

## Quality of life outcomes with sublingual immunotherapy<sup>☆,☆☆,★</sup>

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Received 27 February 2008

### Abstract

**Purpose:** Immunotherapy is the titrated exposure of allergens to induce immunologic tolerance and offers long-term immune modification. Traditional subcutaneous immunotherapy (SCIT) has resulted in several deaths and raised safety concerns. Sublingual immunotherapy (SLIT) is an alternative administration route for allergen-specific immunotherapy. Compared to SCIT, SLIT has a shorter escalation phase, equal or greater efficacy for rhinitis, and an improved safety profile. The purpose of this study was to evaluate quality of life measures in a preliminary patient sample initiating SLIT at our institution.

**Materials and methods:** Patients with appropriate allergen reactivity were given the option to pursue immunotherapy by traditional SCIT or by SLIT techniques. Patients choosing SLIT completed the mini-Rhinoconjunctivitis Quality of Life Questionnaire (m-RQLQ), a 14-item Likert-type questionnaire, at baseline and during maintenance therapy. Patients typically reached maintenance dosing in less than 5 weeks.

**Results:** Paired m-RQLQ data were available for 15 patients after antigen titration. Initial m-RQLQ results indicate statistically significant ( $P < .05$ ) improvement on 12 of 14 domains, including impact on regular and recreational activities, sleep, nose rubbing and nose blowing, stuffy nose and runny nose, itchy eyes, sore eyes, watery eyes, thirst, and tiredness. In addition, total m-RQLQ score showed statistically significant improvement ( $P = .001$ ). No serious adverse events occurred with the initiation of SLIT.

**Conclusion:** These results indicate that SLIT is effective in controlling allergic symptoms and is safe in an introductory patient sample. Double-blind placebo-controlled trials are needed to confirm our preliminary results.

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<sup>☆</sup> Presented at the spring meeting of the American Rhinologic Society, San Diego, CA, April 27, 2007.

<sup>☆☆</sup> Dr Wise has received grant support from XoranTech, Inc., Ann Arbor, MI; Acclarent, Inc., Menlo Park, CA; NeilMed Pharmaceuticals, Inc., Santa Rosa, CA; Flight Attendants Medical Research Institute, Miami, FL; and Cystic Fibrosis Foundation, Bethesda, MD. Dr. Schlosser is a consultant or advisor for BrainLAB, Inc., Westchester, IL; GyruS ACMI, Inc., Southborough, MA; Medtronic, Inc., Jacksonville, FL; and Schering Plough, Kenilworth, NJ. Dr. Schlosser is on the speaker's bureau for GlaxoSmithKline, Brentford, Middlesex, UK. Ms Woody and Ms Koepf have no financial interests to declare. None of the above-noted financial interests had a direct impact on the design, data collection, data analysis, or interpretation performed in this study.

<sup>★</sup> Approval for this study was granted by the Institutional Review Board of the Medical University of South Carolina HR16707, (Charleston, SC).

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### 1. Introduction

Billions of dollars are spent yearly in treating the 25% of Americans with inhalant allergies. Most expenditure is for pharmacotherapy, which aims to reduce allergy symptoms rather than targeting the immunologic disease process. Immunotherapy (IT) involves titrated patient exposure to offending allergens to induce immunologic tolerance. Immunotherapy is the only treatment option that offers long-term modification of the underlying immune system and is the only potential “cure” for the atopic patient.

Traditional IT is most commonly given via subcutaneous injections. The mechanism of action of subcutaneous immunotherapy (SCIT) is thought to be through immune system alterations. Subcutaneous immunotherapy is efficacious in controlling allergy symptoms but unfortunately

requires frequent injections, thus decreasing patient acceptance and tolerance. In addition, in 1986, the British Committee for the Safety of Medicine documented several deaths caused by SCIT and raised concerns regarding the safety of SCIT [1]. This prompted interest in additional routes of administration for IT such as intranasal, oral, bronchial, and sublingual.

