THIS TOPIC?

Despite our opposing views in San Antonio, we both agree that debating and investigating this topic will ultimately benefit patients who are eligible for AIT. Additional reviews of SLIT have appeared since the San Antonio meeting and so the debate on efficacy continues.^{79,80} We have the following observations and recommendations.

- We need well-powered DBPC RCTs trials of multiallergen AIT (whether SCIT or SLIT) in patients with polyallergy who have AR. To somewhat simplify interpretation, it makes sense to limit the number of mixed extracts to 2 or 3 (eg, grass pollen plus HDM). This process now appears to be underway.⁸¹
- We need head-to-head clinical and health economics comparisons of multiallergen AIT and single-allergen AIT (whether SCIT or SLIT). Trial design will be challenging. Blinding may be particularly problematic; it will be hard to prevent the patient and (above all) the investigator from knowing whether a monoallergen and multiallergen has been prepared and/or administered. For consistency (and regardless of whether multiallergen SLIT or multiallergen SCIT is being

investigated, the mixing method (one vial or separate vials) must be specified. Health economics issues also will influence the single-allergen versus multiallergen debate. Single-allergen formulations are most likely to be SLIT tablets, whereas multiallergen formulations are most likely to be SCIT injections; differences in cost to the patient and/or the payer will inevitably be taken into account when comparing therapeutic modalities.

- We need a simple surrogate marker of the clinical efficacy of AIT. The primary efficacy criteria currently requested by regulatory authorities in Europe and the United States (total symptom scores or combined symptom-medication scores) may not be suitable in trials of multiallergen AIT versus single-allergen AIT in patients with polyallergy.
- When studying patients with polyallergy in clinical trials, clinical efficacy should be evaluated over 12, 24, or even 36 months to encompass seasonal and/or environmental fluctuations in exposure to all potential disease-inducing allergens. “Confounding” allergens are often excluded from clinical studies but must be taken into account as part of the patient’s treatment needs.
- Take care when defining a “single allergen.” Physicians will generally consider that “grass pollen” or “HDM extract” is a single allergen. However, biochemists will say that a single allergen is a single protein with a unique amino acid sequence and 3-dimensional structure (ie, the Phl p 1 and Phl p 5 major allergens and Phl p 7 and Phl p 12 minor allergens from *P pratense* pollen). To take this argument one step further, each major or minor allergen usually is present *in vivo* as a set of isoforms with minor structural (genetic or posttranslational) differences. “Single-allergen” pollen or HDM formulations (such as the grass pollen SLIT tablets tested in the recent “big trials” [Table I]) contain dozens or even hundreds of different proteins, each of which may be the disease-inducing allergen in at least a non-negligible proportion of patients. Nevertheless, some physicians will consider that a 5-grass pollen extract is a multiallergen formulation, whereas others will consider it to be a single-allergen (“grass”) formulation. In fact, only formulations that contain a recombinant peptide would truly correspond to single-allergen AIT.
- Consider potential immunologic and clinical differences between “multiallergen” modalities. It remains to be firmly established whether there are significant differences in clinical efficacy and immune responses between (i) concomitant, successive treatments with several liquid SLIT formulations in different vials (eg, daily grass pollen SLIT drops in the morning and daily HDM drops in the evening), and (ii) premixed SLIT drop formulations (eg, daily grass pollen and HDM SLIT).

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REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;I:1572-3.
2. Freeman J. Further observation on the treatment of hay-fever by hypodermic inoculation of pollen vaccine. *Lancet* 1911;II:814-7.
3. Finegold I, Dockhorn RJ, Ein D, Dolen WK, Oppenheimer J, Potter LH. Immunotherapy throughout the decades: from noon to now. *Ann Allergy Asthma Immunol* 2010;105:328-36.
4. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007;(1):CD001936.

5. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;(8):CD001186.
6. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010;(12):CD002893.
7. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol* 2010;127:30-8.
8. Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol* 2013;131:1361-6.
9. Calderón MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol* 2012;129:929-34.
10. Bahceciler NN, Galip N, Cobanoglu N. Multiallergen-specific immunotherapy in polysensitized patients: where are we? *Immunotherapy* 2013;5:183-90.
11. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009;103:451-9.
12. Tucker MH, Tankersley MS, ACAAI Immunotherapy and Diagnostics Committee. Perception and practice of sublingual immunotherapy among practicing allergists. *Ann Allergy Asthma Immunol* 2008;101:419-25.
13. Sikora JM, Tankersley MS, ACAAI Immunotherapy and Diagnostics Committee. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. *Ann Allergy Asthma Immunol* 2013;110:194-7.
14. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986;16:483-91.
15. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4-12.
16. Canonica GW, Bousquet J, Casale T, Lockett RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;64(Suppl 91):1-59.
17. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013;131:1288-96.
18. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
19. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25.
20. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
21. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125:131-8.
22. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-25.
23. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
24. Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300 IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy* 2013;43:568-77.
25. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80.
26. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc* 2011;32:239-47.
27. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambrosio L, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol* 2012;130:1327-34.
28. Nolte H, Maloney J, Bernstein D, Berkowitz R, Nekam K, Kaur A, et al. Efficacy and tolerability of a novel ragweed allergen immunotherapy tablet during peak season in North American and European patients. *J Allergy Clin Immunol* 2012;129:AB142.
29. Creticos P, Maloney J, Nolte H, Berman G, Cheema A, Kaur A, et al. Efficacy and safety of a novel ragweed allergy immunotherapy tablet (AIT) during peak season in North America. *J Allergy Clin Immunol* 2012;129:AB143.
30. Röder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007;119:892-8.
31. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-173.e7.
32. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-166.e3.
33. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
34. de Bot CM, Moed H, Berger MY, Röder E, Hop WC, de Groot H, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol* 2012;23:150-8.
35. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy* 2009;39:387-93.
36. Nelson H, Blaiss M, Nolte H, Würtz SO, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy* 2013;68:252-5.
37. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol* 2009;123:763-9.
38. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. *N Engl J Med* 1965;273:675-9.
39. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. *Pediatrics* 1968;42:793-802.
40. Hedlin G, Wille S, Browaldh L, Hildebrand H, Holmgren D, Lindfors A, et al. Immunotherapy in children with allergic asthma: effect on bronchial hyperactivity and pharmacotherapy. *J Allergy Clin Immunol* 1999;103:609-14.
41. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy* 2005;35:572-8.
42. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59:45-53.
43. Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *J Allergy Clin Immunol* 2011;128:808-15.
44. Yuskelen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol* 2012;157:288-98.
45. Chelladurai Y, Suarez-Cuervo C, Ereosima N, Kim J, Ramanathan M, Segal J, et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Allergy Clin Immunol Pract* 2013;1:361-9.
46. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol* 2012;130:1097-107.
47. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol* 2009;124:150-6.
48. Swamy RS, Reshamwala N, Hunter T, Vissamsetti S, Santos CB, Baroody FM, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol* 2012;130:215-24.
49. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Canonica W, Merk H, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65:1525-30.
50. Marseglia GL, Incorvaia C, La Rosa M, Frati F, Marcucci F. Sublingual immunotherapy in children: facts and needs. *Ital J Pediatr* 2009;35:31.

51. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012. *Ann Allergy Asthma Immunol* 2013;110:402-15.
52. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377-83.
53. Bousquet PJ, Castelli C, Daures JP, Heinrich J, Hooper R, Sunyer J, et al. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). *Ann Epidemiol* 2010;20:797-803.
54. Silvestri M, Rossi GA, Cozzani S, Pulvirenti G, Fasce L. Age-dependent tendency to become sensitized to other classes of aeroallergens in atopic asthmatic children. *Ann Allergy Asthma Immunol* 1999;83:335-40.
55. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol* 2007;17:85-91.
56. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT-study. *Allergy* 2007;62:943-8.
57. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35.
58. Passalacqua G, Canonica GW. Sublingual immunotherapy for allergic respiratory diseases: efficacy and safety. *Immunol Allergy Clin North Am* 2011;31:265-77.
59. Calderón MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy* 2012;67:302-11.
60. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol* 2012;130:25-43.
61. Cox L, Calderón M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. *Immunotherapy* 2012;4:601-16.
62. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110:274-8.
63. Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. *Clin Exp Allergy* 2011;41:1235-46.
64. James LK, Bowen H, Calvert RA, Dodev TS, Shamji MH, Beavil AJ, et al. Allergen specificity of IgG(4)-expressing B cells in patients with grass pollen allergy undergoing immunotherapy. *J Allergy Clin Immunol* 2012;130:663-70.
65. Moingeon P, Mascarell L. Induction of tolerance via the sublingual route: mechanisms and applications. *Clin Dev Immunol* 2012;2012:623474.
66. Tripodi S, Frediani T, Lucarelli S, Macrì F, Pingitore G, Di Rienzo Businco A, et al. Molecular profiles of IgE to *Phleum pratense* in children with grass pollen allergy: implications for specific immunotherapy. *J Allergy Clin Immunol* 2012;129:834-9.
67. European Medicines Agency. Guideline on allergen products: production and quality issues. London 2008 EMEA/CHMP/BWP/304831/2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf. Accessed October 15, 2013.
68. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess* 2013;17:vi, xi-xiv, 1-322.
69. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008;63:1624-9.
70. Slater JE, Menzies SL, Bridgewater J, Mosquera A, Zinderman CE, Ou AC, et al. The US Food and Drug Administration review of the safety and effectiveness of nonstandardized allergen extracts. *J Allergy Clin Immunol* 2012;129:1014-9.
71. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(Suppl):S1-55.
72. Grier TJ, LeFevre DM, Duncan EA, Esch RE, Coyne TC. Allergen stabilities and compatibilities in mixtures of high-protease fungal and insect extracts. *Ann Allergy Asthma Immunol* 2012;108:439-47.
73. Lockey RF, Hankin CS. Health economics of allergen-specific immunotherapy in the United States. *J Allergy Clin Immunol* 2011;127:39-43.
74. Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006;27:159-63.
75. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)* 2005;33:296-302.
76. Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 2008;121:227-32.
77. Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol* 2010;104:79-85.
78. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2013;131:1084-91.
79. Lin SY, Ereksima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278-88.
80. Kim JM, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013;131:1155-67.
81. Pfaar O, Biedermann T, Klimek L, Sager A, Robinson DS. Depigmented-polymerized mixed grass/birch pollen extract immunotherapy is effective in polysensitized patients. *Allergy* 2013;68:1306-13.

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