The efficacy assessment of a self-administered immunotherapy protocol
Frederick M. Schaffer, MD1,2, Larry M. Garner, BA1, Myla Ebeling, RA3, Jeffrey M. Adelglass, MD4, Thomas C. Hulsey, ScD3 and Andrew R. Naples, BS1

Background: We previously reported the safety of a self-administered subcutaneous immunotherapy (SCIT) protocol. Here we report the results of the retrospective efficacy trial of the United Allergy Service (UAS) self-administered SCIT protocol. We hypothesized that by utilizing a slow SCIT buildup phase, designed to attain recommended allergen concentrations on a cumulative basis, efficacious outcomes and clinical relevance would be achieved.

Methods: We enrolled 60 SCIT patients and 56 control patients. The study contrasted baseline and treatment period combined symptom plus medication scores (CSMS) as the primary outcome measure and rhinoconjunctivitis quality of life questionnaire (RQLQ) scores as the secondary study outcome measure. Changes in pollen counts were also examined with regard to effects on these efficacy parameters.

Results: The treatment group showed significantly improved CSMS (standardized mean difference [SMD]: −1.57; 95% confidence interval [CI], −1.97 to −1.18; p < 0.001) and RQLQ (SMD: −0.91; 95% CI, −1.23 to −0.59; p < 0.001). These treatment group outcome measures were respectively improved by 33% and 29% compared to baseline and greater than 40% in comparison to the control group (p < 0.0001). Significant results were also shown when examining these outcome measures with regards to either monotherapy or poly-allergen SCIT. Furthermore, a comparison to recent meta-analyses of SCIT studies showed equivalent efficacy and clinical relevance. Assessment of pollen counts during the baseline and treatment periods further corroborated the efficacy of the UAS SCIT protocol.

Conclusion: These efficacy results, and our previous safety results, show that a carefully designed and implemented self-administered SCIT protocol is efficacious and safe. © 2015 The Authors International Forum of Allergy & Rhinology published by Wiley Periodicals, Inc., on behalf of ARS-AAOA, LLC. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Key Words: allergic rhinitis; allergy immunotherapy; allergy injections; subcutaneous immunotherapy; aeroallergens

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with multiallergen sensitivities. Specifically, we present and discuss the results of a self-administered SCIT retrospective efficacy study using the United Allergy Services (UAS) immunotherapy protocol.

Patients and methods

Patients

All subjects were diagnosed with seasonal or seasonal plus perennial allergic rhinitis (AR) as described. Patients with contraindications consistent with the current recommendations for allergy skin prick testing (SPT) and SCIT utilization were excluded. All patients underwent SPT utilizing relevant extracts consistent with standard practices. Both male and female patients aged 18 to 65 years with diagnosed AR were openly enrolled in the study. Patients who were enrolled and opted for SCIT were deemed treatment patients and those that declined SCIT were deemed control patients.

Study design

To control for geographic differences, patients were primarily recruited from clinics located in Dallas, TX, and San Antonio, TX. Research personnel were blinded to patient identification, age, gender, and primary care clinic affiliation. The study design, informed consent, and execution were approved by the Salus Independent Review Board (IRB) (Austin, TX).

All study subjects were allowed to continue oral and topical antihistamines and nasal steroids prescribed by their physician. Study subjects using systemic steroids were excluded. Individuals enrolled in the study completed validated questionnaires as discussed below (see Assessment).

UAS immunotherapy protocol

Immunotherapy formulation guidelines were in accordance with published recommendations. Due to the documented increased risk of systemic reactions (SR) during the immunotherapy buildup phase (ie, escalation phase), the UAS protocol was designed to complete the buildup phase over a 6-month period. Also, based upon the administration frequency and allergen concentrations used, cumulative allergen dosing is equivalent to current recommendations.

A more detailed description of the UAS SCIT protocol has been recently published.

Assessment

Enrolled subjects completed validated questionnaires for rhinoconjunctivitis symptom scores (SS) in accordance with both the U.S. Food and Drug Administration (FDA) and World Allergy Organization (WAO) recommendations. The medication scores (MS) paralleled the methods of Stelmach et al. The aggregate of the SS and the MS (CSMS) followed previously utilized methods. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) used consists of 28 queries divided into 7 domains.

