Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: Looking at the published evidence

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In allergen immunotherapy there is debate as to whether polysensitized patients are best treated with many allergens simultaneously (chosen according to the sensitization profile, a predominantly North American approach) or a single allergen (chosen according to the most clinically problematic allergy, a predominantly European approach). In patients seeking treatment for moderate-to-severe respiratory allergies, polysensitization is more prevalent (range, 50% to 80%) than monosensitization in both the United States and Europe. Safe, effective, single-allergen preparations will most likely have been tested in polysensitized patients. In robust, large-scale clinical trials of grass pollen sublingual tablets, polysensitized patients benefited at least as much from allergen immunotherapy as monosensitized patients. A recent review of multiallergen immunotherapy concluded that simultaneous delivery of multiple unrelated allergens can be clinically effective but that there was a need for additional investigation of therapy with more than 2 allergen extracts (particularly in sublingual allergen immunotherapy). More work is also required to determine whether single-allergen and multiallergen immunotherapy protocols elicit distinct immune responses in monosensitized and polysensitized patients. Sublingual and subcutaneous multiallergen immunotherapy in polysensitized patients requires more supporting data to validate its efficacy in practice. (J Allergy Clin Immunol 2012;129:929-34.)

Key words: *Allergy, allergen immunotherapy, polysensitization, monosensitization, polyallergic, subcutaneous immunotherapy, sublingual immunotherapy, safety, efficacy*

In the field of allergen immunotherapy, there is much debate as to whether polysensitized patients are best treated with several allergens (chosen according to the individual's sensitization profile)[1] or a single allergen (corresponding to the most clinically problematic allergy).[2] We looked at the evidence for the efficacy and safety of these 2 approaches in polysensitized patients. We consider here that single-allergen immunotherapy includes the use of extracts containing several closely related allergens (eg, a 5-grass-pollen extract). Conversely, we consider that multiallergen immunotherapy refers to mixtures with little or no cross-reactivity (eg, grass pollen, tree pollen, weed pollen, house dust mite [HDM], and animal dander).

POLYSENSITIZATION IS MORE PREVALENT THAN MONOSENSITIZATION

Data from 11,355 participants in the first European Community Respiratory Health Survey (median age, 34 years) tested with a panel of 4 to 9 skin prick tests, 4 to 5 serum allergen-specific IgE measurements, or both showed that, depending on the center and the test methods, 57.0% to 67.8% of European populations were not sensitized to any of the test allergens, 16.2% to 19.6% were monosensitized, and 12.8% to 25.3% were polysensitized.[3]

Skin sensitization to common indoor and outdoor allergens in the US general population aged 6 to 59 years was investigated in the second and third National Health and Nutrition Examination Surveys (NHANES II [1976-1980] and NHANES III [1988-1994]). In NHANES III 10,863 patients participated in skin testing: 45.7% were not sensitized to any of the test allergens, 15.5% were monosensitized, and 38.8% were polysensitized.[4] Baatenburg de Jong et al[5] tested allergen sensitization in 9044 children referred to a regional clinical laboratory in The Netherlands: 60.1% were found not to be sensitized to any of the 13 food and inhalant allergens tested, 12.4% were monosensitized, 18.9% were sensitized to 2 to 4 allergens, and 8.6% were sensitized to 5 or more allergens. Hence polysensitization is more prevalent than monosensitization in the general population.

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Abbreviations used
DBPC: Double-blind, placebo-controlled
HDM: House dust mite
NHANES: National Health and Nutrition Examination Survey
SCIT: Subcutaneous allergen immunotherapy
SLIT: Sublingual allergen immunotherapy

Polysensitization is much more prevalent in patients consulting allergists. In the French Odissee study, 62% of 4227 patients registered by 264 physicians were polysensitized.[6] In a US study of 1338 patients with objectively diagnosed mild-to-moderate asthma, Craig et al[7] reported that only 5% were not sensitized and that 81% of the sensitized patients reacted to 3 or more allergens. The use of component-based diagnostic tests with purified natural or recombinant allergens has revealed that a significant minority of polysensitized patients have IgE against highly cross-reactive panallergens (ranging from 10% for calcium-binding proteins to around 40% for profilin).[8] Similarly, the majority of participants in recent allergen immunotherapy clinical trials were polysensitized.[9,10]

