

Allergen immunotherapy and asthma: Efficacy, safety, and other considerations

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ABSTRACT

The efficacy of allergen immunotherapy (AIT) for allergic asthma is often debated despite multiple controlled trials and three meta-analyses that have established a significant effect on subjective and objective outcomes. Indications for AIT in allergic asthma include suboptimal control with medications, adverse effect of medications, and/or environmental control measures; patient's desire to avoid long-term pharmacotherapy; and presence of comorbid allergic conditions. Symptomatic asthma is a risk factor for AIT systemic reactions (SRs) and asthma should be controlled at the time of the AIT administration. The vast majority of studies in AIT for asthma have used single allergens although the majority of allergic patients in the United States are not monosensitized. There have been conflicting results in the limited number of studies that have investigated the effect of multiallergen AIT or as add-on therapy to asthmatic patients who are optimally controlled with medications and environmental controls. Several studies have suggested that AIT may prevent the development of asthma in subjects with allergic rhinitis and new allergen sensitizations. The recently updated Allergen Immunotherapy Practice Parameters lists possible prevention of asthma in patients with allergic rhinitis as one of the indications for AIT. Currently, subcutaneous immunotherapy is the only route with Federal Drug Administration approved formulations in the United States but sublingual immunotherapy is currently under investigation. This review examines the efficacy, safety, and preventive effects of these two routes of immunotherapy.

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Key words: Allergen immunotherapy, allergic rhinitis, asthma, monosensitized, multiallergen, subcutaneous immunotherapy, sublingual immunotherapy

Allergen immunotherapy (AIT) is currently indicated for the treatment of allergic rhinitis, asthma, and Hymenoptera sting hypersensitivity. Multiple controlled studies have shown the efficacy of AIT in terms of reducing symptoms, medication use, and improved quality of life in both allergic rhinitis and asthma and preventing insect sting anaphylaxis in patients with Hymenoptera hypersensitivity. There has been little debate about the effectiveness of AIT in allergic rhinitis or Hymenoptera hypersensitivity but there continues to be some debate regarding the effectiveness of AIT in the treatment of allergic asthma, which is somewhat paradoxical considering allergens can play a significant role in the pathogenesis of both allergic asthma and rhinitis. This controversy is noted in the introductory statement from the Cochrane meta-analyses of AIT in asthma: "Allergen specific immunotherapy has long been a controversial treatment for asthma. Although beneficial effects upon clinically relevant outcomes have been demonstrated in randomized controlled tri-

als, there remains a risk of severe and sometimes fatal anaphylaxis. The recommendations of professional bodies have ranged from cautious acceptance to outright dismissal."¹

A review article that analyzed unfavorable studies on AIT for asthma from two meta-analyses concluded that, "It is difficult to compare results from the various studies of AIT because of the large number of variations in the clinical trial protocols. Given the heterogeneity of IT clinical trials as a group, it is not surprising that variable results occur. The use of multiple studies in a meta-analysis with its underlying assumption of homogeneity is problematic."²

There is considerable heterogeneity in AIT studies for allergic asthma and rhinitis and most studies had relatively small patient populations. One potential problem with small studies is that they may not be sufficiently powered to establish a positive effect when one is present, which is referred to as a type II error. A meta-analysis can combine the results of individual studies and increase the power of the analysis providing the interventions and outcomes in the various studies are sufficiently similar. However, because of the significant heterogeneity of AIT studies, it may be difficult to directly compare studies unless the results of each study are standardized by calculating the standardized mean difference

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Standardised Mean Difference (SMD)