These questionnaires were initially completed at the end of the baseline year of therapy (2010 to 2011). During this period, all study participants were undergoing pharmacotherapy and avoidance therapy only. After undergoing a further 12 or more months of immunotherapy (2011 to late 2012), the second set of surveys were completed. This survey methodology is consistent with the format used in several previous trials. (See the online Supporting Information for the questionnaires.)

Statistical methods

For each study subject, their SS, MS, CSMS, and RQLQ were averaged for both the baseline and the follow-up assessments. The difference in mean scores between baseline and follow-up was obtained and within group differences were assessed by use of a paired Student t test. Group differences between mean scores at baseline and at follow-up were assessed by use of the Student t test. Standardized mean differences (SMDs) were computed as the mean difference divided by the standard deviation of the mean difference. The SMD inclusion was so that the results from this project could be compared to other published reports which may have used modified assessments of symptom and medication scores.

Adverse events, safety, and compliance determination

Patients were required to report all suspected adverse events to their primary care clinics as soon as possible and to cease continued treatment until evaluated and provided guidance by their physician.

To promote safety and compliance, all patients were only given a single unit-dose vial set and a preprinted IT injection log book that enumerated all required doses to utilize. Patients were instructed to maintain the injection log and to record any pertinent events related to the injections. All patients were interviewed and their logs were reviewed when they returned to the clinic to acquire their next unit-dose vials.

Pollen count analyses

Atmospheric sampling for aeroallergens was performed and reported by certified staff through the American Academy of Allergy, Asthma and Immunology Aerollen Network. Aeroallergen samplers used were approved by the National Allergy Bureau (NAB) and identification/measurements met NAB requirements.

The grass pollen seasons were determined by examining pollen counts of greater than 15 grains/m³ for 3 consecutive days, which defined the season starting date. Whereas, grass pollen counts that were less than 15 grains/m³ for 3 consecutive days defined the season ending date. Weed-based and tree-based pollen seasons were determined by examining the raw data for respective pollen counts of greater than 20 grains/m³ for 3 consecutive days, which defined the season starting date, whereas respective pollen counts...
that were <20 grains/m³ for 3 consecutive days defined the season ending date. The delineation of pollen seasons by these levels are consistent with NAB-defined “moderate” pollen exposure.42–44

**Results**

**Protocol compliance**

One of the 60 individuals in the SCIT treatment group did not comply with the specified treatment protocol and that individual was excluded from the study. Another treatment group participant was compliant for 75% of scheduled injections and he was not excluded from study participation. All other treatment and control group study participants were fully compliant.

**Adverse events and systemic disorders**

One study subject in the SCIT treatment group reported a WAO grade II SR.45 After medical assessment and advisement, this patient’s SCIT protocol was appropriately addressed.5 His SCIT regimen subsequently continued without further clinical incident. Three other participants in the SCIT treatment group reported local reactions without sequelae. There were no reported adverse events by subjects in the control group.

**Patient demographics**

The patient demographics are shown in Table 1.

**Identified allergies**

The most common allergies manifested by both the treatment and control groups are: cedar and oak tree pollens (>60% of treatment group and 40% of controls); Bermuda and Timothy grass pollen (>62% of treatment group and 58% of controls); ragweed pollen (57% of treatment group and 45% of controls); and dust mites (>67% of treatment group and 57% of controls). Also, allergies to oak tree pollen, Timothy grass pollen, and dust mites are shared by 35% of the treatment group and 27% of the control group.

**Rhinoconjunctivitis SS**

Assessment showed that individuals in the treatment group (ie, SCIT therapy) experienced a 35% SS improvement over their baseline scores. The treatment group’s SS improvement in comparison to that of the control group is consistent with a >45% improvement (p < 0.0001; data not shown). Also, the control group experienced a significant increase in SS in year 2 vs year 1 of this study (data not shown; p = 0.05).

**MS**

MS analyses showed that the treatment group had a 30% decrease in medication use (data not shown, p < 0.001). Also, there is a significant decrease in the MS of the treatment group in comparison to the control group’s scores (p < 0.001). In contrast, the control group experienced a significant increased use of medications in the second vs the initial study year (paired SMD of −1.57; p < 0.0001, Table 2). Furthermore, there was a 33% improvement for the treatment group with respect to baseline results and a >40% improvement in comparison to the control group (p < 0.001).

The treatment group’s RQLQ showed a 29% improvement in comparison to baseline results and a 42% improvement in comparison to the control group (p < 0.0001). In contrast, the control group results did not show a significant RQLQ SMD score change during the intervals under assessment (p = 0.7, Table 2). A comparison of RQLQ scores for each of the 7 domains further showed that the treatment group attained significant improvement in 6 of the 7 domains (data not shown).

