Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy

Noel Rodríguez-Pérez, MD*; María de Jesús Ambriz-Moreno, MD*; Giorgio Walter Canonica, MD†; and Martin Penagos, MD, MSc†‡

Background: Several studies have demonstrated the efficacy and safety of sublingual immunotherapy in the treatment of respiratory allergy.

Objective: To determine the frequency of systemic adverse reactions in patients treated with standardized extracts of sublingual immunotherapy.

Methods: Allergic patients with rhinitis with or without asthma and sensitized to at least 1 allergen were included. Increasing doses of standardized allergens were administered until reaching an average dose accumulated of 7,200 U after 26 weeks of treatment. Adverse events were graded according to the European Academy of Allergy and Clinical Immunology immunotherapy position paper.

Results: Forty-three patients with a median age of 11 years (interquartile range, 8–20 years) were included. All the patients had allergic rhinitis, and 63% had asthma; they were sensitized mostly to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Four patients (9%) presented with an immediate and 1 (2%) with a late systemic reaction. In total, 7 systemic reactions occurred in 23,154 doses, and all were associated with wheezing or worsening of nasal symptoms (grade 2); in addition, 1 patient had angioedema and urticaria (grade 3).

Conclusions: In this group, systemic reaction frequency was 11.6%, and all were classified as grade 2 or 3. Further assessments in larger samples of patients are required in the context of randomized controlled trials.

Ann Allergy Asthma Immunol. 2008;101:304–310.

INTRODUCTION

Allergen-specific immunotherapy, together with drug therapy, patient education, and allergen avoidance, is a cornerstone in the management of respiratory allergy, and it is now recognized as the only treatment capable of modifying the immune response to allergens.[1–5] The efficacy of subcutaneous immunotherapy (SCIT) for allergic respiratory diseases has been confirmed in systematic reviews and meta-analyses for asthma and recently for seasonal allergic rhinitis.[6–8]

Despite these results, adverse event (AE) frequency is a central concern in the validation of the risk-benefit ratio of this treatment.[1,6,8] The risk associated with the subcutaneous route was not fully appreciated until 1985, when Lockey et al[9] reported 24 fatalities associated with immunotherapy between 1945 and 1985 and 17 fatalities between 1985 and 1989.[9–11] Although systemic reactions (SRs) have been registered from 0.001% to 46.7% of patients treated with SCIT, in controlled studies[3,12–14] evaluating SCIT safety to date have reported severe systemic adverse effects and lower risk when guidelines are strictly followed. However, severe SRs are an inherent risk in patients treated with SCIT. The recent multicenter study by Whinter et al[15] found SRs in 33% of 1,038 patients treated with SCIT (23,047 injections); 78% were grade 2 (mild) reactions, 20% were grade 3, and 1% were grade 4 (severe).

Some variables have been explored as risk factors for severe reactions in patients treated with specific immunotherapy (eg, the allergen administered, the potency and formulation of the extract, concomitant drug therapy, the updosing regimen and top dose, the severity and type of disease before treatment, premedication, and differences in practical performances of the therapy).[16–18] Only a few of these factors have been identified as risk conditions for SRs with SCIT.[11,19] For example, Ohashi et al[19] identified asthma, atopic dermatitis, and high IgE levels as risk factors for SR development in patients treated with SCIT.

The sublingual route has emerged as an effective alternative to SCIT. The indications are broadly similar, and where both treatments are available, patient preference becomes an important determinant of choice.[8] In addition, a more favorable safety profile makes this treatment suitable for home use and, therefore, more accessible to a broader range of patients.[8,20] During the past few years, much evidence on the clinical efficacy of sublingual immunotherapy (SLIT) in rhinitis and asthma in children and

Affiliations: * Allergy Clinic, Autonomous State University of Tamaulipas, Matamoros, Tamaulipas, Mexico; † Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy; ‡ Infants Service, Pediatrics Hospital, CMN "Siglo XXI", IMSS, Mexico City, Mexico.

Disclosures: Authors have nothing to disclose.

Received for publication April 30, 2008; Received in revised form May 19, 2008; Accepted for publication June 15, 2008.

adults has been provided, together with objective evaluations of its safety and compliance.[21–29] Safety itself seems to be the major advantage of SLIT because neither life-threatening systemic events nor fatalities have ever been reported during 20 years of clinical use and controlled trials, and the occurrence of adverse effects seems not to differ between adults and children.[24–26,28,30] Di Rienzo et al,[31] in an evaluation of children younger than 5 years, reported 9 SRs in 7 children (5.6% and 0.2 per 1,000 doses).