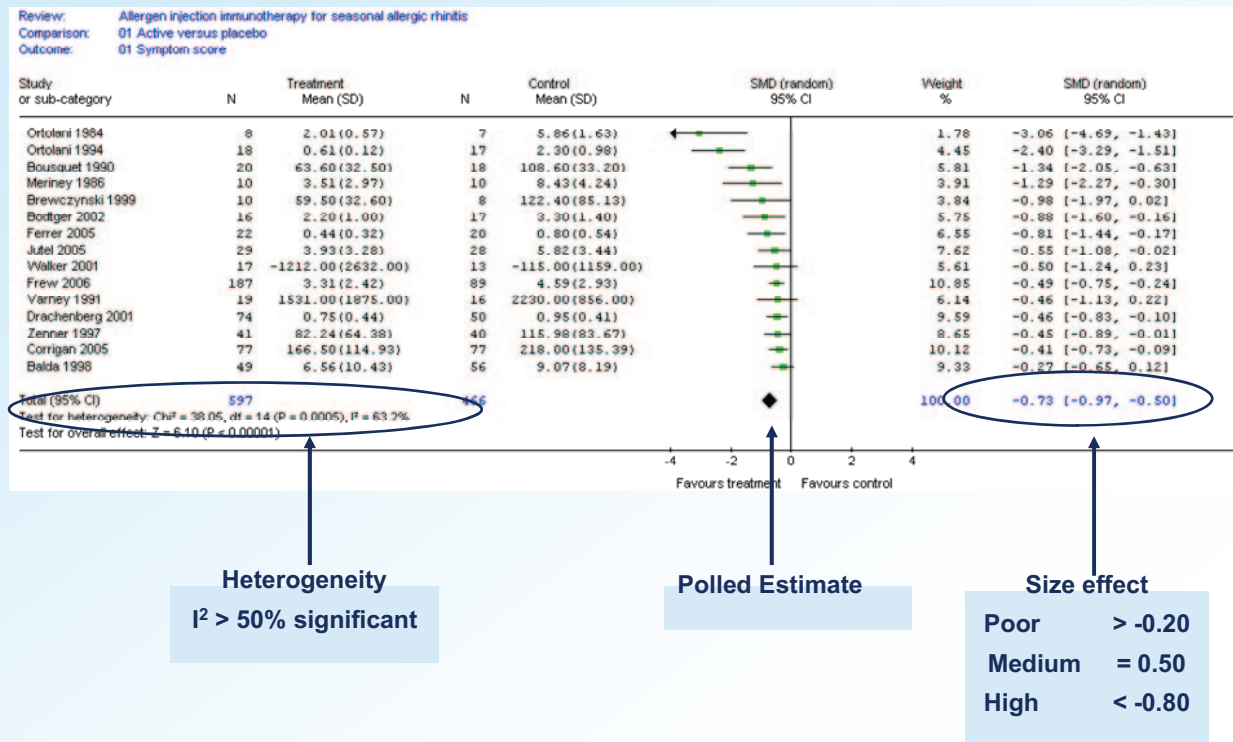


Figure 1. Forest plots show the information from the individual studies used in meta-analysis.

(SMD). The SMD is the difference of the means of both treatment arms divided by the pooled SD. In this way, the treatment effect in each study is expressed in standard units (instead of the original units) and the results of all studies can be combined by calculating a weighted SMD. The results of the individual studies in the meta-analysis can be shown in a forest plot (Fig. 1) as squares centered on the point estimate of the result of each study. The diamond point at the bottom represents the pooled effect with its horizontal tips representing the confidence interval (CI). Significance is achieved if the diamond is clear of the line of no effect.

Three published meta-analyses of AIT for asthma concluded that there was a significant improvement in asthma symptoms and medication use in the AIT patients compared with patients in the matched control groups.^{1,3} The first meta-analysis reviewed all of the 20 prospective, randomized, placebo-controlled (PC) trials of immunotherapy for asthma that were published between 1954 and 1990 and expressed categorical outcomes as odds ratios (ORs) and continuous outcomes as effect sizes.³ Statistically significant improvement

was seen in symptoms, medication use, and bronchial hyperreactivity (BHR; Table 1) as well as a mean improvement in forced expiratory volume in 1 second (FEV₁) of 0.71 L (95% CI 0.43–1.00) corresponding to an average FEV₁ increase of 7.1%. The authors noted that the benefits of AIT in asthma could be overestimated because of unpublished negative studies but concluded that it would take 33 negative studies to overturn these positive results.

These authors subsequently performed a Cochrane database systematic review on AIT for asthma. The most recent update published in 2003 analyzed 75 trials involving 3188 asthma patients, which included 52 of the 54 studies from the previous Cochrane review and 23 new trials.¹ The allergens used in the trials reviewed were 33 dust-mite allergens, 3 house-dust allergens, 20 pollen allergens, 10 animal dander allergens, 2 *Cladosporium* allergens, 1 latex allergen, and 6 multiple allergen trials. A significant reduction in asthma symptom scores (SMD, -0.72; 95% CI, -0.99 to -0.33), medication use, and BHR was found in this review. The authors determined that the concealment of allocation was clearly adequate in only 15 of these

Table 1 Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy in 20 randomized placebo-controlled trials¹

	Dust Mite	Other Allergens	All Allergens
Symptomatic improvement	OR, 2.7 (95% CI, 1.7–4.4)	OR, 4.8 (95% CI, 2.3–10.1)	OR, 3.2 (95% CI, 2.2–4.9)
Reduction in medication	OR, 4.2 (95% CI, 2.2–7.9)	ND	ND
Reduction in bronchial hyperresponsiveness	OR, 13.7 (95% CI, 3.8–50)	OR, 5.5 (95% CI, 2.8–10.7)	OR, 6.8 (95% CI, 3.8–120)

CI = confidence interval; ND = not done; OR = odds ratio.

trials and that there was significant heterogeneity among the studies.

Efficacy can be expressed as “numbers needed to treat” (NNT), which is the number of people who need to be treated to benefit one additional person over placebo and can be calculated by the following formula:

$$\text{NNT} = \frac{1}{(\% \text{responders}_{\text{active}} - \% \text{responders}_{\text{placebo}})}.$$

The ideal NNT is 1, where everyone improves with treatment and there is no improvement in any of the control group. Generally, the higher the NNT, the less effective is the treatment. However, prophylactic interventions that produce small effects in large numbers of patients will have high NNTs, perhaps 20–100 (*e.g.*, aspirin after a myocardial infarction). NNTs of 2–5 are indicative of effective therapies, such as analgesics for acute pain (*e.g.*, for ibuprofen the NNT is 2.7 patients for 1 patient to experience adequate pain relief). To provide some perspective in patients with allergic rhinitis, the NNT for the antihistamine class in the treatment of rhinitis is 15.2 (mean) and nasal corticosteroid class is 4.4 (mean).⁴

The authors of the “Cochrane Systematic Review” concluded that it would be necessary to treat the following¹

- Four patients (95% CI, 3–5) with AIT to avoid one deterioration in asthma symptoms.
- Five patients (95% CI, 4–6) with AIT to avoid one requiring increased medication.

