

Single vs multiallergen sublingual immunotherapy in the polysensitized patient: a pilot study

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Background: Sublingual immunotherapy (SLIT) has emerged as an effective and exceptionally safe method of treatment of the atopic patient. However, the optimal number of allergens that should be included in the SLIT treatment regimen for the polysensitized patient is not known and practices vary widely. This study aims to compare the efficacy of single-allergen SLIT with pauci-allergen vs multiallergen aqueous SLIT in polysensitized patients.

Methods: Sixteen subjects sensitized to 6+ allergens were enrolled in the study. Subjects were blinded and randomized to SLIT treatment groups that included 1 (single), 3 (pauci), or all sensitized allergens (multi). Allergens selected were those to which the patient was most sensitized and correlated with history. Primary outcomes included daily allergy medication use, weekly Rhinoconjunctivitis Symptom Score (RCSS), and the mini-Rhinoconjunctivitis Quality of Life Questionnaire (m-RQLQ). All metrics were measured at baseline, 6 weeks, 3 months, 6 months, and 9 months.

Results: There were significant decreases from baseline in RCSS and m-RQLQ scores in all study groups at each

interval after beginning SLIT ($p < 0.05$). There was no significant decrease in number of daily allergy medications used regardless of number of allergens in patient's treatment vial ($p = 0.50$). No significant differences emerged based on number of allergens used.

Conclusion: Single-antigen, pauci-antigen, and multiantigen aqueous SLIT significantly improved allergy symptoms. There was no significant difference observed in efficacy of single-allergen SLIT vs pauci-allergen or multi-allergen SLIT in polysensitized patients. © 2018 ARS-AAOA, LLC.

Key Words:

allergens; aeroallergens; sublingual immunotherapy; allergy immunotherapy; allergic rhinitis

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Over the past several years, sublingual immunotherapy (SLIT) has emerged as an effective, and potentially safer, method of allergy immunotherapy compared to subcutaneous immunotherapy (SCIT).¹ Unlike SCIT, SLIT can be administered safely at home and has an exceptionally low risk of systemic reactions and anaphylaxis. While the rate of anaphylaxis in SCIT is 3:100,000, only 11 cases of SLIT anaphylaxis have been reported with over 1 billion

doses administered.¹ However, the number of allergens included in SLIT varies widely, with particular disparity between typical U.S. and European practices.

Polysensitization and polyallergy are very common, with some studies showing nearly an 80% rate of multiple-allergen sensitivities.²⁻⁴ Additionally, it has been proposed that polysensitized patients may have a lower level of immune reactivity than monosensitized patients, making immunotherapy less clinically effective in these patients.⁵ In Europe, patients are typically treated with their most robustly positive antigen alone. This has been shown to be effective in reducing symptoms.^{6,7} Alternatively, in the United States, patients are more commonly treated with several, or sometimes, all, of the allergens to which they are allergic.² This difference in treatment algorithm is due, in part, to the lack of high-quality studies directly comparing single-allergen, pauci-allergen, and multiallergen SLIT in the polyallergic patient. One previous study has attempted to answer this question, but their results failed to

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produce symptom reduction in treatment arms vs placebo.⁸ Another study indicated that SLIT therapy with 2 allergens was more effective than a single allergen, but it included patients who were only sensitized to 1 of the targeted allergens and no others.⁹ The present study attempts to determine if treatment with single-allergen SLIT, pauci-allergen SLIT (3 antigens), or multiallergen SLIT (6+) yields superior results in patients who are allergic to 6+ allergens.

Subjects and methods

Subjects

Institutional Review Board approval was obtained from San Antonio Military Medical Center protocol number C.2015.094 prior to initiation of this study. Subjects were identified from all new patients seen in the Otolaryngic Allergy clinic at Brooke Army Medical Center from April 2015 to July 2016. In order to be included, subjects had to be over 18 years of age and have at >6 allergens to which they were both clinically affected and to which they reacted on skin-prick or immunoglobulin E (IgE) testing. Wheal size of 4 mm or more on skin-prick and IgE values of >0.70 kU/L on specific IgE testing were considered positive test values. The majority of patients had both seasonal and perennial allergens to which they were positive on testing and history (15/17). The 2 patients who experienced only seasonal allergy symptoms and corresponding test results were randomized to separate groups. Exclusion criteria were: patients <18 years old, asthmatics, pregnant women, human immunodeficiency virus (HIV)-positive patients, and vulnerable populations including prisoners, institutionalized individuals, or patients mentally unable to give informed consent. Subjects were voluntarily recruited into the study and were allowed to withdrawal at any time during the course of the investigation.