STRATEGIES FOR ALLERGEN IMMUNOTHERAPY IN POLYSENSITIZED PATIENTS

Meta-analyses of double-blind, placebo-controlled (DBPC) trials and recent, large, well-designed, well-powered studies using standardized allergen preparations have generated high levels of evidence in favor of the efficacy of allergen immunotherapy.[11] However, the European and US practice guidelines for subcutaneous allergen immunotherapy (SCIT) differ significantly. In Europe most formulations are single-allergen extracts, whereas preparations in the United States contain an average of 8 different components.[12] The prevailing view in Europe is that (1) a polysensitized patient is not necessarily polyallergic and (2) depending on the seasonality of multiple allergen exposure, multiple allergies do not always constitute a clinical problem. The most troublesome allergy is then treated with a single-allergen preparation.[2] The predominant view in the United States is that there is an advantage in treating as many of the patient's actual or potential sensitizations/allergies as possible.[1] American allergists prefer to include all relevant allergens because of the concern over the significant time investment needed in SCIT, especially during the build-up phase. If a patient with both seasonal grass and weed symptoms and perennial cat-induced symptoms is only treated for one of these 3 allergens after a lengthy build-up schedule, the allergist might have difficulties explaining the use of this strategy if exposure to the 2 untreated allergens provokes troublesome symptoms. In this situation standard US practice is to treat all relevant allergens.

SINGLE-ALLERGEN SUBLINGUAL ALLERGEN IMMUNOTHERAPY IN MONOSENSITIZED VERSUS POLYSENSITIZED PATIENTS

Efficacy

Given that only a small proportion of allergic patients are monosensitized, most clinical trials of allergen immunotherapy will have been performed in polysensitized participants (unless monosensitization is an inclusion criterion). Most such trials include a sensitization screening panel of single-allergen extracts. Malling et al[9] performed a *post hoc* analysis of a recent multinational, well-powered, DBPC clinical trial of a once-daily 5-grass-pollen sublingual tablet formulation (Table I).[13] The Average Rhinoconjunctivitis Total Symptom Score during the pollen season in the placebo group and 2 treatment groups did not differ significantly according to sensitization status. Malling et al[9] concluded that sensitization status was not a significant baseline covariate and that "the risk-benefit ratio validates the use of 300 IR [five-grass pollen] tablets in clinical practice in all of these patient subgroups, regardless of … sensitization status." However, the trial in question featured a somewhat narrow definition of polysensitization/polyallergy; patients sensitized to allergens other than grass pollen were included in the study only if the said allergens did not induce potentially confounding symptoms during the grass pollen season. Hence a common clinical situation for which multiallergen immunotherapy is often considered (ie, ≥1 seasonal allergies with a concomitant allergy to ≥1 perennial allergens, such as animal dander or HDM) was not taken into account by the latter study.

The results of a similar *post hoc* analysis of the first year of a 3-year DBPC trial[14] evaluating the efficacy of sublingual allergen immunotherapy (SLIT) with a once-daily *Phleum pratense* tablet were reported in abstract format by Emminger et al.[10] Three sensitization groups were constituted (Table I): grass pollen monosensitization, polysensitization to grass pollen and tree pollen (and possibly other allergens), and polysensitization to grass pollen and at least 1 other allergen (but not tree pollen). A narrow definition of polysensitization/polyallergy was again applied: patients with confounding allergies were not included. Compared with the placebo group, all 3 sensitization groups had significantly lower median daily symptom (all $P < .0001$) and medication (all $P < .0001$) scores (Table I). Indeed, the tree-polysensitized group showed the greatest reduction in median daily symptoms, and the non–tree-polysensitized group showed the greatest reduction in median daily medication scores, although the statistical significance of these differences was not tested. Hence single-allergen SLIT was again found to be clinically effective in both polysensitized and monosensitized patients.