They also noted in their conclusions that “one trial found that the size of the benefit (of AIT) possibly comparable to inhaled steroids.”

A third meta-analysis of 24 prospective, randomized, double-blind, PC studies involving 962 asthmatic patients found that there were significant improvements in asthma symptoms (OR, 2.76; 95% CI, 2.22–3.42), pulmonary function (OR, 2.87; 95% CI, 1.82–4.52), protection against bronchial challenge (OR, 1.81; 95% CI, 1.32–2.49), and medications use (OR, 2.00; 95% CI,

1.46–2.72) in the AIT group compared with the placebo group.⁵ Immunotherapy was judged effective in 17 (71%) of the 24 studies, ineffective in 4 (17%) studies, and equivocal in 3 (12%) studies. Like the previous meta-analyses, the authors concluded that AIT is effective in a population of patients with allergen-triggered asthma.

In the foregoing three meta-analyses, only subcutaneous immunotherapy (SCIT) studies were considered. SCIT is the only form of AIT with Federal Drug Administration–approved formulations in the United States. Sublingual immunotherapy (SLIT) is an alternative method of AIT delivery, which has been used with increased frequency in Europe over the past 20 years and is currently under investigation in the United States. One systematic review on the SLIT for asthma using the Cochrane collaboration method analyzed 25 randomized controlled trials that included 1706 patients (see Table 2 for comparison between the SCIT and SLIT systematic reviews).⁶ The review found that SLIT significantly reduced asthma severity when parameter compositions were analyzed by combined analysis of the following outcomes: asthmatic symptoms, need for symptom relief medication, respiratory function test, and lung hyperreactivity. Although there was a nonsignificant reduction in asthma symptoms using SMD (–0.38 [95% CI, –0.79–0.03]), there was very significant improvement in the SLIT group compared with placebo when all allergic symptoms were considered including asthma (*e.g.*, rhinitis, conjunctivitis, etc.), with an SMD of –1.18 (95% CI, –.93 to –0.43). The NNT was 3.7 patients to prevent 1 patient from worsening or staying the same. The authors concluded that SLIT was beneficial for asthma albeit the magnitude of the effect was not large. A subsequent study noted several numerical and logistical discrepancies in this systematic review primarily because many of the studies included in the analysis were on patients with rhinitis/rhinoconjunctivitis with or without intermittent or mild persistent asthma and subanalysis for the “asthma” patients were generally not provided.⁷ Both studies were in agreement that there was a need for

Table 2 Comparison of the systematic reviews of sublingual and subcutaneous immunotherapy

Immunotherapy Route	Asthma Symptoms Scores SMD (95% CI)	Asthma Medication Scores SMD (95% CI)	Allergen-Specific BHR SMD (95% CI)	Pulmonary Function Test (FEV ₁)
Subcutaneous ³	SMD, -0.72, (-0.99, -0.33)	-0.90 (-1.13, -0.40)	-0.66 (-0.87, -0.45)	-0.13 (-0.83, 0.57)
Sublingual ⁶	-0.38 (-0.79, 0.03)	-0.91 (-1.94, 0.12)	"no significant improvement favoring SLIT"	1.48 (0.13, 2.82)

BHR = bronchial hyperreactivity CI = confidence interval; FEV₁ = forced expiratory volume in 1 s; SMD = standardized mean difference.

more randomized, controlled trials with standardizations of the outcome measures. The World Allergy Organization task force recently published recommendations for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy (Table 3).⁸

CLINICAL IMMUNOTHERAPY TRIALS: NEGATIVE, MULTIALLERGEN, AND ADD-ON THERAPY STUDIES

One of the negative studies on AIT for asthma was designed to evaluate two questions: (1) Does AIT provide additional benefits above pharmacotherapy and environmental controls (*i.e.*, "add-on therapy")? and (2) Is multi-AIT effective?⁹ In this double-blind, placebo-controlled study 121 allergic children with moderate to severe perennial asthma who were randomized after a year of observation and stabilization to receive SCIT with up to seven aeroallergens or placebo injections. Throughout the observation period and subsequent 24 months of treatment, medications were adjusted every 2–3 weeks based on peak flow rates and reported symptoms during the previous 14 days. The study also included home visits to evaluate the environment and sample house dust. The principal outcome was the daily medication scores. There was a significant decline in medication use in both the SCIT and the placebo groups but no significant difference between the groups. However, there was a trend toward favoring immunotherapy in 8 of 10 of the outcomes monitored including the primary outcome, medications scores. In a subgroup analysis, a younger age (≤ 8.5 years; $p = 0.02$) and mild asthma (medication score, ≤ 5 ; $p = 0.19$ and no inhaled corticosteroid use) approached statistical significance as factors suggesting a treatment effect in favor of immunotherapy. In the discussion, the authors suggest that "future investigations should focus on the potential prophylactic use of immunotherapy in children with allergic rhinitis, who are at high risk for asthma, or in highly allergic children with the recent onset of mild asthma." This study suggests that AIT

does not offer any additional benefits over pharmacotherapy and environmental controls. However, there were several variables in this study that should be considered. One potential limitation of this study is that it did not include an important allergen, cockroaches, which have been shown to correlate with asthma severity in other studies of inner-city asthmatic children.¹⁰ Another consideration in this study was the required medication reduction protocol, which created a source of variability in the primary outcome, medication use. Although many clinical trials allow medication reductions when indicated, they generally measure this as an outcome, rather than using them as independent variables.² Another potential variable was the use of multiallergen SCIT, the efficacy of which has not been clearly established possibly because of the paucity of studies that have evaluated this.