A recent review regarding SLIT safety conducted by Gidaro et al[24] analyzed 25 controlled studies involving 747 patients. They found grade 2 or 3 SRs in 14.7% of treated patients (110 per 198,553 doses); no anaphylactic shock or life-threatening or fatal reactions were registered. Recently, 4 cases of anaphylaxis in patients receiving SLIT have been published.[32–35] Two of these patients received more than 1 allergen.[32,34] Although causality in these studies has to be reanalyzed, physicians should be aware that these reactions can occur, and they should be trained in emergency management. For this reason, only a certified allergist should prescribe this treatment.[1,3,8,9,12] The objective of this study was to determine the frequency of systemic adverse effects in patients receiving standardized extracts of SLIT.

METHODS

Study Design

This study is part of a prospective, open-label, single-arm intervention study.[36] Patients were recruited consecutively between November 1, 2002, and October 31, 2003, at the Allergy Clinic affiliated with the Autonomous State University of Tamaulipas. Written informed consent was obtained from patients before study entry, and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Patients

The inclusion criteria were as follows: 6 to 50 years old, at least a 2-year clinical history of significant allergic rhinoconjunctivitis or mild to moderate asthma (forced expiratory volume in 1 second >70% of predicted), and allergen sensitization demonstrated by at least 1 positive skin prick test reaction (wheal diameter >4 mm). Skin tests were performed on the flexure aspect of the forearm using a standard panel that included most common allergens (IPI ASAC, Madrid, Spain). Specific or total serum IgE levels were not measured as part of the protocol. The exclusion criteria were as follows: severe asthma (forced expiratory volume in 1 second <70% of predicted), primary or secondary immunodeficiency, pregnancy, and other general contraindications for immunotherapy as established in the European Academy of Allergy and Clinical Immunology position paper.[3]

Immunotherapy Protocol

We used commercial extracts standardized in either equivalent biological units per milliliter or specific protein units per milliliter (IPI ASAC). Patients were treated with house dust mite, pollen, or cockroach preparations, depending on individual sensitizations. The first dose of SLIT was administered at the clinic.

During a 90-day dose progression phase, therapy consisted of five 5-mL vials with physiologic saline concentrations of 1.13 U/mL (vial 0), 5.24 U/mL (vial 1), 28.4 U/mL (vial 2), 142 U/mL (vial 3), and 710 U/mL (vial 4) with 50% vol/vol of glycerol and 0.4% wt/vol of phenol. Drops (0.05 mL per drop) were administered first thing in the morning before eating, drinking, or brushing teeth and were held sublingually for 3 minutes and then swallowed. Each vial contained only 1 extract. When a patient was selected to receive an additional allergen, the extracts were administrated in individual dispensers, and the doses were separated by a minimum of 120 minutes. In this case, patients were advised to use the vial containing *Dermatophagoides* before any other one. According to the schedule, by the end of the buildup phase, a cumulative dose of 729.82 U was reached. Patients were instructed to receive during the maintenance phase 1 daily drop (vial 4) for 6 months, so the cumulative dose given in this period was 7,200 U, corresponding to 14.5 μg of Der p 1, 4.5 μg of Der p 2, and 6.5 μg of Der f 1.

Adverse Reactions

Patients recorded symptoms and any adverse effects in diaries, and they were also instructed to contact the centers when they needed medical advice. Patients were provided with an antihistamine (loratadine). Because this was the first SLIT trial performed in the Allergy Clinic affiliated with the Autonomous State University of Tamaulipas, we were advised by the ethics committee to provide all the patients with 1 epinephrine vial (Pinadrina, 1 mg/mL; Pisa Laboratory, Guadalajara, Mexico) to have on hand with dose administration, and they were instructed in its use.[37] The epinephrine dose was 0.01 mL/kg in children (maximum, 0.3 mL) and 0.5 mL/kg in adults, administered via the intramuscular route in the thigh. Asthmatic patients received 1 albuterol metered-dose inhaler.