Ciprandi et al[15-17] have published several reports on the use of primarily single-allergen SLIT in polysensitized adults and children. In a prospective, open, observational study, 165 polysensitized adult patients with confirmed allergic rhinitis, asthma, or both (Global Initiative for Asthma criteria) received 1 year of SLIT with a single extract, and 65 received a mixture of 2 extracts.[15] The mean number of skin sensitizations per patient was 3.65, with the most common being grasses (81.6%), *Parietaria* species (48.4%), and *Dermatophagoides* species (46.7%). The significant decrease in symptom and medication scores for the study population as a whole and the lack of systemic reactions after 1 year of treatment in both groups prompted the authors to conclude that single-allergen SLIT (administered to 71% of the patients) was safe and effective in polysensitized patients. Efficacy results for the groups of patients treated with single and multiple allergens were not reported separately. A further report on a similar cohort of 167 polysensitized patients treated primarily (73.6%) with a sublingual single-allergen extract (grass or HDM) stated that the mean score on the Rhinoconjunctivitis Quality of Life Questionnaire improved from 3.96 at baseline to 2.89 after 1 year of allergen immunotherapy relative to placebo ($P < .01$: a 1-point reduction is considered clinically relevant).[16]

TABLE I. Summary of 2 large-scale DBPC clinical trials of single-allergen grass pollen sublingual tablet formulations in polysensitized and monosensitized patients with allergic rhinoconjunctivitis

	Malling et al[9]	Emminger et al[10]
Study description and population	*Post hoc* analysis of a DBPC clinical study of a total of 628 adults with moderate-to-severe grass pollen–induced allergic rhinoconjunctivitis	*Post hoc* analysis of year 1 of a 3-year DBPC clinical study of a total of 568 adults with grass pollen–induced allergic rhinoconjunctivitis
SLIT formulation	Once-daily sublingual tablets containing extracts of 5 related grass pollens at doses of 100, 300, or 500 IR or placebo	Once-daily sublingual tablets containing *Phleum pratense* pollen extract) at a dose of 75,000 SQ-T/2,800 bioequivalent allergen units or placebo
SLIT regimen	Once daily, with 4 months of preseasonal treatment and then coseasonal treatment	Once daily, with 4 months of preseasonal treatment and then coseasonal treatment
Efficacy end point	ARTSS	ARTSS plus 2 additional ocular symptoms (eye redness and grittiness)
Sensitization groups	Monosensitization vs polysensitization (>51.5% of the participants were polysensitized)	Monosensitization to grass pollen (28%); polysensitization to grass pollen and tree pollen (and possibly other allergens [37%]); polysensitization to grass pollen and ≥1 other allergens (but not tree pollen [35%])
Efficacy results	Placebo group (ARTSS) Overall: 4.93 ± 3.23 Monosensitized: 4.59 ± 3.06 Polysensitized: 5.18 ± 3.34 300-IR group (ARTSS) Overall: 3.58 ± 2.98 Monosensitized: 3.93 ± 3.01 Polysensitized: 3.25 ± 2.93 500-IR group Overall: 3.74 ± 3.14 Monosensitized: 3.74 ± 2.90 Polysensitized: 3.74 ± 3.35	No direct monosensitization vs polysensitization comparison but significantly lower ($P < .0001$) median symptom scores (by 31%, 44%, and 30% for the treated monosensitized, polysensitized grass plus tree, and polysensitized grass plus other patients, respectively) and medication scores (by 49%, 27% and 60%, respectively) than for placebo
Safety profile	Similar safety profiles across all sensitivity/sensitization subgroups	Not reported

ARTSS, Average Rhinoconjunctivitis Total Symptom Score; *IR*, index of reactivity.

Likewise, a significant improvement in quality of life was observed after 2 years of SLIT in 87 patients (two thirds of whom received a single allergen extract).[17] However, the open design and the lack of a control group decreased the level of evidence provided by this work.