From a multiallergen perspective, Table 2 depicts the CSMS and RQLQ SMD differences for patient groups with common allergies to oak trees, dust mites, and Timothy grass. In a similar manner, Table 2 shows the results for sizeable patient populations manifesting respective common allergies to ragweed and dust mites, respectively. The CSMS results for the treatment groups with common allergens to oak tree, dust mites, and Timothy grass, or the individual allergens of ragweed or dust mites (all in Table 2) show significant improvement. In contrast, each respective control group showed significant increases (or worsening) of their CSMS scores. With regard to other combinations of manifested allergies, either shared dual-pollen or single-pollen allergies, similar results were evident (data not shown).

The RQLQ SMD results (Table 2) show significant improvement for subjects in the treatment group (mean

### Table 1. Characteristics of treatment and control patients

|                          | Treatment | Control |
|--------------------------|-----------|---------|
| Sex (n)                  |           |         |
| Male                     | 24        | 5       |
| Female                   | 36        | 51      |
| Race (n)                 |           |         |
| White                    | 37        | 34      |
| African American         | 12        | 7       |
| Hispanic                 | 2         | 7       |
| Other                    | 9         | 8       |
| Age (years), mean ± SD   | 37.09 ± 13.92 |       |
| Duration of therapy (years), mean ± SD | 1.22 ± 0.27 |       |
| Administered SCIT-based Aeroallergen extracts (n), mean ± SD | 9.08 ± 1.84 | N/A |

SCIT = subcutaneous immunotherapy; SD = standard deviation.
## TABLE 2. Differences in CSMS and RQLQ for the treatment and control groups

|                                   | n   | Diff: T2-T1 | Paired SMD | CI               | p*  |
|-----------------------------------|-----|-------------|------------|------------------|-----|
| **Medication use in the second vs the initial study year** |     |             |            |                  |     |
| CSMS                              |     |             |            |                  |     |
| Control                           | 56  | 0.56        | 0.34       | -0.06 to 0.73    | 0.01|
| Treatment                         | 60  | -1.84       | -1.57      | -1.97 to -1.18   | <0.0001|
| RQLQ                              |     |             |            |                  |     |
| Control                           | 56  | 0.07        | 0.05       | -0.32 to 0.41    | 0.7 |
| Treatment                         | 60  | -1.24       | -0.91      | -1.23 to -0.59   | <0.0001|
| **Common allergies to oak, dust mite, and Timothy grass** |     |             |            |                  |     |
| CSMS                              |     |             |            |                  |     |
| Control                           | 48  | 0.62        | 0.39       | -0.02 to 0.81    | 0.009|
| Treatment                         | 56  | -1.83       | -1.54      | -1.95 to -1.14   | <0.0001|
| RQLQ                              |     |             |            |                  |     |
| Control                           | 48  | 0.19        | 0.13       | -0.27 to 0.52    | 0.39|
| Treatment                         | 56  | -1.22       | -0.87      | -1.20 to -0.54   | <0.0001|
| **Common allergies to ragweed**   |     |             |            |                  |     |
| CSMS                              |     |             |            |                  |     |
| Control                           | 22  | 0.73        | 0.49       | 0.08 to 1.06     | 0.03|
| Treatment                         | 34  | -1.86       | -1.46      | -2.02 to -0.91   | <0.0001|
| RQLQ                              |     |             |            |                  |     |
| Control                           | 22  | 0.11        | 0.07       | -0.54 to 0.69    | 0.7 |
| Treatment                         | 34  | -1.20       | -0.83      | -1.27 to -0.39   | <0.0001|
| **Common allergies to dust mites**|     |             |            |                  |     |
| CSMS                              |     |             |            |                  |     |
| Control                           | 47  | 0.59        | 0.37       | -0.05 to 0.79    | 0.01|
| Treatment                         | 40  | -1.86       | -1.70      | -2.21 to -1.20   | <0.0001|
| RQLQ                              |     |             |            |                  |     |
| Control                           | 47  | 0.18        | 0.12       | -0.29 to 0.52    | 0.4 |
| Treatment                         | 40  | -1.16       | -0.79      | -1.16 to -0.41   | <0.0001|

*pBold values are significant.