Sublingual immunotherapy (SLIT), an alternative route of administration for allergen-specific IT, is performed by the patients themselves and most commonly requires the placement of 1 to 5 drops of allergen under the tongue each day. The drops are kept in place for approximately 2 minutes, then swallowed. In contrast to SCIT that typically has an escalation phase of many months, maintenance dosing for SLIT is frequently reached in 4 to 5 weeks. Although severe adverse reactions during SLIT have been limited to a few recent case reports, SCIT has a systemic reaction rate of 0.5% to 5.6% [2–4]. In 1998, the World Health Organization and the European Academy of Allergology and Clinical Immunology concluded that SLIT is a viable alternative to SCIT [5,6]. Research has shown SLIT to be efficacious in controlling allergy and asthma symptoms. In addition, recent studies comparing SLIT to SCIT have found SLIT to have equal or greater efficacy for control of rhinitis symptoms [7–9].

In European countries, SLIT is a routine method of IT administration. A number of randomized and double-blind placebo-controlled trials assessing the efficacy and safety of SLIT have been published in the European and worldwide literature. However, despite its efficacy in controlling allergy symptoms and its excellent safety profile, SLIT remains uncommon in the United States and has not been approved by the US Food and Drug Administration. The lack of US Food and Drug Administration approval for SLIT is likely a result of the paucity of US SLIT trials.

We have been offering SLIT as one of the available IT methods at our institution for approximately 2 years. We sought to evaluate the subjective symptom response of patients who chose SLIT in a preliminary patient cohort. It is our hope that the information gained from this preliminary work will provide a basis for larger placebo-controlled US trials of the efficacy, safety, and immunologic changes effected by SLIT.

## 2. Materials and methods

### 2.1. Patients and testing methods

This study was approved by the Institutional Review Board of the Medical University of South Carolina (Charleston, SC). Patients referred to the Otolaryngology Department at the Medical University of South Carolina who were felt to be candidates for allergy evaluation underwent allergy testing by established protocols. Based on patient

factors, allergy testing was undertaken preferentially by modified quantitative testing protocols or skin end point titration [10]. In patients with dermatographism, skin abnormalities, uncontrolled asthma, or those who were unable to discontinue antihistamines, in vitro blood testing for allergen reactivity is typically offered.

### 2.2. Skin testing

For skin testing protocols, panels included representative allergens from 5 allergen classes determined to be significant reactors for our geographic area. An example panel is included in Table 1. Screening was typically performed with panels of approximately 16 to 18 antigens, with representative allergens from fungal, perennial, grass, weed, and tree categories. Patients suspected of having allergic fungal sinusitis by classic criteria were also tested with an expanded fungal panel [11]. Of note, during the initiation of SLIT at our institution, some antigens were added or deleted from our standard panel over time. Table 1 delineates all allergens included in the panel during the period of this study.

### 2.3. Sublingual immunotherapy protocol

Patients with appropriate allergen reactivity (defined as end point of  $\geq 3$  on skin testing) were given the option to pursue IT by traditional SCIT or by SLIT techniques. Before initiating any IT, patients were advised that the SLIT method is not currently approved by the US Food and Drug Administration.

Patients choosing SLIT had treatment vials prepared according to a protocol developed at our institution (Figs. 1 and 2). For patients with positive reactions to multiple

Table 1  
Skin test allergen panel

Fungus	Grasses
Alternaria	Bahia
Candida	Bermuda
Aspergillus	Timothy/Perennial rye
Cladosporium	
Penicillium	Weeds
Cephalosporium <sup>a</sup>	Pigweed
Helminthosporium <sup>a</sup>	Ragweed
Fusarium <sup>a</sup>	English plantain <sup>b</sup>
Mucor <sup>a</sup>	
Curvularia <sup>a</sup>	Trees
	Hickory/Pecan
Perennial allergens	Oak mix
Roach mix	Pine mix
Cat	Cypress
Dog	White ash <sup>b</sup>
Dust mite mix	

<sup>a</sup> Denotes fungal antigens added for testing of patients with criteria of allergic fungal sinusitis.