The adverse effects were subdivided into eye symptoms, rhinitis, asthma, edema of the tongue or lips, gastrointestinal complaints (nausea, vomiting, abdominal pain, and diarrhea), urticaria, and anaphylaxis. Any other suspected AEs possibly related to SLIT had to be described.[25,26] The SRs were categorized as immediate (≤30 minutes) or late (>30 minutes). They were graded according to the European Academy of Allergy and Clinical Immunology immunotherapy position paper.[12] Grade 0 is lack of AEs; grade 1, nonspecific mild symptoms probably not IgE mediated (discomfort, headache, arthralgia, etc); grade 2, mild SRs (mild rhinitis or asthma responding adequately to antihistamines or inhaled β_2-agonists); grade 3, non–life-

threatening SRs (urticaria, angioedema, or severe asthma responding well to treatment); and grade 4, anaphylactic shock.[3,12,13]

Statistical Analysis

The main qualitative variables are expressed as frequencies and proportions. We used the adjusted Wald method to calculate 95% confidence intervals for the proportion of patients with SRs.[38] Patient age and sensitization numbers are presented as medians and interquartile ranges (IQRs) (Q1-Q3). Owing to low power considerations, neither factor risk exploration nor multivariate analysis was performed.[39] Statistical analyses were performed by means of the GraphPad QuickCalcs Web site[40] and StatXact 4.1.[41]

RESULTS

Patients

Forty-three consecutive patients were included. The median patient age was 11 years (IQR, 8–20 years). Thirty-two patients were children (median age, 10 years; IQR, 7–14 years) and 10 were adults (median age, 32 years; IQR, 24–38 years). Twenty-four patients were female and 19 were male. All the patients had allergic rhinitis, 27 (63%) had asthma, and 11 (26%) had atopic dermatitis or urticaria. Ten patients (23%) were sensitized to 1 or 2 allergens and 33 (77%) to 3 or more. The most frequent sensitizations were to *Dermatophagoides pteronyssinus* (72%, n = 31), *Dermatophagoides farinae* (63%, n = 27), molds (28%, n = 12), *Periplaneta americana* (23%, n = 10), and pollens (21%, n = 9). In all cases, the SLIT schedule was prescribed according to patient preference. During this study, patients received a total of 23,154 doses of SLIT.

Eleven patients (26%) had received a previous course of SCIT, during which 6 patients experienced SRs. Four of these SRs were noted to be laryngeal manifestations: 2 were described as changes in the voice (dysphonia) and 2 as laryngeal stridor minutes after receiving the injections. The other 2 SRs were described as wheezing (Table 1). Three of these patients developed SRs during the current SLIT schedule and 3 did not.

AEs With SLIT

Most patients in this study tolerated SLIT. The most frequent complaints were local symptoms, such as sublingual and oral itching (n = 16) and tongue sensitivity changes (n = 4), and only 1 patient had gastrointestinal manifestations (nausea and pain).

Five patients (11.6%; 95% confidence interval, 4.6%–24.9%) presented with 7 SRs in 23,154 doses (0.3 per 1,000 doses). All these patients had been treated with *Dermatophagoides* and 1 with *P americana* extracts, but all the reactions were reported after *Dermatophagoides* extract use. Four of these patients (9%) reported an immediate SR 20 to 30 minutes after SLIT; 3 of them presented with dyspnea, wheezing, or nasal symptoms (grade 2) (patients 1, 2, and 3), and patient 4 reported dyspnea, wheezing, urticaria, and upper lip angioedema at the same time (grade 3). One patient (2%) presented with a late SR 60 minutes after SLIT characterized by dyspnea, wheezing, and nasal symptoms (patient 5) (Table 2). Patients contacted investigators by telephone and received indications to initially take an antihistamine and albuterol. Patients 1 and 2 were treated as a precaution with epinephrine owing to the persistence of manifestations despite initial treatment (wheezing, dyspnea, anxiety, flushing, and dizziness). All the patients were seen as outpatients at the Allergy Clinic the same day the SR occurred. At examination, patients 1, 2, 3, and 5 were asymptomatic, and only patient 4 presented with urticaria-angioedema; these skin lesions disappeared gradually. No patient required hospitalization. The SLIT was temporarily stopped, but it was resumed at a lower dose once the patients were asymptomatic (Table 2).

