

Multiallergen immunotherapy for allergic rhinitis and asthma

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The English and non-English language literature on allergen immunotherapy was reviewed for studies simultaneously using 2 or more distinct allergen extracts in either subcutaneous or sublingual immunotherapy. Thirteen studies were identified, 11 using subcutaneous injections, 1 using sublingual administration, and 1 using both. In studies with adequate information, administration of 2 extracts by means of either subcutaneous immunotherapy or sublingual immunotherapy was effective. In studies using multiple allergens, 3 studies showed clear efficacy, whereas in the other 2 studies, lack of efficacy might have been due to inadequate doses of extract or omission of clinically relevant allergens in the treatment regimen. It is concluded that simultaneous administration of more than 1 allergen extract is clinically effective. However, more studies are needed, particularly with more than 2 allergen extracts and with sublingual administration. (J Allergy Clin Immunol 2009;123:763-9.)

Key words: Allergen extracts, allergic rhinitis, bronchial asthma, multiallergen, polysensitization, subcutaneous immunotherapy, sublingual immunotherapy

The administration of allergen immunotherapy by means of subcutaneous injection, which was introduced a century ago,^{1,2} has been shown to be effective in the management of allergic rhinitis^{3,4} and bronchial asthma.^{3,5} More recently, the sublingual administration of allergen extracts has become popular in many European countries and has also demonstrated efficacy in both allergic rhinitis⁶ and bronchial asthma.⁷ By using either route of administration, allergen immunotherapy has been shown not only to reduce symptoms and the need for medication but also to prevent the development of additional sensitivities in monosensitized patients⁸⁻¹⁰ and asthma in patients with allergic rhinitis^{11,12} and to provide continuing benefit after the completion of several years of treatment.^{8,13-16}

Most randomized controlled studies demonstrating efficacy with subcutaneous immunotherapy (SCIT) or sublingual

Abbreviations used

SCIT: Subcutaneous immunotherapy

SLIT: Sublingual immunotherapy

immunotherapy (SLIT) have been conducted with single-allergen extracts. Although some guidelines have recommended against the use of multiple allergen mixes in treatment,¹⁷ allergists in the United States commonly administer a mixture of multiple allergens to which the patient is sensitive with the rationale that effective immunotherapy should include all major sensitivities.¹⁸

The purpose of the current study was to search the English and non-English language literature for reports on the administration and clinical efficacy of the administration of 2 or more unrelated allergen extracts using either SCIT or SLIT.

METHODS

Articles reviewed in the current study were selected in a 2-part process. Part 1 consisted of searching existing English and non-English language review articles and meta-analyses to identify studies that used 2 or more allergen extracts. Part 2 involved searching 3 databases (Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE) to identify relevant articles published between 2002 and 2007. Using the year 2002 allowed the capture of all studies published after the meta-analyses were written, with some overlap. A total of 877 articles (Cochrane, n = 284; MEDLINE, n = 241; and EMBASE, n = 352) were identified. The following search terms were used: (immunother* OR hyposens* OR desens*); (asthma OR wheeze OR rhin* OR hay NEXT fever); and (random* OR control*).

RESULTS

In total, 13 studies published between 1961 and 2007 were identified that reported the administration of 2 or more unrelated allergens. Seven of the studies used combinations of 2 non-cross-reacting extracts; of these, 3 studies also included some patients receiving only 1 extract, and outcomes in the 2 groups (single versus multiple allergens) were not reported separately. In the other 4 studies using 2 simultaneously administered extracts, clinical outcomes were superior to placebo and, when investigated, equal to single-extract treatment. One other study used between 1 and 4 extracts; clinical outcomes were superior to pharmacologic therapy, but the results were not reported separately for single or multiple allergens.

Five relevant studies that used mixes that contained several allergen extracts were identified. Three of the studies demonstrated that multiallergen immunotherapy was effective, whereas 2 of the studies did not. In the latter studies dose insufficiency or lack of treatment of key sensitivities might have led to suboptimal outcome.