<sup>b</sup> White ash and English plantain were removed from the standard panel over time.

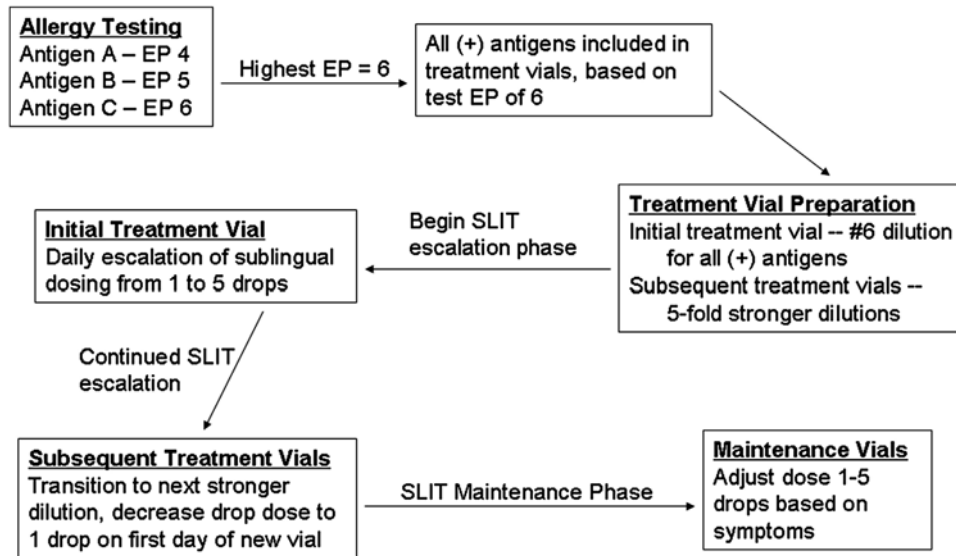


Fig. 1. Example of SLIT protocol.

antigens, the highest end point was identified among all positive antigens. Treatment vials were then prepared with all positive antigens based on the end point of the highest reactor. Escalation vials were made in 5-fold dilutions, based on previous experience with SCIT. Antigens used in our SLIT protocols were standardized extracts purchased from Greer (Lenoir, NC).

The SLIT escalation phase begins with the weakest dilution vial. From this vial, sublingual drops are placed once daily, beginning with a single drop and escalating by one drop each day. After using 5 drops on day 5, on day 6, the patient transitions to the next strongest dilution vial

and decreases dosage to 1 drop on the first day of the new vial. Thus, 1 drop of the new vial is equivalent to 5 drops of the previous vial, adding a measure of safety during the escalation period. This progression is followed through each of the subsequent escalation vials until maintenance dosing is reached. Patients had the ability to reach maintenance dosing in as little as 20 days, based on this protocol. Once maintenance dosing was reached, patients were instructed to adjust their dosing between 1 and 5 drops, dependent upon their symptoms, with the goal being maintained on the fewest drops that provided symptom control.