CI = 95% confidence interval; CSMS = combined symptom plus medication scores; Diff: T2-T1 = difference in average CSMS and RQLQ scores from final patient surveys in comparison to initial or baseline surveys; Paired SMD = standard mean difference calculated per patient from baseline survey to follow-up survey; RQLQ = rhinoconjunctivitis quality of life questionnaire.

improvement of 28% over baseline and a >40% improvement with respect to the control group). The control group results showed no significant change in RQLQ scores during the study period. With regard to other allergy combinations, similar results were evident (data not shown).

**Pollen count assessment**

Figure 1A and B show respective total seasonal pollen counts for both metropolitan locations in which the participants reside. These figures display pollen counts for the periods encompassing the baseline year (2010 to 2011) and the second year of study (2011 through 2012 inclusive).

An assessment of the pollen results available for the years of 2011 through 2012 in comparison to 2010 to 2011 in San Antonio show that total seasonal pollen counts were relatively unchanged for mountain cedar tree and oak tree (Fig. 1A), while in contrast, a significant decrease in total pollen counts for ragweed occurred. Furthermore, there
was increased grass pollen counts documented (Fig. 1A). Analysis of the Dallas pollen seasons reveals that during this same time period, unchanged pollen counts for oak tree and mountain cedar tree pollen were evident (Fig. 1B). In contrast, significant increased total grass pollen and ragweed pollen counts were recorded.

**Discussion**

In this study we assayed the efficacy of the UAS polyallergen SCIT protocol by examining changes in the study outcome measures of CSMS as the primary measure and RQLQ results as the secondary outcome measure.

The total SS, MS, CSMS, and RQLQ scores were significantly improved for those undergoing SCIT (ie, treatment group) when examined at a mean of 1.22 years of therapy in comparison to baseline data and the control group scores (Table 2). When analyses focused on the 6 most common individual allergen sensitivities (cedar tree, oak tree, ragweed mix, Bermuda grass, Timothy grass, and dust mites, in part shown in Table 2) or combinations shared by both groups (in part shown in Table 2), similar significant improvement in the respective treatment group CSMS and RQLQ results were shown in comparison to baseline and control group results.

Because statistical significance may not equate to clinical relevance, several means of evaluating clinical significance or relevancy have historically been used. For non-placebo controlled studies (eg, current study), Erekosima et al. determined that a difference of ≥15% in the efficacy outcome measures in comparison to the control group were considered clinically significant. Furthermore, the WAO taskforce recommended that efficacy study outcomes of 20% or more than placebo are consistent with clinical significance. Thus, the current study changes in the primary efficacy outcome measures are both statistically significant and clinically relevant.

The RQLQ results showed a significant treatment group improvement compared to its baseline results and in comparison to the control group results. In order to address clinical significance, a change in RQLQ of greater than ±0.5 surpasses the threshold of clinical relevance and is evident in the current study treatment group (with an RQLQ SMD of −0.91). It is understood that differences in study design, methodology used, and scoring methods warrant careful consideration in contrasting study results. In a review by Nelson, the majority of published SCIT efficacy studies to date include only monotherapy trials. Thus, in our comparisons several of the trials are monotherapy studies. A comparison of the current study CSMS-SMD to the majority of studies (ie, those with study populations >20 subjects) referenced by Dretzke et al. and DiBona et al. is illustrated in Figure 2A. Evident in Figure 2A is the statistical equivalency of our results with those reviewed by Dretzke et al. and DiBona et al. When assessing the CSMS-SMD for the grouped or individual allergens reviewed in this study, the same statistical equivalency of our results is evident (data not shown).

For analysis of RQLQ, Figure 2B shows (study population) weighted RQLQ-SMD with 95% confidence intervals (CIs) for the 8 studies reported by Dretzke et al. and DiBona et al. (where the mean of all studies is depicted in red), and the CSMS-SMD for the current UAS protocol study (depicted in blue). Evident in this figure is the statistical equivalency of our results with those reviewed by Dretzke et al. and DiBona et al. When assessing the CSMS-SMD for the grouped or individual allergens reviewed in this study, the same statistical equivalency of our results is also noted (data not shown).

Therefore, the results of our primary and secondary outcome measures show that the utilization of the UAS protocol has statistically equivalent efficacy and comparable...
Consistent with these results, in order to minimize the effects of this potential bias, it has been recommended to use standardized well-structured surveys. Although we hypothesize that the efficacy of the UAS SCIT protocol is dependent upon cumulative allergen dosing as exemplified by the results of previous IT reports, further studies are warranted to substantiate this thesis.