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TABLE I. Clinical trials in the treatment of allergic rhinitis, asthma, or both with multiallergen immunotherapy

Study	Design	Subjects	Allergens	Multiallergen findings
A. Trials using both single- and 2-allergen extracts without separate reporting of outcomes				
1. Haugaard and Dahl (1992) ¹⁹	Part 1: DBPC trial Part 2: All patients treated with SCIT	Twenty-four adults with asthma	Cat dander, dog dander, or both	Results were not reported separately for 1- and 2-allergen treatment.
2. Möller et al (2002) ¹¹	RCT SCIT	Two hundred eight children with AR	Grass pollen, birch pollen, or both	Results were not reported separately for 1- and 2-allergen treatment.
3. Guardia et al (2004) ²⁰	Open controlled trial SCIT	One hundred ninety-one adults and children (ages 7-50 y) with AR with or without asthma	Olive tree pollen, grass pollen (orchard grass, fescue, ryegrass, timothy, and <i>Poa</i> species), or both	Results were not reported separately for 1- and 2-allergen treatment.
B. Trials using 2-allergen extracts with separate reporting of results				
1. Hedlin et al (1999) ²¹	DBPC trial SCIT	Twenty-nine children with asthma	Birch or timothy grass plus cat, house dust mite, or placebo	Bronchial allergen challenge was significantly improved with cat or dust mite SCIT compared with placebo.
2. Cirila et al (2003) ²²	RCT SCIT and SLIT	Thirty-six adults with rhinoconjunctivitis with or without mild asthma	SCIT: grass mix (timothy, orchard, rye, meadow, and fescue) SLIT: birch/hazel or placebo	Symptoms of cough and conjunctivitis were significantly improved with combined immunotherapy compared with preseasonal grass SCIT alone. Combination therapy decreased the use of asthma medication and increased the threshold for nasal grass and inhaled methacholine challenges.
3. Alvarez-Cuesta et al (2005) ²³	Randomized DBPC trial SCIT	Fifty-three adults with AR	Orchard grass and olive tree vs placebo	Symptoms, medication use, and quality of life were significantly improved with 2-allergen SCIT compared with placebo.
4. Marogna et al (2007) ²⁴	Open-label RCT SLIT	Forty-eight adults with rhinoconjunctivitis and mild asthma	Birch pollen, grass pollen, or both or placebo	Clinical symptoms, inflammation, pulmonary function test results, and nasal scraping results for eosinophils were significantly improved with grass plus birch pollen or with single-allergen treatment in respective seasons.
C. Results of a trial using 1-4 extracts without separately reporting outcome				
1. Moncayo Coello et al (2003) ²⁵	RCT SCIT	Fifty-four children with AR	Cat, dust mite, German cockroach, or American cockroach	Results with ≥ 1 allergens were not reported separately.
D. Trials using multiple allergen extracts				

(Continued)

TABLE I. (Continued)