Table 1. Patient Characteristics

Characteristics	Patients with SRs (n = 5)	Patients without SRs (n = 38)
Age, median (IQR), y	11 (8.0–25.5)	11.5 (8.0–18.5)
Female sex, No.	4	20
Rhinitis, No.	5	38
Asthma, No.	5	22
Skin disease, No.	1	10
Conjunctivitis, No.	1	0
Sensitizations, median (IQR), No.	4 (3.0–4.5)	4 (2.0–5.0)
Dermatophagoides sensitization, No.	5	34
Periplaneta americana sensitization, No.	3	17
Receiving inhaled corticosteroids, No.	3	9
Previous immunotherapy course, No.	3	8
Previous immunotherapy with HDM, No.	3	5
Patients had SRs during previous SCIT, No.	3	3
Wheezing events during previous SCIT, No.	2	3
Laryngeal manifestations during previous SCIT, No.	3	1

Abbreviations: HDM, house dust mite; IQR, interquartile range (Q1-Q3); SCIT, subcutaneous immunotherapy; SRs, systemic reactions.

DISCUSSION

One of the major rationales for specific immunotherapy is to minimize or abolish the risk of AEs. With SCIT, the rate of SRs is variable and depends on the patient's diagnosis, concomitant therapy use, extract standardization, administration schedule, allergen type, and dose.[42,43] The frequency of SRs with SCIT ranges from 0.001% to 46.7% of treated patients, although higher figures have been reported in children.[11–14,42–44] Although the risk of fatalities is estimated to be less than 1 death per 2 million injections, the risk of severe systemic adverse effects is real, although it is lower if SCIT is administered correctly.[1,7,8]

A different scenario is observed with SLIT. Since its introduction in 1986, no fatalities have been reported in the literature or in clinical practice. The most frequent AEs are local and involve the site of administration: oral or sublingual itching, stomachache, and nausea. These events are described as mild and self-limited, and they can be managed by a temporary reduction of the dose. In published clinical trials,[43] discontinuation of SLIT because of an adverse effect rarely was required.

Several studies have evaluated SLIT safety. The review by Gidaro et al[24] analyzed 25 controlled studies involving 1,437 patients; those treated with allergen extracts (n = 747) showed 759 AEs (632 local and 127 systemic). Patients treated with placebo (n = 690) had 145 AEs (62 local and 83 systemic). They found grade 2 or 3 SRs in 14.7% of treated patients (110 per 198,553 doses), but no anaphylactic shock or life-threatening or fatal reactions were registered.[24] The postmarketing evaluation by Di Rienzo et al[31] reported just 2 local and 5 gastrointestinal manifestations in a survey that included 126 children aged 3 to 5 years (5.6% of patients and 0.2 per 1,000 doses).

The SLIT Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology conducted an analysis of published studies. In these, approximately 1,251,654 doses were administered to 4,758 patients; in the 72 studies reviewed, no serious life-threatening reactions were registered. Information about total AEs was available in 41 studies; there were 1,047 adverse reactions in 386,149 doses (2.7 per 1,000 doses). In 49 studies, only the total number of patients with adverse reactions was described; 529 of 4,378 patients (12%) reported any AEs. In the studies that specified the type of reaction, 169 of 314,959 (0.056% of doses administered) were classified as SRs.[45]

Because this study evaluated only treated patients, we could not calculate the number needed to harm using these data. The number needed to harm is an epidemiologic measure that indicates how many patients need to be exposed to a risk factor to cause harm in 1 patient who would not otherwise have been harmed; the lower the number needed to harm, the worse the risk factor.[46] Using data reported by Cox et al,[45] it is possible to estimate this measure for the number