Randomization and treatment

Subjects were randomized to 1 of 3 groups using a random number generator. Subjects in the first group (number 1) would receive aqueous SLIT treatment containing only their most strongly-sensitized, clinically significant allergen. If there were multiple allergens to which they were equally strongly-sensitized based on IgE or skin-prick testing, the allergen which correlated most with their clinical history or the allergen which was most abundant in the region was chosen (based on pollen count data collected from the Allergy Clinic at Wilford Hall Medical Center, Lackland AFB, TX). If 1 allergen could not be selected on these bases, then the allergen that was shown to have more cross-reactivity to other allergens to which the subject was sensitized would be chosen. Subjects in the second group (number 2) would receive SLIT treatment containing their top 3 allergens (again chosen based on the above protocol), and subjects in the third group (number 3) would receive SLIT containing all allergens to which they were sensitized on skin-prick testing or IgE testing. This resulted in subjects often receiving a

variety of both seasonal and perennial allergens based upon the above noted protocol. However, some patients (particularly those in the first group [single allergen group]) only received a single seasonal or perennial allergen. Standardized allergens were used when available and subjects underwent escalation and maintenance treatment according to the dosing guidance from the American Academy of Otolaryngic Allergy (AAOA).¹⁰ Therefore, the final dosing of allergens varied based on these recommendations.

Allergens included for use in both testing and aqueous SLIT were as follows: *Penicillium*, cladosporioides, *Helminthosporium*, *Fusarium*, *Epicoccum*, *Curvularia*, *Aspergillus*, *Alternaria*, sagebrush, Russian thistle, ragweed, plantain, pigweed, nettle, marshelder, lamb's quarters, dock sorrel, cocklebur, kochia, cockroach, dog, cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Timothy, rye, Johnson, Bermuda, bahia, walnut, sycamore, pecan, palm, olive, oak, mulberry, mountain cedar, mesquite, hackberry, elm, cottonwood, cypress, box elder, birch, ash, alder, histamine (positive control), and glycerin (negative control).

Data collection

Data included weekly Rhinoconjunctivitis Symptom Scores (RCSS), daily medication logs, and a Mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) every 3 months, as well as an adverse symptoms/continued qualification checklist. These were administered prior to initiation, after beginning SLIT, and were continued every 3 months for 9 months total. Concomitant medications were allowed and documented throughout the study. These included a nasal steroid spray (such as fluticasone), a nasal antihistamine spray (such as azelastine), a second generation antihistamine (such as loratadine, fexofenadine, etc.), and a first generation antihistamine (such as diphenhydramine).

Statistical analysis

Summary statistics for symptom questionnaire scores and number of medications were given as means with standard deviation (SD). They were analyzed using a repeated measures analysis of variance (ANOVA). If the interaction effect was significant then a Bonferroni adjustment for the allergen comparisons was implemented at each time point. Statistical significance was defined as a *p* value of 0.05 or less, and all reported *p* values were based on 2-sided tests. Analysis was performed using JMP v12.0 (SAS Institute, Inc., Cary, NC).

Results

A total of 17 patients were enrolled in the study between April 2015 and June 2016. Sixteen of the patients completed the follow-up visits and questionnaires through 6 months with only 1 patient being lost to follow-up prior to the 6 week visit. The intake data for this 1 patient was

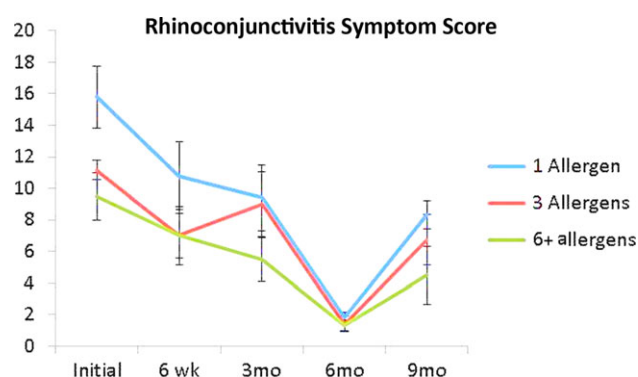


FIGURE 1. RCSS for all groups prior to and throughout SLIT treatment.