Study	Design	Subjects	Allergens	Multiallergen findings
1. Johnstone and Dutton (1968) ²⁶	RCT SCIT	One hundred seventy-three children with perennial bronchial asthma	All allergens elicited positive results on skin testing (no additional information was provided)	A dose-response effect was seen with SCIT; a 78% rate of remission of asthma was observed in patients treated with the highest extract concentration (1:250 wt/vol) compared with 66% in the 1:5000 wt/vol group and 22% in the placebo or very low-dose groups.
2. Lowell and Franklin (1965) ²⁷	DBPC trial SCIT	Twenty-four adults with ragweed-associated rhinoconjunctivitis	Ragweed or placebo and tree, grass, and plantain pollen (no additional information was provided)	Symptom reductions with ragweed pollen plus other pollen extracts was significant vs placebo plus other pollen extracts ($P < .05$).
3. Franklin and Lowell (1967) ²⁸	DBPC trial SCIT	Twenty-four adults with AR	Two doses of ragweed plus multiple pollen allergens (not specified in the study)	Symptom scores were significantly lower with high-dose ragweed extract compared with one-twentieth of the dose.
4. Bousquet et al (1991) ²⁹	DBPC trial SCIT	Seventy adults with AR with or without asthma	Orchard grass or placebo or orchard grass plus olive tree, plane tree, <i>Parietaria</i> species, or placebo	Clinical improvement was significantly greater with grass pollen extract monotherapy compared with placebo but not with grass plus other allergens.
5. Adkinson et al (1997) ³⁰	DBPC trial SCIT	One hundred twenty-one children with moderate-to-severe perennial asthma	House dust mite, ragweed grass mix (timothy, orchard, perennial ryegrass), Bermuda grass, English plantain, white oak, <i>Alternaria alternata</i> , <i>Aspergillus fumigatus</i> , <i>Cladosporium herbarum</i>	Primary outcome (daily medication scores) did not differ between patients receiving multiallergen SCIT and those receiving placebo.

DBPC, Double-blind placebo-controlled; RCT, randomized controlled trial; AR, allergic rhinitis.

See Table I for a summary of multiallergen findings in the 13 studies.^{11,19-30}

Studies using both single- and 2-allergen extracts without separate reporting of outcome

This section summarizes the 3 studies in which separate results were not provided for single- versus 2-allergen treatment arms.

Study 1. In a 2-phase study in 24 patients with asthma caused by allergy to cat dander, dog dander, or both, SCIT was found to be an effective treatment for allergy to cat but not to dog.¹⁹ The first part of the study consisted of a 5-month, double-blind, placebo-controlled phase in which 15 patients were treated with SCIT according to allergy (cat, dog, or both) and 9 patients were treated with placebo. In phase 2 the patients treated with placebo were switched to active treatment based on their respective allergies, and all patients were actively treated for 12 months. After 12 months, bronchial responsiveness to both cat extract and histamine (PD₂₀) was found to be significantly reduced in patients treated with cat extract ($P = .003$ and $P = .01$, respectively), whereas there was no significant decrease in bronchial responsiveness to dog extract or histamine in patients treated with dog extract. The lack of efficacy with dog extract might have correlated with potency (ie, the dog extract used was less potent than the cat extract).

Study 2. A 3-year study evaluating the efficacy of SCIT in preventing the development of asthma symptoms in 208 children with allergic rhinitis and allergies limited to grass ($n = 124$), birch ($n = 43$), and grass plus birch ($n = 41$) found that children randomized to specific SCIT versus an open control group had asthma significantly less often and had significantly improved bronchial provocation test results (odds ratio, 2.52; $P < .05$).¹¹

Study 3. A 3-month prospective multicenter study investigated short-term response to SCIT using a cluster schedule in 191 children and adults with seasonal allergic rhinitis or rhinoconjunctivitis with or without asthma.²⁰ Patients sensitive to olive tree and grass pollen were treated with biologically standardized extracts of olive tree pollen (6 μg of Ole e 1), 5 grass pollens (1 μg , group 5 allergen), or both and experienced significant improvement in wheezing ($P = .035$) and coughing ($P = .014$), as well as a reduction in antihistamine ($P = .045$) and β_2 -agonist use ($P = .004$), compared with patients treated with placebo.

Studies using 2-allergen extracts with separate reporting of outcome

This section summarizes 4 studies in which clinical outcomes using 2 simultaneously administered extracts were superior to placebo and, when investigated, equal to single-extract treatment.