Table 2. Case Descriptions

Patient No./sex/age, y	Diagnosis	Sensitization	SLIT treatment (dose)[a]	Adverse events	Time, min	Severity grade	Treatment and dose	Evolution and SLIT modifications
1/F/27	Rhinitis Asthma (moderate persistent) Conjunctivitis	*Dermatophagoides farinae* *Dermatophagoides pteronyssinus* *Periplaneta americana* Mold mix[b]	*Dermatophagoides* mix (vial 0) (0.05 UBE) Cockroach 1:50	Bronchospasm	20	2	Loratadine, 10 mg Adrenaline, 0.5 mL IM in the thigh	Good, SLIT dose reduction
2/F/7	Rhinitis Asthma (mild persistent)	*D farinae* *D pteronyssinus* Pecan tree	*Dermatophagoides* mix (vial 4) (975 UBE)	Bronchospasm	30	2	Adrenaline, 0.2 mL IM in the thigh Albuterol HHN, 0.15 mg/kg/dose	Good, SLIT dose reduction
3/F/24	Rhinitis Asthma (mild persistent)	*D farinae* *D pteronyssinus* *P americana* Cat	*Dermatophagoides* mix (vial 4) (675 UBE)	Bronchospasm Nasal	20	2	Loratadine, 10 mg OD Albuterol HHN, 2 mg/dose as needed	Good, SLIT dose reduction
4/M/11	Rhinitis Asthma (mild persistent) Urticaria	*D farinae* *D pteronyssinus*	*Dermatophagoides* mix (vial 4) (675 UBE)	Angioedema Urticaria Bronchospasm	20	3	Loratadine, 10 mg Albuterol HHN, 2 mg/dose as needed	Good, SLIT dose reduction
5/F/8	Rhinitis Asthma (mild persistent) Urticaria	*D farinae* *D pteronyssinus* *P americana* Mold mix[b]	*Dermatophagoides* mix (vial 0) (1.13 UBE/mL)	Bronchospasm Nasal	60	2	Albuterol HHN, 0.15 mg/kg/dose Betametasone, 6 mg IM, single dose	Good, SLIT dose reduction

Abbreviations: HHN, hand-held nebulizer; IM, intramuscular; OD, once daily; SLIT, sublingual immunotherapy; UBE, equivalent biological units.

[a] See the "Immunotherapy Protocol" subsection for the contents of the vials.

[b] Mold mix consists of *Aspergillus fumigatus, Penicillium notatum, Alternaria alternata,* and *cladosporium herbarum.*

of doses given. They reported an SR frequency of 0.81 per 1,000 doses in SLIT-treated patients and of 0.40 per 1,000 in the placebo group. Consequently, it is necessary to give 2,439 SLIT doses to observe an SR.[45]

Although the information on safety in controlled trials is important, it must be taken into account that the populations in clinical studies are strictly selected, that the administration of SLIT is usually supervised, and that all adverse effects are recorded. However, a different situation has not been identified in clinical practice and postmarketing surveys, in which patients often self-manage SLIT.[25,26,43]

Four cases of anaphylaxis in patients treated with SLIT have been published. The first reported case was in a 31-year-old woman with a known history of allergic rhinitis, asthma, and tree nut and peanut allergy. On the third day of treatment, she presented with generalized pruritus, swelling of her hands and feet, wheezing, and dizziness. She was not examined during this reaction. She had been treated with a mixture of 17 nonstandardized and standardized allergen extracts. This SR was attributed by the authors to SLIT.[32] It is possible that the risk of a SR is higher with nonstandardized products and with those containing multiple allergens,[1] but this needs to be proved by means of randomized studies.

The second case was a 36-year-old woman with latex allergy, urticaria, and asthma. She had been treated with a standardized extract of latex based on a rushed scheme. Once she reached the maximum scheduled dose she developed a rash, spreading urticaria, asthma exacerbation, and anaphylactic shock. No more details were provided.[33] The third case was an 11-year-old girl with allergic rhinitis. She was polysensitized and was being treated with a combination of sublingual standardized extracts, including house dust mites and grasses. During the maintenance phase, she developed angioedema, chest pain, nausea, and abdominal pain. The patient was treated in an emergency service for anaphylaxis and then was discharged. Data regarding blood pressure, clinical signs, chest examination, and treatment were not provided.[34]

The fourth case of anaphylaxis was described by Blazowski.[35] A 16-year-old girl with a history of perennial allergic rhinitis and intermittent asthma began SLIT with standardized extract of house dust mites. In the third year of SLIT, she self-administered an overdose of the allergen extract equivalent to 9.7 μg of *D pteronyssinus* and 17.2 μg of *D farinae*. Within 5 minutes, she developed generalized pruritus and urticaria, flushing, wheezing, chest pain, and shivering, followed by double short collapse. Hypotension, tachycardia, and loss of consciousness were documented. She required management with intramuscular epinephrine, intravenous fluids, oxygen, and corticosteroids, and she was transferred to the intensive care unit, where she recovered during the next day. Further details about subsequent management were not provided. Nonetheless, this is the first report of anaphylactic shock related to SLIT.[35]