MULTIALLERGEN SCIT

There is some debate about the efficacy of multi-AIT. In general, the few multiallergen trials have generally established efficacy^{11–13} although some failed to provide results specific to the multiallergens.^{14–17} One DBPC study designed to compare the response to AIT of monosensitized patients treated with orchard grass pollen with polysensitized patients treated with a mixed pollen extract indicated significant efficacy only in the monosensitized patients treated with a single allergen.¹⁸

One PC of polysensitized asthmatic children who were randomized to receive placebo or one of three doses of an allergen mixture (10^{-7} weight/volume [w/v], 1/5000 w/v, or "highest tolerated up to 1/250 w/v" of each allergen) found a significant difference in being "free of asthma" at the age of 16 years in the two higher-dose treatment groups compared with the placebo and lowest-dose group.¹⁹ This effect appeared to be dose dependent with the highest-dose group (up to 1/250 w/v) having the lowest number of asthmatic patients (22%) compared with the 1/5000 w/v group (34%). There have been few studies that have evaluated

Table 3 World Allergy Organization's recommendations for standardization of clinical trials with allergen-specific Immunotherapy for respiratory allergy⁸

Item	Description
Study design	Randomized, double-blind, placebo controlled
Randomization	Computer-generated list; block randomization (the method must be clearly stated)
Power	Power not <90%; a 1 type error not >0.05
Patients selection	Ideally monosensitized; if polysensitized the causal role of the allergen used for immunotherapy must be clearly ascertained
Disease	Rhinitis (rhinoconjunctivitis) and/or asthma; diseases must be defined and classified according to GINA and ARIA criteria
Exclusion criteria	Those recommended in the ARIA and WHO guidelines
Extract	Standardized vaccines must be used when available; the cumulative and maintenance dose (possibly in micrograms of allergen) must be recorded
Concomitant medications	Rescue medications (as needed) must be prescribed to all patients and recorded on the diary card
Clinical assessment	Total score of symptoms (nasal + ocular + bronchial) must be recorded daily on the diary card
Primary outcome	Each single symptom graded from 0 = absent to 3 = severe Total clinical score calculated as the sum of symptom score plus drugs usage also calculated as a score
Secondary outcomes	Scores of individual symptoms separately and changes in drug usage Quality-of-life assessment Safety (total number of adverse events, and SIT-related side effects) Functional measures (e.g., lung function, rhinometry) Cost-effectiveness (e.g., QALY)
Surrogate markers	Skin tests Nasal, ocular, or bronchial challenge Antibody measurement Inflammatory parameters
Dropouts/withdraws	Dropouts and the reasons for must be reported

Source: Ref. 8.

GINA = Global Initiative for Asthma; ARIA = Allergic Rhinitis and its Impact on Asthma; WHO = World Health Organization; QALY = quality-adjusted life years.

the efficacy of multiallergen SLIT.^{20,21} One open-label, randomized controlled trial of patients with birch and grass pollen allergic rhinitis and BHR in pollen season compared the effect on clinical symptoms, nasal eosinophils, and BHR in patients randomized to receive SLIT for both allergens, one of the two allergens, or medications only.²⁰ A significant improvement in symptoms and medication scores, nasal eosinophils, and BHR was seen in the single allergen groups compared with baseline and the medication-only group in the target season ($p < 0.01$) and in the unrelated pollen season ($p < 0.05$). There was a greater improvement in clinical symptoms and inflammation in the group treated with both allergens compared with the single allergen SLIT groups. In considering the conflicting results in these very heterogeneous studies, firm con-

clusions about the efficacy—or lack of—multiallergen AIT can not be made and further research is clearly needed.

ADD-ON THERAPY

The question does immunotherapy offer additional benefits over pharmacotherapy and environmental control measures was addressed in one double-blind, PC trial of 72 dust-mite allergic subjects with mild-to-moderate asthma, 8–43 years old (32.6% were <18 years old) randomized to receive dust-mite SCIT or placebo after an observational year of pharmacologic treatment and allergen avoidance.²² Patients were excluded if they were sensitized to other perennial allergens but not if they had sensitivity to seasonal aller-

gens—so they were treated with a single allergen but they were not necessarily monosensitized. The study found that the addition of SCIT was associated with a significant decrease in the number of subjects requiring rescue bronchodilators, an increase in morning and evening peak expiratory flow, and reduced skin test sensitivity to dust mites. There was no significant effect on the cumulative dose of inhaled corticosteroids, asthma symptoms, lung volumes, or bronchial responsiveness to methacholine.

The efficacy of dust-mite SLIT was shown in a multicenter study of 97 children (age range, 6–12 years) with mild-to-moderate asthma who were monosensitized to dust mites and treated with high-dose dust-mite SLIT (cumulative dose over the 24-week treatment was 1.7 mg of *Dermatophagoides pteronyssinus* and 3.0 mg of *Dermatophagoides farinae*).²³ A statistically significant improvement was seen in daily, nighttime, and daytime asthma scores in the SLIT group compared with the placebo group after 24 weeks of treatment. There was also improvement in pulmonary function tests, FEV₁, forced vital capacity, PEFR, and medication scores compared with baseline.