Study 1. In a 3-year, randomized, double-blind, placebo-controlled trial investigating the effect of cat or dust mite immunotherapy on bronchial hyperreactivity, 29 children with asthma or hay fever who were allergic to cat or dust mites were randomly allocated in a double-blind fashion to either cat or dust mite or to placebo immunotherapy, whereas all received birch or timothy grass immunotherapy.²¹ Most children with sensitivity to cat ($n = 28$) also had sensitivity to dog or horse ($n = 26$). Treatment during the build-up phase was once weekly, and the maximum/maintenance dose was administered every sixth week. Budesonide was administered in a standardized protocol based on lung function tests.

After 3 years, bronchial allergen challenge results with cat or house dust mite extract were significantly different between those who received cat or house dust mite and those who received placebo ($P < .001$). Median PC₂₀ values for bronchial responsiveness using methacholine challenge increased in both the cat/house dust mite treatment group and the placebo group, and the difference between groups was not statistically significant.

Study 2. In a 2-year randomized study in 36 matched-pair patients with rhinoconjunctivitis with or without mild asthma who received either preseasonal grass SCIT alone or preseasonal grass SCIT preceded by preseasonal birch/hazel SLIT,²² patients in both groups showed significant improvement in total symptom scores during the peak of the grass pollen season. However, the reduction in conjunctival symptoms and cough was significantly greater with combined immunotherapy than with preseasonal grass SCIT alone. Antihistamine use decreased significantly in both groups, but asthma medication use decreased significantly only in patients treated with combined therapy. Nasal provocation testing with grass revealed a higher threshold in the SLIT-SCIT group ($P = .01$); furthermore, the latter group was the only one in which PD₂₀ methacholine values improved significantly ($P < .05$). Study results therefore suggest that SLIT treatment with a birch/hazel extract improves the outcome of subsequent SCIT with grass pollen extract, probably by decreasing the priming effect of the birch/hazel pollen.

Study 3. A 1-year, randomized, double-blind, placebo-controlled trial in 53 adults with seasonal allergic rhinitis found that symptoms, medication use, and quality of life significantly improved in patients treated with a 2-allergen mixture of polymerized orchard grass and olive tree pollen extracts by means of SCIT compared with those treated with placebo.²³ Patients in the study had negative results for sensitivity to a panel of 20 other standardized allergens. Symptom scores (nose, eye, and chest), as well as 5 of 7 quality-of-life domains in the standardized Rhinoconjunctivitis Quality of Life Questionnaire, were significantly less in the treated group than in the placebo group ($P < .01$ and $P < .05$, respectively). The mean medication score was also significantly lower in the former than the latter group ($P < .001$).

Study 4. A 4-year, open-label, randomized controlled study in 48 evaluable patients with rhinoconjunctivitis and mild asthma with sensitivity to only birch and grass showed that treating 2 seasonal sensitivities with 2-allergen SLIT was as effective as treating each with single-allergen SLIT.²⁴ Patients were divided into 4 study arms (SLIT with birch extract, SLIT with grass extract, SLIT with both birch and grass extracts, and medication only) and were prescribed other medications during pollen seasons according to the Allergic Rhinitis and its Impact on Asthma guidelines (ie, cetirizine or loratadine [10 mg once daily], nasal cromolyn

[10 mg/d], inhaled salbutamol on demand; or intranasal beclomethasone, 2 puffs per nostril twice daily [400 μ g/d], in patients with suboptimal response to antihistamines and cromolyn). In patients receiving mixed SLIT, birch and grass extracts were not combined in 1 vial but were taken sublingually at the same time.

Patients who received SLIT for grass, birch pollen, or both experienced significantly greater clinical improvement during their respective seasons compared with baseline values and medication-only treatment. Of interest, patients receiving grass or birch SLIT showed improvement during both the grass and birch seasons. In the grass season no significant difference was observed in symptom plus medication scores or bronchial hyperreactivity (methacholine) in patients treated with birch plus grass extracts versus grass extracts alone; improvement in both groups was significantly better than that in the birch-only extract group (Fig 1). The reverse was true during the birch pollen season. The observation that SLIT with only birch or grass also provided a measurable improvement in the grass season and birch season, respectively, is unexplained.