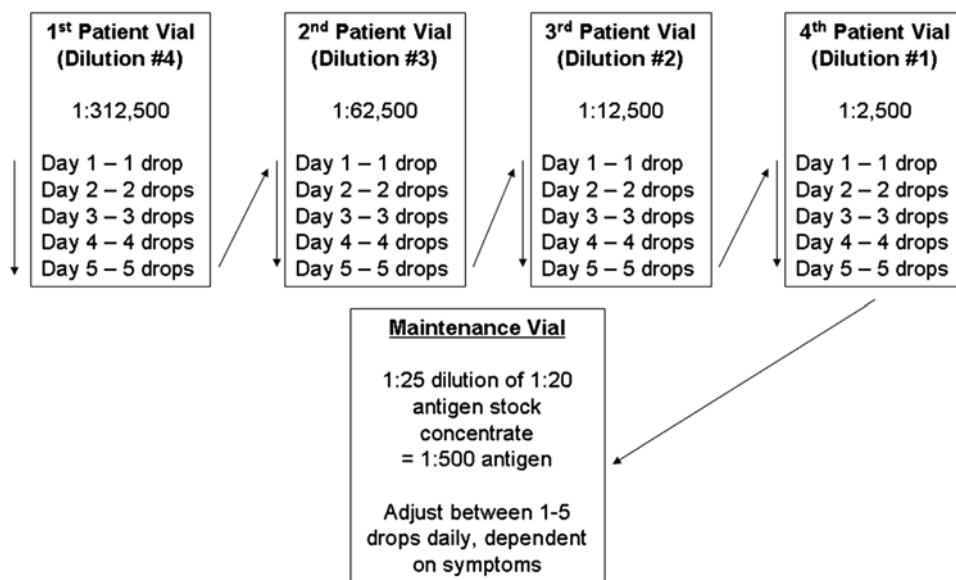


Fig. 2. SLIT escalation protocol, for example, patient with highest reactor end point of 6. Flowcharts outlining SLIT protocol developed at the Medical University of South Carolina. EP indicates end point.

#### 2.4. Quality of life data collection

As part of routine clinical care during SLIT treatment, we routinely ask patients to complete the mini-Rhinoconjunctivitis Quality of Life Questionnaire (m-RQLQ), a previously validated 14-item forced-choice Likert-type questionnaire, at baseline and at each visit during the maintenance phase of therapy [12]. All initial m-RQLQ surveys were obtained before initiating SLIT therapy. Follow-up m-RQLQ assessments were performed during the maintenance phase of therapy. Timing of follow-up m-RQLQ ranged from 5 weeks to 7 months after SLIT initiation, with a mean follow-up m-RQLQ time of 2.9 months.

Items assessed on the m-RQLQ include the effect of allergy symptoms on regular and recreational activities, sleep, sneezing, nose rubbing, nose blowing, stuffy nose, runny nose, itchy eyes, sore eyes, watery eyes, tiredness, thirst, and irritability. Patients are asked to rate each item for the previous 7-day period on a 0 to 4 point scale. A total m-RQLQ score is also calculated by adding the scores on the individual domains together.

This study was a retrospective analysis that compiled previously collected m-RQLQ data from patients undergoing SLIT. The most recently collected maintenance data for each patient was compared to that particular patient's baseline for changes in each m-RQLQ parameter, as well as total score. Therefore, the timing of maintenance follow-up data is somewhat variable across patients.

#### 2.5. Statistical analysis

Statistical analysis was performed via doubly repeated measures analysis of variance with statistical significance

designated as  $P < .05$ . Approval for this study was granted by the Institutional Review Board of the Medical University of South Carolina.

### 3. Results

#### 3.1. Patient characteristics

Paired m-RQLQ data were available for 15 patients who had completed antigen titration and were undergoing SLIT maintenance therapy. There were 5 males and 10 females. Mean age at the initiation of SLIT was 34.5 years, with a range of 13 to 68 years.

#### 3.2. Skin testing results

Allergy testing revealed multiple positive results in all patients who chose to undergo SLIT. All significantly positive antigens (end point of  $\geq 3$ ) were included in each patient's IT treatment regimen. The mean number of antigens included in SLIT regimens in this patient group was 11.6 (range, 3–21 antigens). Mean end points were calculated for each patient. Mean end points ranged from 3.7 to 5.7. It was quite common for patients to have positive reactions to all allergen classes. Ten patients (66.7%) exhibited significant reactions to all 5 allergen classes in our test panel (Table 1).