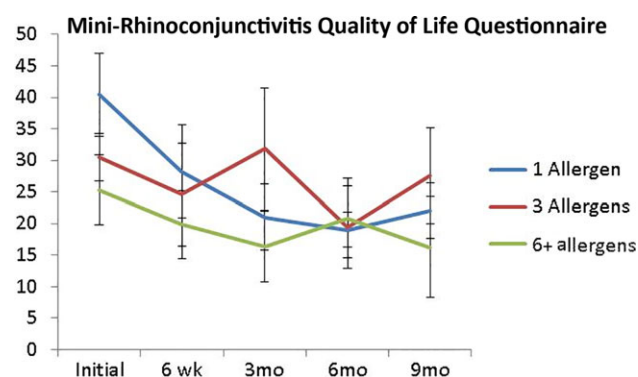


FIGURE 2. m-RQLQ for all groups prior to and throughout SLIT treatment.

excluded from final analysis. Eleven patients completed the follow-up through 9 months. Of the patients enrolled, 7 were female and 10 were male. The majority of patients were positive on testing and history to both a variety of seasonal and perennial allergens (15/17 patients) while the 2 who only had seasonal allergen sensitivities were randomized to separate groups. For seasonal allergens, pollen counts varied substantially over the 15 month course of the study. However, levels of pollen during our study timeframe were typical for the location and the respective seasons compared to prior years.

The mean baseline RCSS score was 12 for all subjects with averages of 40.3 ± 14.8 (mean $\pm$ SD) for single-allergen group, 30.5 ± 9.2 for pauci-allergen group, and 25.3 ± 13.5 for multiallergen group (Fig. 1). There were significant decreases in RCSS scores for all study groups at each measured interval compared to baseline SLIT ($p < 0.0001$). There were no statistically significant differences between allergen groups ($p = 0.593$).

The mean baseline mini-RQLQ score was 32 for all subjects with averages of 15.8 ± 4.3 for the single allergen group, 11.1 ± 1.5 for the pauci-allergen group, and 9.5 ± 3.7 for the multiallergen group (Fig. 2). There were significant decreases from baseline in mini-RQLQ scores in all study groups at each measured interval after beginning

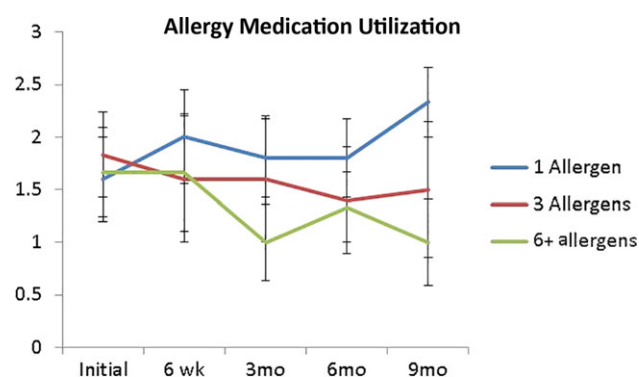


FIGURE 3. Number of allergy medications utilized for all groups prior to and throughout SLIT treatment.

SLIT. There were no statistically significant differences between allergen groups ($p = 0.163$).

The mean number of allergy medications at baseline was 1.8. Medications were recorded 1 month prior to beginning treatment and at 6 weeks, 3 months, 6 months, and 9 months after starting treatment. The subjects kept daily medication logs, which were reviewed at each time interval. The medications were not standardized prior to the beginning of the study, so total number of medications was the only variable tested for significance. Overall, there was no significant decrease in number of daily allergy medications used, regardless of number of allergens in patient's SLIT treatment ($p = 0.50$) (Fig. 3).

Discussion

Polysensitization is more common than monosensitization in the general population. One study of over 10,000 people in the United States showed that 38% were sensitized to more than 1 allergen, while only 15% were sensitized to a single allergen.¹¹ Given this prevalence, the question of the optimal number of allergens to administer to polysensitized individuals is relevant in terms of both efficacy and cost.