One study using between 1 and 4 extracts without separate reporting of outcome

In a clinical trial in 54 children with allergic rhinoconjunctivitis, SCIT treatment with up to 4 allergens (cat, dust mite, German cockroach, or American cockroach) was associated with significant improvement in allergic symptoms at 6 months compared with pharmacologic treatment.²⁵ Additionally, children receiving SCIT were less likely than those receiving pharmacologic treatment to use allergy medications.

Studies using multiallergen extracts

This section summarizes 5 studies that investigated the use of multiallergen extracts.

Study 1. In 1968, investigators reported the results of a 14-year study of multiallergen SCIT in children with perennial bronchial asthma randomized to placebo (saline), 10⁻⁷ extract dilution, 1:5000 extract dilution, or highest tolerated dose (to a maximum 1:250 dilution).²⁶ Extracts included all inhalable allergens to which the children were sensitive by means of skin testing. Results were reported after 4 years of treatment ($n = 173$)³¹ and again after all children had reached age 16 years ($n = 130$). At the end of 4 years, 18% of children in the placebo and low-dose immunotherapy groups were free of asthma compared with 70% of children in the medium- and high-dose immunotherapy groups. At age 16 years, 22% of children in the placebo and low-dose immunotherapy groups were free of symptoms compared with 66% of children in the 1:5000 extract dilution group and 78% of those receiving the highest tolerated dose.²⁶ The results indicated that the greatest improvement was seen in the group receiving the highest tolerated dose.³¹ Although routine skin testing (scratch and intradermal methods) was done with pollens, molds, epidermoids, house dust, bacterial vaccines, and commonly eaten foods,²⁶ no further description of the sensitivities or treatment was provided with respect to which or how many of the allergens were given in each of the 4 treatment groups (Fig 2).

Study 2. In a SCIT study in 24 evaluable adults with ragweed-associated rhinoconjunctivitis who had been symptomatic during the previous ragweed pollen season (despite treatment with immunotherapy containing ragweed), the retention of ragweed allergen in a mixture of multiple allergens was shown to

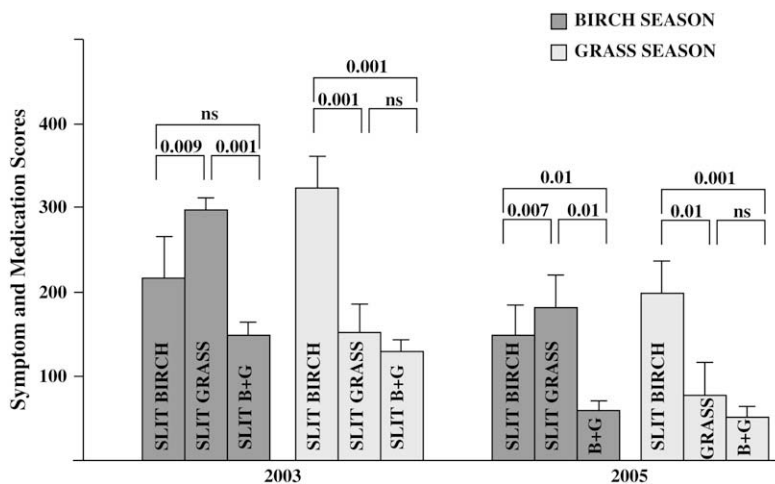


FIG 1. Comparison of the 3 sublingual immunotherapy treatments: effect on symptom and medication scores in 2003 and 2005. *ns*, Nonsignificant; *B+G*, birch plus grass. Reprinted with permission from *Ann Allergy Asthma Immunol.* 2007;98:274-80.

significantly improve outcome.²⁷ Patients in the study were randomized in a matched-pair fashion to SCIT with all relevant allergens versus SCIT with all relevant allergens minus ragweed. Precise details regarding the number of allergens were not reported; however, tree, grass, and plantain pollens were included in the treatments. Symptom and medication scores were recorded throughout the ragweed pollen season (August-October). Median medication scores (in particular symptom scores) showed that significant improvement occurred during the ragweed pollen season when ragweed extract was included in the mixture. A difference in scores was detected between treatment groups, even though the study was conducted over a period of only 8 months (March-October).

