

Dosing of sublingual immunotherapy for allergic rhinitis: evidence-based review with recommendations

Bryan D. Leatherman, MD^{1,2}, Ayesha Khalid, MD³, Stella Lee, MD⁴, Kevin McMains, MD⁵, Jacques Peltier, MD⁶, Michael P. Platt, MD⁷, Robert J. Stachler, MD⁸, Elina Toskala, MD, PhD⁹, Guy Tropper, MD¹⁰, Giri Venkatraman, MD¹¹ and Sandra Y. Lin, MD¹²

Background: Since the mid 1980s, the clinical use of sublingual immunotherapy (SLIT) has dramatically increased. However, 1 of the primary barriers to providing SLIT is lack of a published dosing recommendations. The purpose of this work is to provide a range of effective SLIT dosing based upon a rigorous review of the existing evidence base. An appendix with SLIT dosing recommendations is also included.

Methods: A comprehensive search of the past 25 years of the medical literature using PubMed was performed for specific antigens. Inclusion criteria for articles included: randomized, placebo-controlled studies of SLIT, studies with clinical allergic rhinitis outcomes, and dosing units available to determine the micrograms per month of major allergen administered. The extracted data was used to compile a range of effective SLIT dosing for individual antigens.

Results: Seventy-five articles met the inclusion criteria, providing a range of effective dosing for some allergens. There was commonly a wide range in doses for particular antigens between the individual studies. For some antigens,

there was significant overlap in dosage amount between studies showing efficacy and lack of efficacy. Clinical trials meeting inclusion criteria are not available for many allergens.

Conclusion: This study provided a comprehensive review of the published sublingual dosing ranges for specific antigens. The review provided a range of effective sublingual doses for some allergens, whereas for other allergens there was insufficient published data to determine specific doses. Recommendations for SLIT dosing were produced based on the data revealed in the review and expert opinion.
© 2015 ARS-AAOA, LLC.

Key Words:

type I allergy; subcutaneous immunotherapy; evidence-based medicine; aeroallergens; allergic conjunctivitis; allergy injections; asthma; sublingual immunotherapy

How to Cite this Article: Leatherman BD, Khalid A, Lee S, et al. Dosing of sublingual immunotherapy for allergic rhinitis: evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2015;5:773-783.

Allergy immunotherapy can be considered for those patients with allergic rhinitis who demonstrate symp-

toms on exposure to allergens and whose diagnosis is confirmed with specific immunoglobulin E (IgE) testing (skin testing or blood testing). Patients are candidates for immunotherapy if their symptoms are not controlled by avoidance and medication, they cannot tolerate medication, or

¹Coastal Sinus and Allergy Center, Gulfport, MS; ²Coastal Ear Nose and Throat Associates, Gulfport, MS; ³Massachusetts Eye And Ear Infirmary, Boston, MA; ⁴Department of Otolaryngology-Head and Neck Surgery, Division of Sinonasal Disorders and Allergy, University of Pittsburgh Medical Center, Pittsburgh, PA; ⁵Otolaryngology, South Texas Veterans Health Care System, San Antonio, TX; ⁶North Oaks ENT and Allergy, Hammond, LA; ⁷Department of Otolaryngology-Head and Neck Surgery, Boston University School of Medicine, Boston, MA; ⁸Henry Ford Medical Group, Sterling Heights, MI; ⁹Department of Otolaryngology-Head and Neck Surgery, Temple University School of Medicine, Philadelphia, PA; ¹⁰Avant Garde Medical Care, Boucherville, QC, Canada; ¹¹Dartmouth-Hitchcock Medical Center, Lebanon, NH; ¹²Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, MD

Correspondence to: Bryan D. Leatherman, MD, 9000 Lorraine Rd., Gulfport, MS 39503; e-mail address: Leathermanmd@coastalent.net

Additional Supporting Information may be found in the online version of this article.

Funding sources for the study: This article is a product of a work group appointed by the American Academy of Otolaryngic Allergy (AAOA). Funding in the form of facilitating a face-to-face meeting was provided by the AAOA.