IMMUNOTHERAPY AND ASTHMA: INDICATIONS, CONTRAINDICATIONS, AND SAFETY

According to the recently updated Allergen Immunotherapy Practice Parameters (AIPP), “allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens.”²⁴ The decision to begin AIT depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications.²⁴ In asthmatic patients, “immunotherapy is indicated in individuals who experience symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND one of the following:

- Poor response to pharmacotherapy, allergen avoidance, or both;
- Unacceptable adverse effects of medication;
- Wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- Co-existing allergic rhinitis and allergic asthma.”²⁴

Relative contraindications for immunotherapy are any medical conditions that would reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment.

The AIPP also recommends that immunotherapy should not be initiated in asthmatic patients unless the patient's asthma is stable with pharmacotherapy rec-

ognizing that symptomatic asthma is an AIT risk factor.^{25,26} Other risk factors for AIT include error in dosage, high degree of hypersensitivity, use of β -blockers, injections from new vials, and injections made during periods of exacerbation of symptoms.²⁶

SCIT SR rate may vary with the schedule. In one review, the SR rate with conventional SCIT build-up schedules (one dose increase per visit) ranged from 0.05 to 3.2% of injections and 0.84 to 46.7% of patients (mean, 12.92%; SD, 10.8%).²⁷ Excluding one study of highly sensitive ragweed-allergic patients,²⁸ the SR rate was $\leq 0.6\%$ /injection in the collective studies in this review article.

Cluster immunotherapy, which entails administering several injections at increasing doses (generally, two to three per visit) sequentially in a single day of treatment on nonconsecutive days is associated with the same or slightly increased SR rate as conventional schedules.²⁹ Rush immunotherapy schedules, which entail administering incremental doses of allergen at intervals of 15–60 minutes over 1–3 days, have considerably higher SR rates if no premedication is used. Premedication was shown to significantly reduce the SR rate with rush immunotherapy in one DBPC study to from 73% of patients in the placebo premedicated group to 27% of patients in the premedicated group.³⁰

In an American Academy of Allergy, Asthma, and Immunology (AAAAI) survey of fatal reactions (FRs)²⁵ and near FRs (NFRs),³¹ which was defined as respiratory compromise and/or hypotension requiring emergency epinephrine, during the period of 1990–2001, the estimated fatality rate was 1/2.5 million injections or an average of 3.4 deaths a year.²⁵ This fatality rate is similar to the two previously published AAAAI surveys,^{32,33} one of which reported 76% of patients who had FRs had asthma.³² The incidence of confirmed NFR was 4.7/year or 1 NFR/million injections and the incidence of unconfirmed NFRs was 23/year or 5.4 events/million injections.³¹ Of the 17 FRs that detailed information was provided, 15 had asthma and the majority, 9/15 (60%), were considered not optimally controlled at the time of the fatal injection. In the NFR group, the most severe reaction was respiratory failure (7 patients, 10% of NFR), which occurred exclusively in asthmatic patients, 4/7 (57%) of whom had baseline FEV₁ values of <70% of predicted.

These surveys suggest that asthma may be a risk factor for serious immunotherapy SRs, particularly if the asthma is not optimally controlled. The AIPP suggests the following measures as a means to reduce the risk for anaphylaxis with AIT²⁴:

- Assess the patient's general medical condition at the time of injection (e.g., asthma exacerbation).
- Consider obtaining a peak expiratory flow rate (PEFR) before administration of the injection. If the

PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.

SLIT appears to be associated with a lower incidence of SRs. In a comprehensive review of the SLIT literature in an AAAAI/American College of Allergy, Asthma, and Immunology Joint Task Force report there were no fatalities in the 1,181,000 doses of unmodified allergen administered to 4765 patients in the 66 studies that provided safety information.³⁴ The calculated SR rate for the studies that provided information on the number of SRs per doses administered was 0.56 SRs/1000 SLIT doses. There were 14 probable serious adverse reactions and seven of these were asthmatic reactions and one required hospitalization. Subsequent to this review there have been four cases of anaphylaxis associated with SLIT.^{35–38} One case involved hypotension and loss of consciousness in an asthmatic patient who took a dose that was 6 times greater than her usual maintenance dose after a 3-week gap in treatment (equivalent to 9.7 µg of *D. pteronyssinus* and 17.2 µg of *D. farinae*).³⁶ Of note, this dose was used in the pediatric dust-mite SLIT study discussed earlier in this article, which reported no serious adverse reactions.²³ No identified predictors for SRs with SLIT have been established as they have with SCIT (*e.g.*, asthma and high degree of hypersensitivity).

IMMUNOTHERAPY: WHAT ARE THE REQUIREMENTS FOR EFFICACY AND THE CAUSES OF LACK OF EFFICACY?