Study 3. In a study of similar design, the same investigators compared high- and low-dose (1:50 and 1:1000 weight per volume, respectively) ragweed extract in multiallergen SCIT in 24 adults with allergic rhinitis who had symptoms during the previous ragweed season (despite receiving immunotherapy that included ragweed extract). Patients were randomized in a pairwise fashion based on maximum tolerated doses of ragweed extract determined before study initiation in May.²⁸ Symptom scores were significantly lower in the high-dose group in late August and early September. The findings suggest that low doses of ragweed extract might be relatively ineffective in the treatment of pollenosis and that ragweed extract in a multiallergen mixture is effective.

Study 4. A study in 70 immunotherapy-naive adults with allergic rhinitis with or without asthma, who were confirmed by means of skin prick and *in vitro* testing for sensitivity to orchard grass, showed that response to specific immunotherapy differs in patients with allergy only to grass pollens compared with polysensitized patients. Patients sensitive only to orchard grass (*n* = 36) were randomized to either orchard grass SCIT or placebo, whereas patients sensitive to multiple allergens (*n* = 34) were randomized to SCIT with orchard grass and up to 3 other extracts to which they were sensitive or to placebo.²⁹ None of the patients sensitive to multiple allergens had perennial symptoms, even though a few patients had positive skin test results for perennial allergens. Immunotherapy was administered in a 3-day rush protocol that began around April 1, maintenance dosing (2000 biologic units) of each

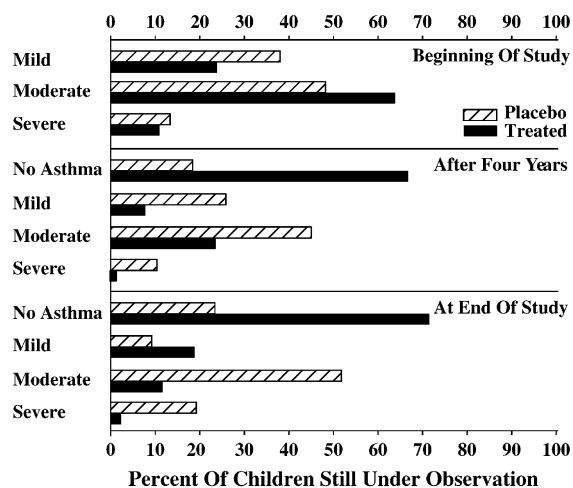


FIG 2. Study results: severity of asthma in the placebo and treated groups before study, after 4 years, and at the end of the study. The percentage of children for the treated and placebo groups in each time period equals 100%. *Mild*, Less than 11 days of wheezing per year; *moderate*, 11 to 70 days of wheezing per year; *severe*, more than 70 days of wheezing per year. Reproduced with permission from *Pediatrics.* 1968;42:799. ©1968 by the American Academy of Pediatrics.

allergen was administered once weekly for 5 weeks, and in-season dosing (1000 biologic units) was administered every 2 weeks during the orchard grass pollen season (May 15-July 1). Only patients monosensitized to grass extract showed significant clinical improvement during the orchard grass pollen season compared with patients treated with placebo. Some patients in the multiallergen group showed a clinical benefit in nasal challenge and symptom/medication scores, even though the mean for the group was not significantly different from that in the placebo group. Study findings confirm that a standardized grass extract is effective in patients allergic only to grass pollens but might be ineffective in patients allergic to multiple pollen species who receive a mixture of standardized pollen extracts. Notably, polysensitized patients were also sensitive to more grass allergens on immunoblotting (mean, 5.64 bands) than were patients sensitized to grass only (mean,

2.03 bands). The study could therefore be considered an investigation of the response of more sensitized to less sensitized patients, as well as one comparing single-allergen and multiallergen immunotherapy. The authors speculated that higher doses might have been necessary for the polysensitized patients, but such doses were not easily attainable in standardized allergen mixes.