Potential conflict of interest: B.D.L.: Speaker for Alk Abello, Merck, and Teva; research support from ALK Abello; Board of Directors for AAOA. K.M.: Board of Directors for American Academy of Allergic Allergy. E.T.: Advisory Board member: Merck, Greer.

Received: 21 January 2015; Revised: 27 April 2015; Accepted: 2 May 2015
DOI: 10.1002/alr.21561

View this article online at wileyonlinelibrary.com.

they desire a therapy that can alter the natural history of the disease. Specific immunotherapy involves repeated dosing of small amounts of allergen over time to decrease allergy symptoms in sensitized individuals by eliciting greater immune tolerance to the offending allergen.¹ Sublingual immunotherapy (SLIT) is a form of immunotherapy that involves introduction of the allergen extract under the tongue in either aqueous or tablet form. SLIT has been shown to be effective for allergic rhinitis in several large systematic reviews of randomized controlled trials (RCTs) for inhalant allergens. It has shown efficacy in decreasing allergy symptoms, as well as decreasing medication use, improving allergic asthma, and has shown positive effects on disease-specific quality of life.^{2,3}

Since the first modern reports of SLIT for allergic rhinitis in the mid-1980s,⁴ the clinical use of SLIT has dramatically increased. An analysis of SLIT use in a 2009 publication found that 45% of immunotherapy in Europe is in the form of SLIT, with up to 80% in southern Europe.⁵ In the United States, there are currently no U.S. Food and Drug Administration (FDA) aqueous approved forms of SLIT; however, antigens approved for subcutaneous administration have been used off-label for SLIT in the United States. In April 2014, the FDA approved the first SLIT tablets for use for grass pollen allergy in the United States, followed by approval of a ragweed SLIT tablet. It is likely that more tablets will be approved, but it is unlikely that a tablet form of SLIT will be available for most allergens in the near.

American interest in SLIT has been increasing, with a recent survey of allergists reporting that 10% have used SLIT clinically, nearly doubling since 2007.⁶ One-quarter of those using SLIT reported have extensive experience with SLIT. A separate 2014 survey of 250 physicians treating patients with allergy immunotherapy found that 68% of primary care physicians, 45% of allergy-immunologists, and 36% of otolaryngologists had more than 10% of their immunotherapy patients on SLIT.⁷ However, 1 of the primary barriers to using SLIT cited by those surveyed included lack of a published practice parameter. Evidence of this barrier can be found in a recent survey that revealed almost all otolaryngologists and allergy-immunologists (86% and 93%, respectively) who offer subcutaneous immunotherapy mix the treatment vials in house, whereas 38% of otolaryngologists and 44% of allergy-immunologists outsource the production of SLIT treatment vials.⁸ This suggests the lack of a published practical SLIT vial mixing instructions. The purpose of this work is to provide a range of effective SLIT dosing by allergen based upon a rigorous review of the existing evidence base. This review examines published randomized, placebo-controlled trials of SLIT to determine the evidence-based effective dosing range of specific allergens. It is important to recognize that this document is not a practice guideline on sublingual dosing, but a recommendation of dosing based on the best available published data, combined with expert opinion.

Materials and methods

A comprehensive search of the past 25 years of the medical literature using PubMed was performed on May 7, 2014; MeSH terms used included immunotherapy, allergy immunotherapy, sublingual immunotherapy, and the names of specific allergens (cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria*, cat, ragweed, *Parietaria*, birch, Timothy, cedar, and olive). In addition to the publications obtained from the comprehensive search of the medical literature, the bibliography of the articles and previously published reviews were searched as well. Inclusion criteria for articles in this review are as follows: randomized, placebo-controlled studies of SLIT; studies with clinical allergic rhinitis outcomes; dosing units available to determine the micrograms per month of major allergen administered, and confirmation of allergic status of subjects with skin testing or in vitro testing. Studies that did not include identifiable dosing units were excluded. Studies using mixes of allergens were excluded with the exception of studies using mixes of *D. pteronyssinus* and *D. farinae*, and grass mix, which are well-established and commonly-used mixes. Data abstraction was performed from the studies including: tablet or aqueous SLIT, number of patients which were enrolled/completed the study, age range of study participants, treatment duration, allergen content per dose, dosing frequency, dosing duration, cumulative dose, micrograms of major allergens per month, and clinical outcomes. For each allergen, 2 study members independently reviewed abstracts for study inclusion, and full articles were reviewed for data abstraction; any differences of opinion were resolved with repeat review and consensus decision of the pair of reviewers. Based on the reported research methodology, published clinical studies were rated by category of evidence in order to determine the strength of the recommendation.⁹

Results

Table 1 shows the range of effective SLIT dosing by allergen. Supporting Table 1 summarizes the randomized, placebo-controlled trials of SLIT included in this work.