The efficacy of SCIT appears to depend on allergen dose. Dose-response studies have been performed for dogs,³⁹ cats,^{40,41} ragweed,⁴² and grass^{43,44} and the dose appears to be fairly consistent across these different types of allergens with the range being 5–20 µg of major allergen. A protein is considered a major allergen if it is recognized by >50% of the allergic population, whereas minor allergens are recognized by <50% of the allergic population. However, allergen extracts are complex heterogeneous mixtures of allergenic and nonallergenic proteins, glycoproteins, and polysaccharides. A "minor" allergen, however, does not mean it is clinically unimportant to some allergic individuals. However, major allergen content appears to correlate with the allergen extract's overall biological potency^{45–47} and internationally major allergen content is the recognized way to express allergen extract strength.⁴⁸ The dose-response effect on immunotherapy efficacy has been shown in subjective (*e.g.*, symptom scores and quality-of-life questionnaires) and objective parameters (*e.g.*, titrated skin tests, BHR, and immunologic changes).

Although, some recent studies have suggested a relationship between dose and efficacy with SLIT,^{49,50} a

consistent relationship between allergen dose, treatment duration, and clinical efficacy in the collective literature has not been established.^{34,51} The long-term clinical benefits of SCIT may be dependent on the duration of SCIT.

In a controlled prospective study of 40 asthmatic patients who had been treated with dust-mite SCIT for 12–96 months designed to assess the duration of immunotherapy efficacy, 55% of the patients relapsed within 3 years of discontinuing treatment.⁵² The relapse rate was significantly higher in the group who received SIT for <35 months compared with a group who received treatment for >36 months: relapse in 62% of patients in the <35-month treatment group versus 48% of patients treated for >36 months ($p < 0.04$). In addition to the immunotherapy treatment duration, reduction in skin test reactivity at the end of AIT was also predictive of prolonged efficacy after discontinuation ($p < 0.003$).

The determinants for SCIT efficacy can also be the reasons for lack of efficacy. The quality of the allergen extract can greatly influence immunotherapy outcome. Fungal allergen extracts are particularly problematic in terms of consistency and potency. Source materials for fungal allergenic extracts are derived from stock cultures maintained by the manufacturer. The morphological, biochemical, and antigenic characteristics of a given fungal strain are known to change with variations in the culture medium nutritional composition. Fungi rely on a high rate of somatic mutation and this genetic instability can alter the stock culture's production of allergenic substances.⁵³ This inherent genetic volatility is compounded by the diversity of strains used by the different manufacturers leading to the antigenic heterogeneity commonly observed among commercial fungal allergen extracts.

This commercial extract heterogeneity was confirmed in a study that analyzed the compositional profiles of nine samples of *Alternaria alternata* from seven extract manufacturers with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and found no two companies yielded comparable banding profiles.⁵³ Significant differences were seen in the SDS-PAGE profiles of one extract manufacturer's aqueous and glycerinated *A. alternata* extracts. No significant correlation ($r < 0.5$) was observed between the Alt a 1 concentrations and the respective protein, carbohydrate, and relative potency values.

Other potential causes for lack of SCIT efficacy include missing allergen (either missed on diagnostic testing or sensitivity to an allergen for which there is no available extract), continued high exposure to allergens due to home environment, occupational or other exposures (*e.g.*, household pets and animal laboratory worker), or continued exposure to nonallergen triggers (*e.g.*, tobacco smoke).

Table 4 Summary of four studies showing a preventive effect of immunotherapy on the development of new allergen sensitizations in monosensitized patients

Study	Age (yr; mean)	Immunotherapy Method and Number of Patients in Each Treatment Group	Immunotherapy (% of Patients with New Allergen Sensitizations)	Control (% of Patients with New Allergen Sensitizations)	<i>p</i> Value
Marogna ⁶¹ 2004	5–60 (22.8) 5–58 (21.5)	SLIT, 319 Control, 192	5.9	38	0.01
Des Roches ⁵⁸ 1997	4–6 (5) 3–5 (4)	SCIT, 22 Control, 22	54	100	0.001
Purello-D'Ambrosio ⁶⁰ 2001	Adults and pediatric	SCIT, 7182 Control, 1214	23	68	<0.0001
Pajno ⁵⁹ 2001	6–8 (7.14) 5–7 (6.38)	SCIT, 75 Control, 63	24.6	66.7	<0.0002

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

IMMUNOTHERAPY: CAN IT PREVENT THE DEVELOPMENT OF ASTHMA OR PROGRESSION OF ATOPY?

Allergic rhinitis is recognized as a risk factor for developing asthma.⁵⁴ The AIPP lists “possible prevention of asthma in patients with allergic rhinitis” as one of the indications for AIT in allergic rhinitis.²⁴ Several studies have investigated the effect of AIT in preventing the progression of the allergic disease in terms of development of asthma and new allergen sensitizations in adults and children.

In a 10-year retrospective study of 1104 nonasthmatic adults ± allergic rhinitis designed to investigate the natural history of allergic rhinitis and the potential effect of AIT in reducing the incidence of asthma, the highest risk factor associated with an asthma diagnosis at the end of follow-up was allergic rhinitis at baseline (OR, 7.8; 95% CI, 3.1–20.00).⁵⁵ The lowest risk factor for development of asthma was treatment with SCIT (OR, 0.53; 95%CI, 0.32–0.86).