A weakness in this study, as evident in other retrospective studies, is the potential occurrence of recall bias. In order to minimize the effects of this potential bias, it has been recommended to use standardized well-structured surveys. Consistent with these recommendations, we have employed well-structured questionnaires for assessment of the SS, MS, CSMS, and the validated RQLQ questionnaire.

The efficacy and safety of the UAS SCIT protocol are hypothesized to be due to: a slower than traditional SCIT buildup (ie, escalation) phase that attains recommended allergen concentrations on a cumulative dosing basis, a preselection of low-risk patients, and emphasis on patient education. The rate of allergen dose increase during the buildup phase is considered a prominent factor in the cumulative administered allergen dose has been postulated to be the significant factor in SCIT efficacy. Although we hypothesize that the efficacy of the UAS SCIT protocol is dependent upon cumulative allergen dosing as exemplified by the results of previous IT reports, further studies are warranted to substantiate this thesis. A weakness in this study, as evident in other retrospective studies, is the potential occurrence of recall bias. In order to minimize the effects of this potential bias, it has been recommended to use standardized well-structured surveys. Consistent with these recommendations, we have employed well-structured questionnaires for assessment of the SS, MS, CSMS, and the validated RQLQ questionnaire.

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FIGURE 2. (A) CSMS results compared to previous published results. Blue data point is the SMD for the UAS SCIT trial. The red data point is the mean SMD for all studies enumerated in the graph. CI = confidence interval; CSMS = combined symptom plus medication scores; SMD = standardized mean difference; UAS = United Allergy Service. (B) RQLQ results compared to previous published results. Blue data point is the SMD for the UAS SCIT trial. The red data point is the mean SMD for all studies enumerated in the graph. CI = confidence interval; CSMS = combined symptom plus medication scores; RQLQ = rhinoconjunctivitis quality of life questionnaire; SCIT = subcutaneous immunotherapy; SMD = standardized mean difference; UAS = United Allergy Service.

Clinical relevancy to recently conducted meta-analyses of both American and European based SCIT studies.

A direct correlation has been reported between the level of pollen counts and the corresponding SS and MS (the components of the CSMS) among affected individuals. Because total pollen counts were either unchanged or increased during the second year of the study in Dallas (Fig. 1B), depending on the individual’s allergen sensitivities, their SS and CSMS scores would be expected to be similar or worse during the second year in comparison to the first year of the study. Specifically, each control group’s (eg, Dallas and San Antonio) CSMS worsened from year 1 to year 2 of the study while the treatment groups’ outcomes showed that home-based immunotherapy was safe.

In our recently published study of the largest population of self-administered SCIT patients studied to date, safety results were derived from the medical review of approximately 24,000 patients who had self-administered over 2 million SCIT injections. The systemic reaction rate was only 0.16% per individual and 0.002% per injection in comparison to significantly higher office-based rates of approximately 4% to 14%. Consistent with these results, several other reports have previously documented the safety of self-administered or home-based SCIT (as exemplified in the present study).

The efficacy and safety of the UAS SCIT protocol are hypothesized to be due to: a slower than traditional SCIT buildup (ie, escalation) phase that attains recommended allergen concentrations on a cumulative dosing basis, a preselection of low-risk patients, and emphasis on patient education. The rate of allergen dose increase during the buildup phase is considered a prominent factor in the cumulative administered allergen dose has been postulated to be the significant factor in SCIT efficacy. Although we hypothesize that the efficacy of the UAS SCIT protocol is dependent upon cumulative allergen dosing as exemplified by the results of previous IT reports, further studies are warranted to substantiate this thesis. A weakness in this study, as evident in other retrospective studies, is the potential occurrence of recall bias. In order to minimize the effects of this potential bias, it has been recommended to use standardized well-structured surveys. Consistent with these recommendations, we have employed well-structured questionnaires for assessment of the SS, MS, CSMS, and the validated RQLQ questionnaire.
Previously, several immunotherapy studies have encompassed parallel retrospective periods of analysis, and other studies have used significantly longer periods with valid results despite possible recall bias. 38–41

Conclusion

In conclusion, our results show significant improvement in SS, MS, CSMs, RQLQ, and clinical relevancy associated with the use of the UAS SCIT protocol. These efficacy results, and our previously reported safety results, show that a carefully designed and implemented self-administered SCIT protocol is both efficacious and safe. 42

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Efficacy of self-administered immunotherapy

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