Perennial allergens (*D. farinae*, *D. pteronyssinus*, *Alternaria*, cat)

D. farinae and *D. pteronyssinus*

A PubMed search yielded 19 trials that met inclusion criteria. Ten studies showed significant clinical benefit in primary outcomes measures compared to placebo,^{10–19} whereas 9 studies did not show a difference between groups.^{20–28} Overall doses were highly variable and micrograms per month per antigen ranged as follows:

Der p 1 = 9.6 μ g/month^{12,16} to 1423 μ g/month¹⁵;
Der p 2 = 4.8 μ g/month^{12,16} to 6 μ g/month¹⁰;
Der f 1 = 2 μ g/month¹⁹ to 3650 μ g/month.¹¹

TABLE 1. Recommended SLIT dosing (10-mL treatment vial)

Allergen	Published dosing range ($\mu\text{g}/\text{day}$)	Recommended daily dose range ($\mu\text{g}/\text{day}$)	Labeled potency used for calculations	Amount of concentrate to add for vial mixing in mL (range)
Dust mite				
<i>D. pteronyssinus</i>	0.32–47	16 (10–28)	10000 AU/mL	5 (3–9) ^a
<i>D. farinae</i>	0.07–121	16 (10–28)	10000 AU/mL	5 (3–9) ^a
Standardized extract: grass				
Timothy grass	15–30	15–30	100000 BAU/mL	1 (1–2)
Bermuda grass	5–40	18	100000 BAU/mL	2.5 (1–5)
Standardized extract: weed				
Ragweed	12–124	15–50	1:20 wt/vol or 100000 AU/mL	2 (2–5)
Cat, hair	n/a	n/a	10000 BAU/mL	6 (4–8)
Dog, nonstandardized	n/a	n/a	1:20 wt/vol	2 (2–4) ^b
Nonstandardized extract				
Pollen, other	5–40	18	1:20 wt/vol	2 (2–4) ^{b,c}
Mold/fungi, cockroach	n/a	n/a	1:20 wt/vol	2 (2–4) ^{b,c}

^aIf treating with both dust mites, consider adding one-half of the recommended dose for each because of significant cross-reactivity.

^bBased on 1:20 wt/vol concentrate solution.

^cNonstandardized antigen dosing based on 30 times recommended monthly SCIT dosing (0.5 mL of 1:100 to 1:200 wt/vol solution), because microgram content was not available for the nonstandardized pollens.

AU = allergy units; BAU = bioequivalent allergy unit; n/a = not available; SLIT = sublingual immunotherapy.

A mix of *D. farinae* and *D. pteronyssinus* did show clinical benefit in 1 study, which based dosing on age.¹⁸ For patients aged >14 years, 2250 $\mu\text{g}/\text{month}$ was used, whereas patients <14 years were treated with 750 $\mu\text{g}/\text{month}$.

In the studies that showed clinical benefit dosing ranged as follows:

Der p 1 = 9.6 $\mu\text{g}/\text{month}$ ^{12,16} to 1423 $\mu\text{g}/\text{month}$ ¹⁵;
Der p 2 = 4.8 $\mu\text{g}/\text{month}$ ^{12,16} to 6 $\mu\text{g}/\text{month}$ ¹⁰;
Der f 1 = 2 $\mu\text{g}/\text{month}$ ¹⁹ to 3650 $\mu\text{g}/\text{month}$.¹¹

In the studies that did not show clinical benefit dosing ranged as follows:

Der p 1 = 47.5 $\mu\text{g}/\text{month}$ ²⁶ to 975 $\mu\text{g}/\text{month}$ ²⁰;
Der p 2 = data not available;
Der f 1 = 18 $\mu\text{g}/\text{month}$ ²⁶ to 2350 $\mu\text{g}/\text{month}$.²⁰

There was considerable overlap in dosage between studies that showed benefit in comparison to studies that did not. Based on the review of the published literature, the monthly dosing showing clinical benefit ranged from 9.6 μg to 1423 μg (*Der p 1*) for *D. pteronyssinus*, and 2 μg to 3650 μg for *D. farinae* (evidence grade 1b).