Several studies have documented the preventive effect of AIT in a pediatric population. This preventive effective was suggested in 14-year study investigating the dose response of multiallergen SCIT in children discussed earlier in this article.¹⁹ In one prospective study of 205 children with a clinical history of grass- or birch-induced rhinoconjunctivitis who were randomized to receive SCIT for 3 years or to an open control group, there was a statistically significant reduction in the risk for development of asthma during the treatment period (OR, 2.52; 95% CI, 1.3–5.1).

At the 10-year follow-up (7 years after discontinuing immunotherapy) the children in the immunotherapy group had significantly less asthma compared with the control group: 16/64 (25%) with asthma in the immunotherapy group compared with 24/53 (45%) of the untreated control group (OR, 2.5; CI, 1.1–5.9) in favor

of immunotherapy for prevention of asthma.⁵⁶ The authors concluded that immunotherapy for 3 years with standardized allergen extracts of grass and/or birch results in a long-term preventive effect on the development of asthma in children with only seasonal rhinoconjunctivitis.

A similar preventive effect was seen with SLIT in a 3-year open study of 113 children, aged 5–14 years old, with grass pollen rhinitis randomized to receive coseasonal SLIT for 3 years or standard symptomatic therapy.⁵⁷ Development of asthma after 3 years was 3.8 times more frequent in the control subjects (95% CI, 1.5–10.0.).

Three studies have shown a significantly lower rate of the development of new allergen sensitizations in monosensitized patients who received SCIT compared with untreated matched controls with 23, 24, and 54% of the SCIT patient versus 68, 67, and 100% of the untreated monosensitized patients developing new allergen sensitization during the study period (Table 4).^{58–60} Similar results were found in a 3-year open study of 511 patients with allergic rhinitis ± asthma patients randomized to receive SLIT or pharmacologic treatment.⁶¹ New allergen sensitizations developed in 38% of the control patients and in 5.9% of the SLIT patients (*p* = 0.01).

CONCLUSIONS

AIT for allergic asthma has been shown to be effective in three meta-analyses and multiple controlled clinical trials. Clinical efficacy has been established in objective and subjective parameters such as titrated skin tests, allergen-induced BHR, and symptom and medications scores. Indication for AIT in asthma include poor response to pharmacotherapy and/or allergen avoidance, unacceptable adverse effects of medications, patients' wish to reduce or avoid long-term

pharmacotherapy, and the cost of medications and coexisting allergic rhinitis and/or other comorbid allergic conditions. Relative contraindications for AIT include any medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment. Symptomatic asthma is a risk factor for asthma and AIT should not be administered unless the patient's asthma is stable. Allergen dose, extract quality, and duration of treatment are some of the factors that appear to influence efficacy and missing allergen(s), inadequate duration and/or dose and ongoing exposures to high levels of allergen, and/or irritants may be reasons for lack of efficacy of AIT. A very limited number of studies that have investigated the effect of AIT with multiple allergens or as add-on therapy in asthmatic patients that are optimally controlled with medications and environmental controls have reported conflicting results. Several studies have indicated that AIT can prevent the progression from allergic rhinitis to asthma and the development of new allergen sensitizations. Additional research on the effectiveness of multiallergen AIT is clearly needed.

REFERENCES

- Abramson MJ, Puy RM, and Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003:CD001186.
- Portnoy JM. Immunotherapy for asthma: Unfavorable studies. *Ann Allergy Asthma Immunol* 87:28–32, 2001.
- Abramson MJ, Puy RM, and Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 151:969–974, 1995.
- Portnoy JM, Van Osdol T, and Williams PB. Evidence-based strategies for treatment of allergic rhinitis. *Curr Allergy Asthma Rep* 4:439–446, 2004.
- Ross RN, Nelson HS, and Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: A meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther* 22:329–341, 2000.
- Calamita Z, Saconato H, Pela AB, and Atallah AN. Efficacy of sublingual immunotherapy in asthma: Systematic review of randomized-clinical trials using the Cochrane Collaboration method. 61:1162–1172, 2006.
- Larenas-Linnemann DE, and Cox LS. Sublingual immunotherapy for asthma: Need for high quality meta-analyses to prove the concept. *Allergy* 62:704–705, author reply 6–7, 2007.
- Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 62:317–324, 2007.
- Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 336:324–331, 1997.
- Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 336:1356–1363, 1997.
- Lowell FC, and Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. *N Engl J Med* 273:675–679, 1965.
- Hedlin G, Wille S, Browaldh L, et al. Immunotherapy in children with allergic asthma: Effect on bronchial hyperreactivity and pharmacotherapy. *J Allergy Clin Immunol* 103:609–614, 1999.
- Alvarez-Cuesta E, Aragoneses-Gilsanz E, Martin-Garcia C, et al. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: Changes in quality of life. *Clin Exp Allergy* 35: 572–578, 2005.
- Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002 109:251–256.
- Haugaard L, and Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. *Allergy* 47:249–254, 1992.
- Moncayo Coello CV, Rosas Vargas MA, del Rio Navarro BE, et al. Quality of life in children with allergic rhinitis before and after being treated with specific immunotherapy (cases and controls). *Rev Alerg Mex* 50:170–175, 2003.
- Guardia P, Moreno C, Justicia JL, et al. Tolerance and short-term effect of a cluster schedule with pollen-extracts quantified in mass-units. *Allergol Immunopathol (Madr)* 32:271–277, 2004.
- Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 88:43–53, 1991.
- Johnstone DE, and Dutton A. The value of hyposensitization therapy for bronchial asthma in children—A 14-year study. *Pediatrics* 42:793–802, 1968.
- Marogna MSI, Massolo A, Zanon P, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol* 98:274–280, 2007.
- Cirla AM, Cirla PE, Parmiani S, and Pecora S. A pre-seasonal birch/hazel sublingual immunotherapy can improve the outcome of grass pollen injective treatment in bisensitized individuals. A case-referent, two-year controlled study. *Allergol Immunopathol (Madr)* 31:31–43, 2003.
- Maestrelli P, Zanolla L, Pozzan M, and Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 113:643–649, 2004.
- Niu CK, Chen WY, Huang JL, et al. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 100:1374–1383, 2006.
- Cox L, Li J, Lockey F, Nelson HS. Allergen immunotherapy: A practice parameter second update. *J Allergy Clin Immunol* 120: S25–S85, 2007.
- Bernstein DI, Wanner M, Borish L, and Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 113:1129–1136, 2004.
- Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 81:401–405, 1998.
- Stewart GE II, and Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol* 90:567–578, 1992.
- Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J Allergy Clin Immunol* 69:181–193, 1982.
- Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol* 116:109–118, 2005.
- Portnoy J, Bagstad K, Kanarek H, et al. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy* 73:409–418, 1994.