Safety

In the study analyzed by Malling et al,[9] most of the adverse reactions to active treatment were local (eg, oral pruritus or throat irritation) and mild to moderate in severity and resolved spontaneously without further action.[13] There were no obvious safety profile differences between polysensitized and monosensitized participants.[9] Ciprandi et al[15] did not observe any systemic reactions and concluded that predominantly single-allergen SLIT was safe in both polysensitized and monosensitized patients.

SINGLE-ALLERGEN SCIT IN MONOSENSITIZED VERSUS POLYSENSITIZED PATIENTS

To the best of our knowledge, no single-allergen SCIT trials have been specifically designed to compare efficacy in monosensitized and polysensitized patients. However, a recent, large-scale, DBPC randomized controlled trial demonstrating the safety and efficacy of single-allergen SCIT featured a high proportion of polysensitized patients (77%).[18] There were no significant differences between the polysensitized and monosensitized subgroups in terms of symptom score, medication score, quality of life, and overall satisfaction.

MULTIALLERGEN IMMUNOTHERAPY

Despite the widespread use of multiallergen immunotherapy, a recent review has highlighted the low level of evidence for the efficacy and safety of this approach (whether for SCIT or SLIT). A comprehensive search of the English-language and non–English-language literature on multiallergen immunotherapy for patients with allergic rhinitis and asthma published between 1961 and 2007 by Nelson[19] identified 13 studies in which 2 or more unrelated allergens were simultaneously administered. Few were well-designed, well-powered DBPC trials. Head-to-head comparative data with single-allergen regimens were rarely provided. Population sizes ranged from 24 to 208. Nelson concluded that simultaneous delivery of multiple unrelated allergens can be clinically effective but that there was a need for additional investigation of therapy with more than 2 allergen extracts (particularly in SLIT).

Of course, the investigation of multiallergen immunotherapy in monosensitized patients is discouraged for ethical reasons. Hence most head-to-head studies have compared single-allergen immunotherapy in monosensitized patients with multiallergen immunotherapy in polysensitized patients. Some multiallergen mixtures also face formulation problems (at least with respect to the regulatory situation in Europe) because correct dosage and

pharmaceutical stability can be hard to achieve, with a documented risk of proteolytic degradation of allergens in mixtures containing cockroach or mold extracts.[20,21]

MULTIALLERGEN SLIT IN POLYSENSITIZED PATIENTS

To examine whether the efficacy of SLIT with a single allergen was reduced by combination with other allergen extracts, Amar et al[22] randomized 54 patients to one of three 10-month treatment arms with placebo, single-allergen SLIT (standardized timothy extract administered as drops: 19 μg of Phl p 5 daily) or multiallergen SLIT (the same dose of timothy extract plus 9 additional pollen extracts) and scored symptoms and medication intake during the 2008 grass pollen season in Denver, Colorado. The authors referred to "predominantly polysensitized patients," according to the results of skin prick tests. There were no significant symptom or medication score differences versus placebo in either treatment group. The researchers ascribed this finding to very low grass pollen counts and the small sample size. However, significant posttreatment changes in various immune parameters for the single-allergen group (but not the multiallergen group) prompted Amar et al[22] to suggest that the coadministration of multiple allergens interfered with the effectiveness of timothy grass SLIT.

MULTIALLERGEN SCIT IN POLYSENSITIZED PATIENTS

Efficacy

Bousquet et al[23] performed a DBPC trial of a rush SCIT protocol in 70 immunotherapy-naive adults with allergic rhinitis (with or without asthma). Patients monosensitized to orchard grass received orchard grass extract SCIT or a placebo, whereas polysensitized patients received SCIT with the same dose of orchard grass extract and up to 3 other (many seasonal) allergens. Only the monosensitized patients showed a significant clinical effect of the standardized active treatment versus placebo. The authors suggested that polysensitized patients might require higher doses of allergen for equivalent efficacy.