#### 3.3. Quality of life results

Paired m-RQLQ results revealed statistically significant ( $P < .05$ ) improvement on 12 of 14 domains assessed by this questionnaire (Fig. 3). Improvements were seen in the

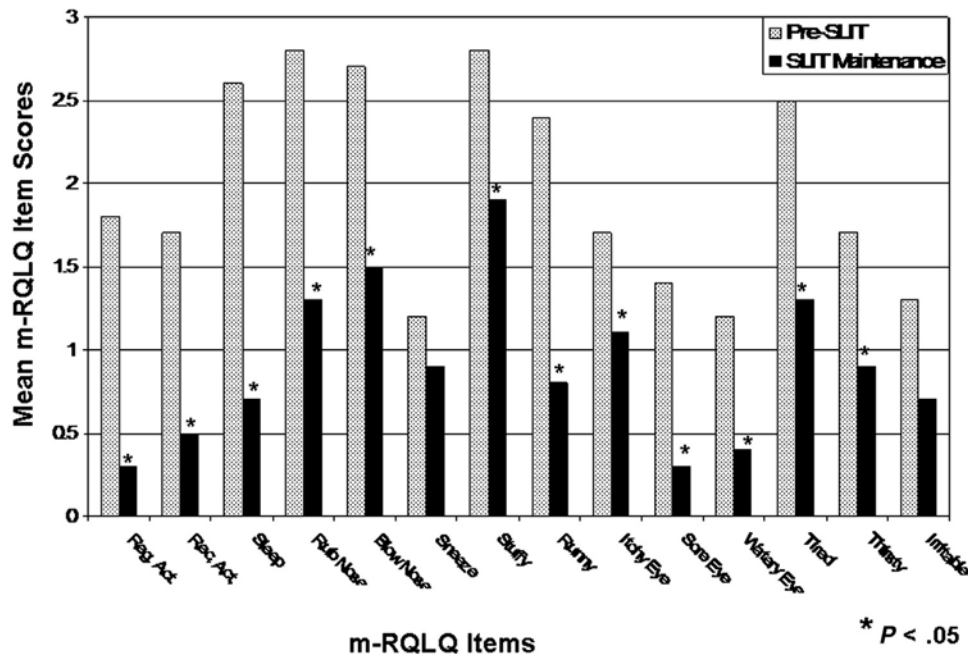


Fig. 3. Mean pre-SLIT and SLIT maintenance m-RQLQ item scores. \* marks m-RQLQ items found to have a statistically significant decrease in score from baseline to maintenance phase.

impact on regular and recreational activities, sleep, nose rubbing and nose blowing, stuffy nose and runny nose, itchy eyes, sore eyes, watery eyes, thirst, and tiredness. Total m-RQLQ score also showed statistically significant improvement ( $P = .001$ ), with a decrease in mean score from 27.8 before initiation of SLIT to 12.6 during the maintenance phase of therapy.

There were no serious adverse events reported with the initiation of SLIT at our institution.

#### 4. Discussion

Initial investigations of SLIT were launched to find a route of IT administration that provided rapid vaccine absorption and an improved safety profile, as compared to SCIT [3]. Although the systemic reaction rate of SCIT may be up to 5.6%, only a few recent case reports of serious systemic reactions exist for SLIT [2-4]. Typical side effects from SLIT administration include oral itching, stomach ache, and nausea that occur within 30 minutes of administration and resolve spontaneously [3]. The potential for improved safety and tolerability of SLIT over SCIT makes SLIT a potentially attractive option, especially in pediatric populations.

In the 1980s, SLIT began to be used with increasing frequency in Europe. Although SLIT remains an uncommon IT modality in the United States, the clinical efficacy of SLIT has been extensively investigated in European studies. Two large multicenter, double-blind, placebo-controlled (DBPC) trials to assess the efficacy of SLIT in controlling symptoms of adult rhinoconjunctivitis have shown promising results [13,14]. In a study of 634 patients with grass pollen allergy, Dahl et al [13] report a 30% reduction in symptom score and 38% reduction in medication use for SLIT patients, which was statistically significant compared to the placebo group. Durham et al evaluated 855 grass pollen allergy patients and showed statistically significant dose-dependent reduction in medication use, improved quality of life scores, and more well days in patients treated with SLIT, as compared to placebo [14]. A meta-analysis of SLIT efficacy in the treatment of adult and pediatric allergic rhinitis by Wilson et al [15] assessed 22 studies and found a statistically significant symptom reduction and a statistically significant reduction in medication use, supporting the efficacy of SLIT in allergic rhinitis. The DBPC studies of pediatric allergic rhinoconjunctivitis to tree pollen (patient ages, 5-15 years) and grass pollen (patient ages, 3-14 years) have also shown significant improvements in symptom scores and reduction in medication use after SLIT [16,17]. This is further supported by a meta-analysis of 10 pediatric allergic rhinitis DBPC SLIT trials, which found improved symptom scores and decreased medication use compared to placebo groups [18].