Thus far, there have been 2 general treatment approaches regarding the number of allergens included in immunotherapy for patients with multiple sensitivities. In Europe, polysensitized patients are typically treated with only their most highly-reactive clinically significant allergen. This practice arises from data that suggest including multiple allergens in a SLIT mixture may make the treatment overall less clinically and immunologically effective.⁸ Another variable that may influence this practice pattern is the fact that SLIT is a covered benefit throughout most of Europe, and reimbursement is independent of number of allergens administered.

Alternatively, in the United States, patients are typically treated with aqueous SLIT including all "relevant" allergens. This typically includes those allergens to which a patient is sensitized and to which they experience clinical symptoms. Based on this practice, the mean number of allergens included in aqueous SLIT treatments in the United States is 8.¹² By contrast to tablet SLIT, aqueous SLIT is not

U.S. Food and Drug Administration (FDA) approved and is therefore, largely uncovered by insurance in the United States.¹² Because recommended dosing of aqueous SLIT already requires 50 to 100 times more allergen than SCIT, establishing relative effectiveness of differing dosing strategies could represent significant cost savings for individual and the U.S. healthcare system as a whole.

Few studies have attempted to compare these opposing approaches to SLIT administration, though none have clearly resolved the question with high-level data. In 2012, Calderon et al.² evaluated the published evidence on the topic of single-allergen vs multiallergen SLIT in polysensitized patients. The article found that, overall, there has not been a definitive study that answers the question of the optimal SLIT dosing. Another study by Malling et al.,⁷ examined the efficacy of a 5-grass SLIT tablet in monosensitized vs polysensitized patients. They found that the tablet was equally effective in both groups. Because of the high level of cross-reactivity between grasses, this was considered to be a “single-allergen” study though there were 5 distinct grass allergens in the tablet. Another study looking at single-allergen use in monosensitized vs paucisensitized patients found that the SLIT treatment was effective in all groups without significant difference in improvement based on sensitization.¹³ Finally, Marogna et al.⁹ examined SLIT treatment with birch and grass allergens, concluding that SLIT treatment with 1 of these allergens had extended clinical efficacy during the peak season for the other allergen. These studies gave credence to the notion that a single-allergen SLIT regimen could be effective in polysensitized patients. However, none compared the efficacy of single-allergen vs pauci-allergen vs multiallergen aqueous SLIT treatment.

Amar et al.⁸ failed to show significant clinical differences (symptoms, medication use) in treatment with any SLIT cocktail vs placebo, which the authors attributed to abnormal climate conditions in their geographic area. By contrast, the present study demonstrated a significant clinical improvement in both validated symptom questionnaires, RCSS and mini-RQLQ, in all treatment groups as early as 6 weeks after beginning therapy. This universal improvement calls into question the practice of treating with multiantigen aqueous SLIT. However, there was a trend

toward even lower symptoms scores in the multiallergen group, which may indicate greater clinical benefit with additional allergens. Failure to demonstrate differences in effect among groups may be secondary to low sample size. There was no significant difference in allergy medication usage throughout the study for any treatment group.

There are several limitations to the present study. A sample size calculation was performed prior to initiation of this study and was found to have adequate power at a sample size of 10 subjects in each group. We were not able to reach the anticipated number of study participants due to facility workflow constraints. This limited the power of our study, possibly resulting in underrepresentation of true differences among treatment groups. Another limitation of our study is the fact that data are available for only 9 months of treatment. Considering data that suggest additional benefit from continuing immunotherapy for 3 years, it is possible that statistically significant differences would emerge with longer duration of therapy and follow up.¹⁴ The final limitation of our study is that we did not include a placebo group to which we could compare changes in symptom scores over time.

These findings are clinically relevant in the United States where SLIT treatment is largely uncovered by insurance and the accepted practice includes multiple allergens. This may translate to a potential cost reduction or improved immunologic response for the patient undergoing allergen immunotherapy.

Conclusion

In polyallergic patients, aqueous SLIT significantly improved allergy symptoms on RCSS and mini-RQLQ. However, there was no significant difference in efficacy of single-allergen, pauci-allergen, or multiallergen SLIT. There was no significant difference in allergy medication usage throughout the study for any treatment group. Further investigation with larger, randomized studies is warranted to evaluate the optimal dosing strategy for aqueous SLIT. ☪

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