31. Amin HS, Liss GM, and Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 117:169–175, 2006.
32. Reid MJ, Lockey RF, Turkeltaub PC, and Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol* 92:6–15, 1993.
33. Lockey RF, Benedict LM, Turkeltaub PC, and Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 79:660–677, 1987.
34. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: A comprehensive review. *J Allergy Clin Immunol* 117:1021–1035, 2006.
35. Antico A, Pagani M, and Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 61:1236–1237, 2006.
36. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 63:374, 2008.
37. Dunskey EH, Goldstein MF, Dvorin DJ, and Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 61:1235, 2006.
38. Eifan AO, Keles S, Bahceciler NN, and Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 62:567–568, 2007.
39. Lent AM, Harbeck R, Strand M, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. *J Allergy Clin Immunol* 118:1249–1256, 2006.
40. Nanda A, O'Connor M, Anand M, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. *J Allergy Clin Immunol* 114:1339–1344, 2004.
41. Ewbank PMJ, Sanders K, Curran-Everett D, et al. A double-blind placebo-controlled immunotherapy dose-response study with standardized cat extract. *J Allergy Clin Immunol* 111:155–161, 2003.
42. Creticos PS, Adkinson NF Jr, Kagey-Sobotka A, et al. Nasal challenge with ragweed pollen in hay fever patients. Effect of immunotherapy. *J Clin Invest* 76:2247–2253, 1985.
43. Bosquet J HA, Soussana M, and Michel F-B. Double-blind placebo-controlled immunotherapy grass-pollen allergoids IV. Comparison of the safety and efficacy of two doses of a high-molecular-weight allergoid immunotherapy. *J Allergy Clin Immunol* 85:490–497, 1990.
44. Frew AJ, Powell RJ, Corrigan CJ, and Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 117:319–325, 2006.
45. Lombardero M, Quirce S, Duffort O, et al. Monoclonal antibodies against *Olea europaea* major allergen: allergenic activity of affinity-purified allergen and depleted extract and development of a radioimmunoassay for the quantitation of the allergen. *J Allergy Clin Immunol* 89:884–894, 1992.
46. Dreborg S, and Einarsson R. The major allergen content of allergenic preparations reflect their biological activity. *Allergy* 47:418–423, 1992.
47. Boluda L, Casanovas M, Prieto JL, and Fernandez-Caldas E. Determinations of Par j 1 by a competitive enzyme immunoassay using human specific IgE and IgG. Validation by skin prick testing. *J Investig Allergol Clin Immunol* 8:207–213, 1998.
48. Larenas-Linnemann D, and Cox LS. European allergen extract units and potency: Review of available information. *Ann Allergy Asthma Immunol* 100:137–145, 2008.
49. Didier A, Malling HJ, Worm M, 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* 120:1338–1345, 2007.
50. Durham S, Yang W, Pedersen M, et al. Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 117:802–809, 2006.
51. Larenas-Linnemann DE. Sublingual immunotherapy: Dosing in relation to clinical and immunological efficacy. *Allergy Asthma Proc* 29:130–139, 2008.
52. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 51:430–433, 1996.
53. Esch RE. Manufacturing and standardizing fungal allergen products. *J Allergy Clin Immunol* 113:210–215, 2004.
54. Passalacqua G, and Durham SR. Allergic Rhinitis and its impact on asthma update: Allergen immunotherapy. *J Allergy Clin Immunol* 119:881–891, 2007.
55. Polosa R, Al-Delaimy WK, Russo C, et al. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: A retrospective cohort study. *Respir Res* 6:153, 2005.
56. Jacobson L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 62:943–948, 2007.
57. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 114:851–857, 2004.
58. Des Roches A, Paradis L, Menardo JL, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 99:450–453, 1997.
59. Pajno GB, Barberio G, De Luca F, et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 31:1392–1397, 2001.
60. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 31:1295–1302, 2001.
61. Marogna M, Spadolini I, Massolo A, et al. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: Clinical efficacy and more. *Allergy* 59:1205–1210, 2004. □

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