The effectiveness of SLIT on asthma has also been shown in multiple studies. Marogna et al [19] showed significant

decreases in bronchodilator use and nasal eosinophils, and increases in forced expiratory volume in 1 second (FEV<sub>1</sub>), mean expiratory flow at 25% of forced vital capacity (FVC), and methacholine threshold dose in adult patients treated with SLIT for birch pollen allergy. In DBPC evaluations of asthmatic children with dust mite allergy, Lue et al [20] and Bahceciler et al [21] have reported significantly reduced asthma symptoms and medication use, reduced number of asthma exacerbations, increased FEV<sub>1</sub>, and increased peak expiratory flow rate with SLIT. A meta-analysis of the efficacy of SLIT in asthma found a statistically significant benefit of SLIT on respiratory function parameters and a reduction in asthma/allergy medication use and symptoms, although the magnitude of these effects was small [22]. Although most SLIT studies lack long-term follow-up data, an interesting study by Di Rienzo et al [23] evaluated 35 pediatric patients 4 to 5 years after completion of a 4 to 5-year course of SLIT (ie, 10-year follow-up after baseline). These authors showed a statistically significant difference in the diagnosis of asthma between SLIT and non-SLIT groups at the completion of SLIT therapy, which was maintained 4 to 5 years after the completion of SLIT. Furthermore, an additional significant difference in peak expiratory flow was seen between groups at 4 to 5 years after completion, with SLIT patients exhibiting higher peak expiratory flow rates than non-SLIT patients.

A number of studies have demonstrated statistically significant effects on allergy and asthma symptoms in SLIT treatment groups. However, additional investigations are necessary to determine the true clinical value of SLIT because of the heterogeneity of these studies and the small magnitude of benefit seen in many of the studies. In addition, questions regarding allergen administration and dosing remain. Most SLIT studies have used single-allergen monotherapy to evaluate efficacy [13-15,18], whereas a few studies have included more than one allergen in the treatment regimen [16-18]. On the basis of our experience with SCIT and multiple positive reactants on patient testing, we chose to treat with multiantigen polytherapy, including extract from all positive reactants in our treatment regimen. However, studies on the efficacy of monotherapy vs polytherapy in SLIT treatment regimens are lacking. Furthermore, although previous work has demonstrated that effective doses of SLIT range between 3 and 375 times the dose of SCIT, this dosing range is wide and often difficult to understand given the lack of unit standardization [24].

Although the efficacy of SLIT in controlling allergy and asthma symptoms has been demonstrated in some reports, the immunologic mechanisms of SLIT have not been extensively evaluated. Some of the immunologic changes observed in SCIT include a shift in allergen-specific T-effector cells to a T-regulatory phenotype, increased production of interleukin 10 (IL-10) and transforming growth factor (TGF)- $\beta$ , and increased allergen-specific IgG4 and IgA [25]. Some similar immunologic changes

have been observed with SLIT; however, investigations of SLIT immunology have shown the changes to be less consistent than those seen with SCIT. Reviews of the current knowledge of SLIT immunology are provided by Moingeon et al [26] and Cox et al [27] and are beyond the scope of this article. Some immunologic highlights of SLIT are presented as follows. Increases in allergen-specific IgG4, IgG1, and IgA have been observed with SLIT, with some of these responses being dose or time dependent [20,26–29]. In most studies, allergen-specific IgE does not significantly increase or decrease, but an increase in the IgG4/IgE ratio is seen [20,26,27]. Although systemic alterations in Th1/Th2 ratios have been documented and correlated with clinical improvement in SCIT, such changes have not been identified in SLIT despite clinical improvement [26,27]. Some systemic inflammatory alterations that have been shown during SLIT treatment include reduced eosinophil cationic protein levels with reduced peripheral eosinophil counts, increased levels of IL-10, increased interferon- $\gamma$ , and decreased soluble intercellular adhesion molecule (ICAM)-1 [26,27,30,31]. Local environment changes with SLIT include a significant reduction in sublingual salivary eosinophil cationic protein levels, as measured by mucosal biopsy [32]. Although many of the above immunologic changes during SLIT therapy have been reported by multiple authors, a number of inconsistencies have been shown as well [17,31,33]. Additional studies of SLIT immunology are necessary to advance our knowledge to the level that we currently understand SCIT.