Alternaria

A PubMed search revealed 2 studies that met inclusion criteria. The 2 studies included for final analysis used aqueous formulations for SLIT. The range of *Alternaria*

concentration was 3.6 μg per month in the first study²⁹ to 6.0 μg per month in the second study.³⁰ Both studies showed favorable and statistically significant outcomes for either primary symptoms of allergic rhinitis or allergy medication reduction. Based on review of the published literature, the dosing range for successful use of SLIT for *Alternaria* mold allergy is between 3.6 and 6.0 μg per month (evidence grade 1b).

Cat

A PubMed search revealed 2 studies that examined the efficacy of SLIT for cat allergy that met inclusion criteria.^{31,32} The studies varied vastly in their dosing, duration, and the endpoints that were measured. Alvarez-Cuesta et al.³² treated their cohort for a year with daily dosing, delivering a cumulative dose of 17.1 μg (1.425 μg per month of *Fel d 1*). The study noted statistically significant ($p < 0.05$) improvement in nasal, bronchial, and eye symptoms. However, the dropout rate from the study was significant (17/50 enrolled).³² Nelson et al.³¹ treated their patients for only 3 months (105 days) with every other day dosing, and noted no statistically significant changes in nasal symptoms. Dosing in the Nelson et al.³¹ study varied from 12.9 to 257.1 μg per months of *Fel d 1*. With the limited information available in the literature, it is not possible to determine a specific effective dose range for cat SLIT at this time.

Seasonal allergens (Timothy grass, other grasses, ragweed, birch, cedar, olive, ash, tree mixes,

Parietaria

Timothy grass

A PubMed search revealed that there were 12 studies which met inclusion criteria.^{33–44} The 12 studies that were included for the final analysis were primarily tablet formulations. One study was an aqueous formulation for SLIT.³³ For Timothy grass, the most common formulation used was a daily dose of a 75000 standardized quality tablet (SQ-T) (or 2800 bioequivalent allergen units [BAU]), which contained 15 μg of the *Phl P 5* allergen. The range of dosing was 450 to 900 μg per month. All 12 studies showed favorable and statistically significant outcomes for the primary symptoms of allergic rhinitis or a reduction in allergy medication. Three studies were done in children.^{34,35,42} These studies showed improvements in rhinoconjunctivitis and asthma scores during pollen seasons. Immunoglobulin G4 (IgG4) levels and IgE blocking factors were significantly increased during these studies. SLIT for grasses was found to be safe in both children and adults.

Most of the studies had a treatment duration that began before the grass pollen season (range, 8 to 35 weeks) and lasted beyond 1 year. The shortest treatment duration studied was 23 weeks. Significant improvements were noted in quality of life^{37–40,42} and improvements in sleep scores.⁴⁰ Lower-dose tablets (25000 tablet [150 μg], 2500 tablet [45 μg]) did not result in statistically significant improvements of rhinoconjunctivitis scores and allergy medication reductions.^{39,44} Based on the published literature, the effective dosage range is between 450 and 900 μg per month (evidence grade 1b).

Other grasses and grass mixes (excluding Timothy grass)

A PubMed search revealed 20 publications which met inclusion criteria. The twenty studies included 14 aqueous and 6 tablet formulations. For grasses (excluding Timothy grass), the range of SLIT concentration was 6 to 1200 μg per month (mean $\pm$ SD: 494 $\pm$ 388). For the 17 studies that showed a favorable and statistically significant outcome for either primary symptoms of allergic rhinitis or allergy medication reduction, the mean SLIT dosing was 540 μg per month. There were 3 studies with doses lower than 1 standard deviation (1SD) below the mean (6 to 16 μg per month) that showed significant improvement in symptom scores.^{45–47} Three studies that failed to show significance in symptom or medication scores had a dosing range of 168 to 275 μg per month.^{48–50} Based on review of the published literature, the effective dosing range of SLIT for grasses (except Timothy grass) is approximately 540 μg per month, with a range of 150 to 1200 μg per month (evidence grade 1b).