Study 5. A study in 121 urban and suburban children with moderate-to-severe perennial asthma who were receiving appropriate medical treatment showed that multiallergen SCIT for a minimum of 18 months provided no discernible benefit. Children in the study were randomized to placebo or a mixture of up to 7 extracts (based on skin test reactions with priority given to perennial allergens).³⁰ No significant difference was observed between treatment arms with respect to the use of medication, asthma symptoms, peak expiratory flow, or sensitivity to inhaled methacholine.³⁰ Perennial allergens administered included house dust mites and *Aspergillus fumigatus*; none of the children received extracts for cockroach,³² cat,³³ or dog,³³ which are important for perennial asthma, especially in an urban environment.³⁰ Although the investigators excluded patients who refused to eliminate furred pets from the environment, these allergens are typically encountered outside of the home and even in the homes of non-pet owners.^{34,35}

DISCUSSION

An extensive search of the English and non-English language literature on allergen immunotherapy revealed only 13 articles reporting the simultaneous administration of more than 1 unrelated allergen extract. Eleven of the studies used subcutaneous administration, 1 study used sublingual administration, and 1 study used a combination of subcutaneous and sublingual administration. In 9 studies allergic rhinitis was the primary condition being treated, whereas bronchial asthma was the primary condition in 4 studies.

In 3 studies (A1, A2, and A3; see Table I), patients received either 1 or 2 allergen extracts, and the results were not reported separately; therefore the effectiveness of 2-allergen treatment could not be assessed. In 4 studies (B1, B2, B3, and B4) the results of 2-allergen treatment were reported separately, and all were superior to placebo; furthermore, in 1 study 2-allergen treatment was shown to be equal to each of the extracts administered separately. In one other study (C1) patients received between 1 and 4 allergen extracts, and clinical outcome was superior to that with pharmacologic therapy; of note, the results for single versus multiple allergens were not reported separately. Thus in 4 studies in which details are adequate, simultaneous immunotherapy with 2 distinct allergen extracts was clearly effective.

Multiple non-cross-reacting allergens were administered in 5 studies, without specification of the exact number of such allergens. The multiallergen mixture was successful in 3 of the studies (D1, D2, and D3). In 1 study (D1) significantly more children with asthma who received moderate-to-high doses of allergen (containing all of the inhalant allergens to which they were sensitive) were free of asthma after 4 years and on reaching age 16 years than were children with asthma who received placebo or very low doses of allergen. In 2 studies by one group of investigators (D2 and D3), the complete removal of or 95% reduction in ragweed from multiallergen treatment resulted in the occurrence of significantly more symptoms the next pollen season. The latter finding clearly indicates that ragweed extract provided significant relief, despite its combination with multiple

other extracts in the treatment program. In a study comparing immunotherapy with grass extract in patients monosensitized or polysensitized to grass (D4), only the monosensitized patients (as a group) experienced significant benefit compared with patients receiving placebo; however, the polysensitized patients were sensitized to many more grass allergens, and thus the 2 treatment groups were not comparable. Finally, an investigation of multi-allergen mixes in children with perennial asthma (D5) failed to show benefit, possibly because cat, dog, and cockroach, important causes of perennial asthma symptoms, were omitted.

The findings of the current review strongly suggest that the simultaneous delivery of multiple unrelated allergens can be clinically effective with the proper identification of relevant allergens, and treatment with adequate doses for a sufficient period of time is essential. However, there is a need for additional studies with more than 2 allergen extracts, particularly using sublingual administration, where there are currently no adequate studies to assess safety and efficacy.

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