The safety of SLIT has been one of its consistently highlighted features. Although some trials report fairly high rates of mild adverse events with SLIT, these reactions are typically limited to oral cavity pruritis, rhinitis, dry throat, throat irritation, nausea, and other gastrointestinal complaints [13,14,16–18,28,29,34]. Commonly, severe systemic reactions and life-threatening adverse events are noted to be absent in SLIT trials [13,14,18,20,29,34]. Withdrawal from SLIT trials because of adverse events is rare, but withdrawal has been documented for blistering or burning of the oral cavity, severe oral cavity pruritis, vomiting and diarrhea, abdominal pain, lingual edema, and asthma exacerbations [16,28,29,34]. A 2005 meta-analysis evaluating safety in 25 published SLIT trials was performed by Gidaro et al [35]. This study found that no anaphylactic shock was reported in any study, adverse reactions did not appear to be dose-related, and high allergen dosing regimens appeared to be safe in adults and children. Two recent case reports of potential anaphylactic reactions related to SLIT were published in 2006. The first involves a patient who experienced generalized pruritis, extremity edema, dyspnea, and dizziness on the second day of at-home SLIT polytherapy for inhalant allergies [2]. This was treated with a course of oral prednisone that resolved the symptoms. The second case is a report of a patient on rush SLIT dosing for latex allergy, who developed anaphylactic shock on reaching the maximum scheduled dose [4]. These 2 reports of

potential severe systemic reactions related to SLIT indicate that, whereas previous SLIT studies have lacked evidence of life-threatening adverse events, administration of any type of IT should be performed with caution.

Preliminary data indicate that initiation of a SLIT program at our institution has shown statistically significant symptom reduction in a small patient cohort from baseline to the maintenance phase of therapy. The only m-RQLQ items that did not reveal significant score reduction were sneezing and irritability. In addition, the total m-RQLQ score was reduced by more than half, from 27.8 to 12.6. Although these results are encouraging, the results should be interpreted with caution, in light of the small patient sample and lack of a control group. In addition, although symptom reduction is an important measure in an overall IT treatment paradigm, this study is limited to subjective ratings of symptom scores. As many SLIT protocols exist worldwide, timing of expected symptom improvement with SLIT is difficult to predict. We have noted symptom improvement as early as 5 weeks after initiating SLIT, immediately after our escalation period. Typical escalation periods with SCIT are months in length, with much slower increases in antigen dosing. Finally, medication use and immunologic parameters were not assessed in this sample and are also important measures to consider. Additional randomized controlled trials with larger sample sizes and longer follow-up are necessary to support the growing body of evidence that SLIT is a viable option for treatment of allergic patients in the United States.

## 5. Conclusions

In a preliminary patient cohort, we have shown a statistically significant reduction in symptoms during maintenance SLIT therapy, as compared to baseline. To our knowledge, this preliminary report is one of the first US studies assessing the efficacy of SLIT. There is growing evidence supporting SLIT as a safe and effective IT method that may ultimately increase the popularity of this method in the United States to match other areas around the world. To increase our body of knowledge for this promising technique, additional controlled trials and investigations of the immunologic changes effected by SLIT are needed.

## Acknowledgment

The authors would like to thank Justin C. Wise, PhD, for his assistance with statistical analysis. As principal investigator, Rodney J. Schlosser, MD, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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