Ragweed

A PubMed search revealed 8 studies^{51–58} which met inclusion criteria. These studies included 3 aqueous and 5 tablet formulations for SLIT. The range of doses used was 372 to 3720 μg per month. For the studies that showed a favorable and statistically significant outcome for either primary symptoms of allergic rhinitis or allergy medication reduction, the range of dosing was 372 to 3720 μg per month. The studies that demonstrated on improvement in either quality of life or other immunologic measures had a dosing range of 372 to 3720 μg per month. Studies that failed to show any efficacy for SLIT had a dosing range of <370 μg per month. Based on review of the published literature, the effective SLIT dosing range for ragweed allergy is between 372 and 3720 μg per month (evidence grade 1b).

Parietaria

A PubMed search revealed 5 studies that met inclusion criteria.^{59–63} The 5 studies included for final analysis were all aqueous formulations. The range of SLIT concentration was 1.9 to 2700 μg per month (542.2 $\pm$ 1206.2 μg). Four of the 5 studies were between 1.9 and 3.6 μg per month (2.75 $\pm$ 0.982 μg), with 1 outlier at 2700 μg per month. All included studies showed a favorable and statistically significant outcome for either primary symptoms of allergic rhinitis or allergy medication reduction. Based on review of the published literature, the dosing range for *Parietaria* is between 1.9 and 2700 μg per month, with 4 of 5 studies showing efficacy between 1.9 and 3.6 μg per month (evidence grade 1b).

Birch

A PubMed search revealed 2 studies^{64–72} that met inclusion criteria. One study demonstrated clinical efficacy of a preparation with *Bet v 1* content of 738 μg /month in a year-round treatment protocol.⁶⁴ Another study using a 4-month pre-coseasonal protocol showed clinical benefit with a monthly *Bet v 1* dose of 862.5 μg .⁶⁵ Based on review of the published literature, the dosing range for successful use of SLIT for birch allergy is between 738 and 862.5 μg per month (evidence grade 1b).

Cedar

A PubMed search revealed 4 studies that met inclusion criteria.^{73–76} Two papers examined^{73,74} treatment with Japanese cedar (*Cry j1*), whereas the others examined^{75,76} mountain cedar/Ashe juniper. In each of the 4 papers, improvement was seen in symptom scores, quality-of-life measures, or allergy medication use. Based on review of the published literature, effective dosing for Japanese cedar ranged from 10 to 60 μg per month of *Cry j 1*. For mountain cedar, effective dosing range was between 2736 and 6840 μg /month *Jun a 1* (evidence grade 1b).

Olive

A PubMed search revealed 1 placebo-controlled study⁷⁷ examining the efficacy of SLIT for the treatment of olive tree allergy. The study showed the efficacy of a preparation containing *Ole e 1* at a dosage of 675 μg per month in a 2-year pre-coseasonal (6 months/year) protocol.⁷⁷ Based on review of the published literature, an effective dosing for olive tree allergy is 675 μg per month (evidence grade 1b).

Discussion

Safety of SLIT

The safety of SLIT has been well documented by multiple reviews of the large number of SLIT clinical trials conducted since the 1980s.^{2,78–80} Although adverse events do occur, the vast majority are usually mild local reactions in the oral cavity, such as itching, burning, or mild swelling. Nausea and stomachaches have also been described. The occurrence of systemic side effects are rarely reported, and are thought to occur in less than 1% of patients. Although 11 episodes of anaphylaxis have been reported in the literature,⁸¹ no fatal event has been documented with SLIT use. No clear risk factors for adverse reactions to SLIT have been identified, including no increased risk associated with dosing techniques (including dose amount and escalation technique), skin test sensitivity, asthma diagnosis, gender, age, or multiple antigen use.⁷⁸ The safety of SLIT has been shown in young children, even children as young as 2 years of age.^{82–84} Because of a lack of specific data in publications concerning the safety of SLIT in special circumstances, such as during pregnancy and with uncontrolled asthma, some of the general precautions recommended for subcutaneous immunotherapy¹ should be considered with the use of SLIT.