Kim et al[24] also compared multiallergen SCIT in polysensitized patients with single-allergen SCIT in monosensitized patients. The study investigated 130 children with allergic asthma: 62 (mean ± SD age, 7.6 ± 0.3 years) were polysensitized to HDM and an average of 4 other allergens and received corresponding mixtures, whereas 68 (mean ± SD age, 6.3 ± 0.3 years) were monosensitized to HDM and received HDM-only extracts. Both groups received the same dose of HDM antigen. The (nonoptimal) scoring system comprised a single interview-based assessment of dyspnea, wheezing, and cough intensity (on a 0- to 2-point scale) before immunotherapy and then again after at least 18 months of immunotherapy. The polysensitized patients had a significantly greater baseline symptom burden than the monosensitized group. In both groups the mean postallergen immunotherapy symptom scores were significantly ($P < .05$) lower than the preallergen immunotherapy scores (with mean decreases from 5.3 ± 0.1 to 2.4 ± 0.1 in polysensitized patients and from 5.0 ± 0.1 to 1.7 ± 0.1 in monosensitized patients). However, the reduction was significantly ($P < .05$) less intense in the polysensitized group. In the monosensitized group HDM-specific IgE levels were significantly lower after immunotherapy (59.2 ± 21.9 IU/mL) than before (97.3 ± 34.2 IU/mL, $P < .05$). In contrast, HDM-specific IgE levels did not change significantly in the polysensitized group (65.8 ± 21.6 IU/mL before immunotherapy and 73.2 ± 40.2 IU/mL afterward). These findings prompted the authors to suggest that multiallergen immunotherapy is less effective in polysensitized patients than single-allergen allergen immunotherapy in monosensitized patients. However, the study had several shortcomings; it lacked 1 or more placebo groups and did not control for differences in seasonal and perennial allergen exposure when comparing polysensitized versus monosensitized patients over an 18-month period.

Safety

Agostinis et al[25] specifically sought to determine whether multiallergen SLIT increases the risk of side effects. In a survey of 433 children (age range, 3-18 years), 179 participants received single commercial extracts (grass, birch, or *Parietaria* species pollen), and 254 participants received a mixture of grass/tree/weed pollen extracts. During a follow-up period ranging from 6 to 24 months, 42.5% of the single-allergen SLIT group had noted an adverse reaction in their study diaries compared with 40.3% of the multiallergen SLIT group. The authors did not observe any significant safety profile differences between the groups.

Barth et al[26] looked at safety in 147 adult patients receiving a single injection or 2 parallel injections of standardized single-allergen extracts (variously pollen, HDM, molds, animal dander, and Hymenoptera venom) from 6 different manufacturers. Even though there was a slightly higher rate of adverse reactions during the dose-increase phase in the parallel-injection group, the difference was not significant. However, the single-allergen injection and parallel-injection groups were not homogenous or matched in terms of allergen dose.

Kim et al[24] did not report on safety for their polysensitized vs monosensitized patients.

IMMUNE RESPONSES TO SINGLE-ALLERGEN OR MULTIALLERGEN SLIT IN MONOSENSITIZED VERSUS POLYSENSITIZED PATIENTS

It is not known whether single-allergen and multiallergen immunotherapy protocols elicit distinct immune responses. However, studies in this field are complicated by the fact that monosensitized and polysensitized patients appear to differ in terms of their immune reactivity. For example, Prigione et al[27] monitored 40 monosensitized immunotherapy-naive children with allergic rhinitis, asthma, or both over a 2-year period. They found that PBMCs from patients who remained monosensitized produced higher levels of IFN-γ in response to allergen challenges than cells from patients who had become polysensitized. Likewise, a higher percentage of IL-10–producing cells was detected in allergen-specific T-cell lines derived from patients who remained monosensitized. Similarly, Pène et al[28] found that PBMCs from monosensitized and polysensitized patients had different IL-4 and CD23 profiles.

Few studies have investigated immune parameters in head-to-head comparisons of single-allergen versus multiallergen SLIT regimens. Amar et al's comparison[22] of a single grass pollen extract with a mixture of 9 pollen extracts found a lower increase in serum allergen-specific IgG_4 levels and less downregulation of IFN-γ levels when using the allergen mix, prompting the researchers to suggest a reduction in SLIT efficacy in the

multiallergen group. Likewise, the absence of a significant change in specific IgE levels in the sera of polysensitized asthmatic children during allergen immunotherapy prompted Kim et al[24] to suggest that multiallergen SLIT in polysensitized patients was less effective than single-allergen SLIT in monosensitized patients. These observations suggest competition between the various allergens for targeting immune cells.