In the present study, we found at least 1 SR in 11.6% of treated patients and 7 SRs in 23,154 doses (3 per 10,000 doses); 4 patients had grade 2 reactions, and 1 had grade 3; all were controlled using the office's measures. Although a limitation of this study is that we evaluated a small population, these findings are similar to those reported previously.[24,25] The risk of severe SR, including anaphylaxis, has been a key concern in relation to SCIT. Encouragingly, no treatment-related severe systemic AE requiring intervention with adrenaline has occurred during diverse large-scale randomized multicenter trials using SLIT.[47,48] In a preliminary report of a Cochrane systematic review including 48 randomized, double-blind, placebo-controlled clinical trials, none of the studies reported anaphylaxis or the use of adrenaline.[49] Indeed, in countries where SLIT is available, it is not recommended that patients treated with SLIT have injectable epinephrine at home. During this study, we prescribed its use in 2 patients because their symptoms initially did not improve despite initial management.[50]

When risk factors associated with SRs have been explored in patients treated with SLIT, some studies have not identified a strong relationship of allergen dose, induction schedule, phase, and age with SRs.[24,45,51] In the present study, all the SRs occurred after *Dermatophagoides* extract administration, but this association has to be proved in a different study design. In this regard, Fiocchi et al[51] conducted a safety evaluation in children using SLIT. They identified that most adverse effects were reported after SLIT with house dust mites, mainly during the first 30 minutes after administration, and 54% of reactions occurred during the buildup phase, but a specific risk analysis was not executed.[51] Owing to low power considerations, in the present study, neither a risk factor analysis nor a multivariate analysis was performed.

The safety of SLIT with multiple allergens was analyzed recently by Lombardi et al.[52] In a postmarketing study, they compared 2 groups of patients with rhinitis or asthma allergic to pollens; patients were treated with either a single (n = 76) or multiple (n = 83) standardized extracts. A quarter of the patients received up to 4 allergens. No differences were found regarding AE frequency. Most AEs were local (45 vs 51 episodes, respectively). No asthma exacerbations, urticaria, or anaphylaxis was reported.[52] Because only pollens were used, this study does not allow any assumptions regarding other allergen combinations.

In summary, in this group of patients, SR frequency was 11.6%. They were classified as grade 2 or 3. A major limitation of this study is the reduced number of patients evaluated. Further assessments in larger samples of patients regarding identification of high-risk patients, allergen dose effect, and safety of mixing multiple extracts are required in the context of randomized, double-blind, placebo-controlled clinical trials.