SLIT dosing

As with all forms of immunotherapy, the goal in dose selection is to provide sufficient amounts of allergen to produce the maximum benefit, while limiting adverse events. Delivering a dose that is below the level needed for clinical efficacy is not beneficial to the patient. Likewise, delivering a dose that contains more than the necessary amount of antigen may subject a patient to unnecessary additional risk, and drive up the cost of treatment. Optimally, all immunotherapy dosing would be based on randomized, double-blind, placebo-controlled dose-response studies where multiple dose variations are assessed to determine the dose that achieves the optimal balance of efficacy and adverse event frequency. Unfortunately, there are few large dose-response studies available from which to determine the optimal dose of various antigens for use with all forms of immunotherapy, including injection and sublingual. Determining the optimal dose of immunotherapy is also complicated by difficulty of determining the amount of antigen delivered in many of the available studies.^{1,2,79}

The SLIT efficacy studies were also performed in various countries with antigen products that may not be available in other regions of the world. Therefore, the reality for both injection and SLIT dosing is that often the optimal dose for a particular antigen has to be estimated or extrapolated using the best available data, and generally recognized ranges of dosing efficacy.^{1,3} With immunotherapy in general, safety is of utmost concern. Fortunately, a wide range of doses have been published that have showed efficacy and safety.

To achieve the goal of this publication to provide a practical dosing strategy for practitioners who desire to provide SLIT as a therapeutic option for their patients, the published dosing information presented in this work was combined with expert opinion to help determine an acceptable dosing range for various antigens. As with subcutaneous dosing recommendations, many individual antigens do not have specific dose-related efficacy data published, and dosing recommendations are made based on extrapolation from other allergens and published likely effective dosing ranges.³ For more commonly-studied antigens, using the brief summaries of the reviewed published dosing data presented in the results section, a dosing recommendation based on best currently available data is presented (see Appendix A: Practical Guideline for SLIT Dosing). Once again, it is important to recognize that this document is not a practice guideline on sublingual dosing, but a recommendation of dosing based on the best available published data, combined with expert opinion.

Limitations and future research needs

There are several limitations to our current study for the U.S. practitioner. One limitation is that the majority of RCTs in this review were not of North American origin. There are some potential limitations when comparing European to U.S. allergens,^{85–87} including: methods used for determining potency of extract; national (U.S.) vs in-house reference standards (Europe); and potential increased potency of U.S. extracts vs European extracts.

Another limitation is that for some antigens there is an overlap in dosage amounts that were found effective in 1 study, but not effective in another study. The overlap in effective and non-effective dosages makes it more difficult to determine what is an effective dose. Also, although our project focused on effective doses presented in RCTs, it is possible that lower dosages are effective. For example, in the case of birch, although these studies were excluded from our project, a short-term study from Horak et al.⁶⁶ documented the efficacy of a monthly dosage that could be estimated to 41 μg /month from a conversion factor published by Kervliet et al.⁶⁷ Three studies^{69–71} suggested clinical efficacy for a *Bet v 1* dosage range between 8.3 μg /month (Marogna et al.⁶⁹) and 100 μg /month (Marogna et al.⁷¹), but did not include a placebo arm.

The need for further research is evident for those allergens in which few RCTs exist regarding efficacy. Future

dose-response studies will be helpful in further delineating a range of effective doses for SLIT.

Conclusion

SLIT is effective for the treatment of allergic rhinitis. The study shows a range of effective dosing for allergens based on existing RCTs. Future dose-response studies will be helpful in further refining effective doses for SLIT.