IMMUNE RESPONSES TO SINGLE-ALLERGEN OR MULTIALLERGEN SCIT IN MONOSENSITIZED VERSUS POLYSENSITIZED PATIENTS

Limb et al[29] investigated long-term changes in serum-specific IgE antibody levels in 82 children having undergone at least 18 months (median, 27 months) of SCIT (with an average of 5 allergens) or placebo injections. All but one of the patients were polysensitized at study entry, with an average of 7 positive skin test results. The mean age at study entry was 8 years (range, 5-12 years), and that at follow-up was 23 years (range, 19-31 years). At follow-up, there were no significant differences between the treatment groups (whether considering either individual allergens or all allergens pooled) and the placebo group in terms of serum specific IgE levels. Eight to 16 years after treatment discontinuation, patients in the allergen immunotherapy group showed a significantly greater reduction in skin test sensitivity when results from all allergens were pooled (36% vs 26% in the placebo group, $P = .03$).

The wider issue of potential antigenic competition has been investigated by the vaccine industry in the context of subcutaneously administered combination pediatric vaccines against multiple infectious diseases; it has been reported that a combination vaccine elicits a weaker immune response than equivalent doses of the separate components.[30]

DISCUSSION

When looking at the evidence for multiallergen and single-allergen immunotherapy in polysensitized patients, the practitioner should adopt an evidenced-based approach.[11] In patients with seasonal allergic rhinitis, subcutaneously and sublingually administered single-allergen preparations (grass pollen extracts) are clearly efficacious and safe in study populations featuring a majority of polysensitized participants. Further studies with different allergens and patient profiles are required to provide absolute confirmation.

Is there an advantage in administering multiple allergens? There are too few well-designed clinical trials of multiple-allergen immunotherapy, and as pointed out by Nelson,[19] the results have been contradictory. The US practice parameter update states that "inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective."[1] Most published studies on multiallergen immunotherapy featured 2 to 4 unrelated allergens. Thus the current US practice of using an average of 8 allergens in "named-patient preparations" is not presently supported by direct evidence from large clinical trials.[12] Multiallergen immunotherapy also faces formulation issues in a new era of registered and standardized allergen immunotherapies with numerous quality, efficacy, and safety constraints.[20,21]

There is also a need for more work on (1) *in vivo* antigen competition, (2) the relationship between immunologic parameters and clinical symptoms of allergy, (3) potential SLIT versus SCIT differences in the processing and recognition of allergens, and (4) the relationship between sensitization and treatment effects (ie, Is allergen immunotherapy with a perennial allergen as effective in patients with concomitant seasonal allergies and *vice versa*?).

CONCLUSION

The US practice guidelines recommend that physicians treat with "relevant" allergens, although the interpretation of "relevant" can be problematic. For grass pollen allergens, high-quality data from well-designed DBPC trials show that polysensitized patients benefit just as much from single-allergen immunotherapy as monosensitized patients. On the basis of the published data, multiallergen immunotherapy in polysensitized patients, whether delivered sublingually or subcutaneously, requires more supporting evidence from well-designed, well-powered DBPC clinical trials to validate its efficacy in practice.

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Key messages

- **Epidemiologic and clinical trial data show that 51% to 81% of US and European patients are polysensitized (according to skin prick test results, IgE assay results, or both). However, a polysensitized patient is not necessarily clinically polyallergic.**
- **In Europe most allergen immunotherapy formulations are single-allergen extracts (even for polysensitized patients), whereas preparations in the United States contain an average of 8 different components.**
- **In recent, large, well-designed, well-powered clinical trials, single-allergen immunotherapy with grass pollen extract has proved to be as safe and effective in polysensitized patients as in monosensitized patients.**
- **Sublingual or subcutaneous multiallergen immunotherapy in polysensitized patients needs more supporting data from large clinical trials to validate it as a treatment option.**

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