REFERENCES

1. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Al-

lergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol*. 2007;120:S25–S85.
2. Bachert C, van Cauwenberge P. The WHO ARIA (Allergic Rhinitis and its Impact on Asthma) initiative. *Chem Immunol Allergy*. 2003;82: 119–126.
3. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases: WHO position paper. *Allergy*. 1998; 102:558–562.
4. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol*. 2004;93:3–12.
5. Passalacqua G, Lombardi C, Canonica GW. Sublingual immunotherapy: an update. *Curr Opin Allergy Clin Immunol*. 2004;4:31–36.
6. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003;(4):CD001186.
7. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007;(1):CD001936.
8. Durham SR. Tradition and innovation: finding the right balance. *J Allergy Clin Immunol*. 2007;119:792–795.
9. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol*. 1987;79:660–677.
10. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TAE. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol*. 1993;92:6–15.
11. Nettis E, Giordano D, Ferrannini A, Tursi A. Systemic reactions to allergen immunotherapy: a review of the literature. *Immunopharmacol Immunotoxicol*. 2003;25:1–11.
12. Malling H, Weeke B. Immunotherapy: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 1993;48: S9–S35.
13. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy*. 2004;34:527–531.
14. Rodríguez-Perez N, Ambriz-Moreno MJ, Pizarro-Esquivel U. Non-fatal systemic reactions caused by immunotherapy and skin tests. *Rev Alerg Mex*. 2002;49:69–73.
15. Winther L, Arnvedw J, Malling HJ, Noltez H, Mosbech H. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. *Clin Exp Allergy*. 2006;36:254–260.
16. Rossi RE, Monasterolo G, Coco G, Operti D. Possible relationship between systemic side effects and sensitization to rPar j 2 in allergic patients submitted to an ultra-rush (20 min) sublingual immunotherapy and selected by component resolved diagnosis. *Int Arch Allergy Immunol*. 2005;138:105–110.
17. Mellerup MT, Hahn GW, Poulsen LK, Malling H. Safety of allergen-specific immunotherapy: relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. *Clin Exp Allergy*. 2000;30:1423–1429.
18. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D. Systemic reactions to immunotherapy: influence of composition and manufacturer. *Clin Exp Allergy*. 2003;33:470–474.
19. Ohashi Y, Nakai Y, Tanaka A, et al. Risk factors for adverse systemic reactions occurring during immunotherapy with standardized *Dermatophagoides farinae* extracts. *Acta Otolaryngol Stockh*. 1998;538: S113–S117.
20. Canonica GW. Noninjection routes for immunotherapy. *J Allergy Clin Immunol*. 2003;111:437–448.
21. Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy*. 2004;59:45–53.
22. Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy*. 1996;26: 1253–1261.
23. Baena-Cagnani C, Passalacqua G, Baena-Cagnani R, Croce VH, Canonica GW. Sublingual immunotherapy in pediatric patients: beyond clinical efficacy. *Curr Opin Allergy Clin Immunol*. 2005;5:173–177.
24. Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy*. 2005;35:565–571.
25. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy*. 1999;54:1110–1113.
26. Lombardi C, Gargioni S, Melchiorre A, et al. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy*. 2001;56:889–892.
27. Wilson DR, Torres-Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy*. 2005; 60:4–12.
28. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled and double-blind trials. *Ann Allergy Asthma Immunol*. 2006;97: 141–148.
29. Penagos M, Passalacqua G, Compalati E, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest*. 2008;133:599–609.
30. Andrè C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual swallow immunotherapy in children and adults. *Int Arch Allergy Immunol*. 2000;121:229–234.
31. Di Rienzo V, Minelli M, Musarraz A, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy*. 2005;35:560–564.
32. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy*. 2006;61:1235.
33. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy*. 2006;61:1236–1237.
34. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy*. 2007;62:567–568.
35. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy*. 2008;63:374.
36. Evans C, Ildstad S. *Small Clinical Trials: Issues and Challenges*. Washington, DC: Institute of Medicine; 2001.
37. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2004;93:425–430.
38. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. *Am Stat*. 1998;52:119–126.
39. Demidenko E. Sample size determination for logistic regression revisited. *Stat Med*. 2007;26:3385–3397.
40. Confidence interval of a proportion or count. GraphPad QuickCalcs Web site. http://www.graphpad.com/quickcalcs/ConfInterval1.cfm. Accessed May 3, 2008.
41. *StatXact 4.1* [computer program]. Cambridge, MA: Cytel Software.
42. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2001;87:S47–S55.
43. Canonica GW, Compalati E, Fumagalli F, Passalacqua G. Sublingual and oral immunotherapy. *Immunol Allergy Clin North Am*. 2004;24: 685–704.
44. Van Metre TE Jr, Adkinson NF Jr, Amodio FJ, et al. Comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J Allergy Clin Immunol*. 1982;69:181–193.
45. Cox LS, Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol*. 2006;117:1021–1035.
46. Holden WL. Benefit-risk analysis: a brief review and proposed quantitative approaches. *Drug Saf*. 2003;26:853–862.
47. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;117:802–809.

48. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118:434–440.
49. Radulovic S, Calderon MA, Wilson DR, Durham SR. Cochrane Systematic Review: safety profile of sublingual immunotherapy (SLIT) for allergic rhinitis (AR) [abstract]. *J Allergy Clin Immunol*. 2008;121:S142.
50. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
51. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol*. 2005;95:254–258.
52. Lombardi C, Gargioni S, Cottini M, Canonica GW, Passalacqua G. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy*. 2008;63:375–376.

Requests for reprints should be addressed to:
Noel Rodríguez-Pérez, MD
Allergy Clinic
Autonomous State University of Tamaulipas
Calle 5a, # 217-altos, H. Matamoros
Matamoros, Tamaulipas 87300, Mexico
E-mail: rnoel@prodigy.net.mx