Appendix A: Practical guidelines for SLIT dosing

Surveys have shown that most physicians offering allergy immunotherapy prepare injection immunotherapy vials in their office, whereas a significant percentage outsource the production of SLIT vials. The leadership of the American Academy of Otolaryngology (AAOA) recognized this as an indication that physicians are in need of some direction as to how to create SLIT vials, particularly regarding what doses of antigens to use. The AAOA Board of Directors authorized a committee tasked with reviewing the SLIT dosing literature, and creating a practical dosing recommendation based on the currently available information. The committee worked together by conference calls, e-mail correspondence, and a 2-day face-to-face work meeting sponsored by the AAOA. The task given to the authors in preparing this document was to create a set of instructions that would assist physicians in the preparation of SLIT vials for their patients when a physician considers it an appropriate treatment option. Acknowledging that clear dose-response studies are not available for most antigens to direct the “best” dose to deliver during SLIT, the authors have compiled the latest data available to give dosing recommendations based on the best available data published. This is not unique to SLIT; most antigens used in subcutaneous/injection immunotherapy suffer from the same data limitations. In an effort to make dosing recommendations that are practical on a clinical level, the targeted dose and dosing ranges were calculated by choosing ranges toward the mid-portion of the published effective dosing ranges. The authors had to make calculations based on published commercially available stock vial contents that often had wide ranges, so concentration numbers near the mid-portion of these ranges were chosen. The resulting recommended target dose and dosing ranges were then rounded to practical numbers that could be reliably measured for vial creation. After rounding to practical numbers, the dosing calculations were then rechecked to make sure the amount recommended fell within the published effective dosing range for each antigen. Given the wide range of published effective doses, and the wide range of antigen content in the commercially available antigen products, is recognized by the authors that doses above and below the recommended dosing could still be effective. As more dosing data becomes available over time, these

recommendations will be reviewed and altered as appropriate. The authors highly recommend that physicians make diligent efforts to keep up to date with the latest recommendations. It is important to recognize that this document is not a practice guideline on sublingual dosing, but a recommendation of dosing based on the best available published data, combined with expert opinion.

These dosing recommendations are based on the goal of creating a 10 mL treatment vial. With a daily maintenance dose of approximately 0.3 mL, there is enough volume for approximately 33 days of treatment. Some physicians choose to prepare larger or smaller quantities. In those circumstances, the physician will need to make appropriate adjustments to the amounts of materials added to the vials to maintain the targeted antigen concentration in the treatment vial.

Although the relative safety of SLIT has been widely accepted in the literature, it is important for the reader to recognize that all forms of immunotherapy carry some risk of serious or fatal systemic reactions. The safety data of SLIT, and the recognition and management of adverse events is beyond the scope of this work. As with all forms of immunotherapy, the practitioner must educate themselves of the potential risks of the treatment, and have the knowledge necessary to manage any potential problems.

Supplies Antigen

Liquid-based antigens are available commercially from several companies in the United States. It is preferable to use antigens supplied in 50% glycerin.

Diluent

The diluent of choice in preparing SLIT vials is 50% glycerin. The glycerin not only helps with the preservation of antigen in the treatment vial, it also provides a sweetness that helps mask the taste of the antigens. When using drops to deliver SLIT, it is important to recognize that the viscosity of the fluid affects the amount of fluid contained in each drop. Therefore, if one chooses to use a different diluent than 50% glycerin, the amount of fluid delivered with each drop, and therefore the amount of antigen, will likely be different.

Vial type

There are multiple device options available for the delivery of SLIT. Multiple types of vials are available commercially, including plastic squeeze vials, glass vials with droppers that are inserted into the liquid, and metered-dose pump vials that have a consistent amount of liquid delivered with each pump. Drops can even be delivered via tuberculin (TB) syringes with the needle removed. During the initial escalation the solution is administered by drops. During maintenance, the antigen solution can be administered by drops, metered-dose pump vials, or by delivering the appropriate amount with a TB syringe (once again with needle

removed). Most antigen supply companies will have SLIT device options available, and TB syringes are readily available through multiple suppliers.

Other supplies

Various other supplies will be necessary in order to mix the sublingual antigen vials. These include similar supplies necessary when creating subcutaneous immunotherapy vials. Even though SLIT does not have to be prepared in sterile vials, one should still practice accepted vial mixing techniques published for the creation of subcutaneous immunotherapy vials, because it is important to maintain sterility of the antigen stock vials, especially if they are also used to create injection vials.⁸⁸

Vial mixing
Antigen content

Table 1 lists the recommended milliliter amount of antigen stock concentration that should be added to a 10-mL sublingual treatment vial. These recommendations are based upon the best available data concerning the likely effective daily antigen dose range determined by the extensive review of literature in this publication. To arrive at the recommended amount of antigen stock concentration, the authors also relied on the best available data on the range of antigen contained within the commercially available antigen products in the United States. This information was obtained by previously published data¹ on the ranges of antigen content contained in commercially available products, and by information provided by individual antigen supply companies. It should be recognized that the actual antigen content of each individual vial lot, even from the same manufacturer, can have significant variation. Fortunately, as with injection immunotherapy, there is a sufficient range of potentially effective doses to help offset the inconsistencies in stock vial antigen content. The milliliter amount of stock antigen product recommended for addition to a 10-mL vial was derived by assuming the each stock vial will have an antigen content in the middle of the published range of antigen contents in commercially available products.

For antigens that do not have sufficient published data to determine an effective SLIT dose and for nonstandardized allergens that do not have adequate information about the average antigen content in available commercial products, a daily dose was chosen that is approximately 30 times the monthly subcutaneous immunotherapy dose as defined by a published practice parameter.¹ Some recent publications have suggested that a SLIT dose that is 30 times the currently recommended subcutaneous immunotherapy dose falls within the effective dosing range of several well-studied antigens.⁸⁹ As is the case with subcutaneous immunotherapy, the majority of nonstandardized antigens do not have specific dosing recommendations based on dose-response studies, and therefore require an extrapolation of other efficacy data.

TABLE 2. Sublingual vial creation instructions

Initial maintenance vial and escalation vial creation
Make the first 2 dropper bottles at one time (will be numbered in reverse so #1 is first vial used by patient and is the most dilute)
Dropper vial #2 (10-mL vial) (This vial will contain maintenance dose concentration)
Add the amount of concentrate for each antigen (as listed on the vial formula sheet) to a 10-mL dropper vial
Add enough 50% glycerin to achieve total volume of 10 mL
Dropper vial #1 (5-mL vial)
Add 0.5 mL of solution from vial #2
Add 2 mL 50% glycerin
Subsequent maintenance dropper vial creation: 10-mL vial
Add the amount of concentrate for each antigen (as listed on the vial formula sheet) to a 10-mL dropper vial
Add 50% glycerin to achieve total volume of 10 mL

When using the recommended formula for preparing a 10-mL SLIT treatment vial, one should refer to the recommended amount of stock antigen product provided in Table 1. Although list practical, one could also request information from the manufacturer about the estimated antigen content in each vial of antigen purchased and recalculate the proper amount of concentrate to add each time.

Sublingual vial mixing

During the mixing of the initial SLIT vials, 2 separate vials will be created. Initially, a maintenance vial with the maintenance concentration of antigens will be created. Subsequently, a smaller volume escalation vial will be created using solution from the maintenance vial. Even though the maintenance vial is actually created first, it is desirable to have the escalation vial labeled as “Vial #1” and the maintenance vial labeled as “Vial #2” so the patient will not be confused about the order in which they should be used them.

When creating the maintenance vial, first determine which antigens will be included in the vial. Even though SLIT vials do not have to be sterile, one should practice sterile technique when handling the stock vials and diluent vials, especially if they will also be used for mixing of injection immunotherapy vials. Once the antigens to be included have been determined, proceed with mixing the vials as outlined in Table 2. Refer to Table 1 to determine the proper amount of antigen stock concentration to include for each individual antigen. The goal is to make a 10-mL final volume vial. Therefore, if 5 antigens are included in the treatment vial, and each antigen requires 1 mL of stock concentrate solution, then a full of 5 mL of volume of antigen will be added to the sublingual treatment vial.

To bring the total volume to 10 mL, one would then add an additional 5 mL of 50% glycerin to the treatment vial.

For creation of the escalation vial, it is not necessary to make a 10-mL vial. Because the escalation vial will only be used for 7 days (with a total of 28 drops consumed), making a larger escalation vial would waste expensive antigen. To create a 1:5 dilution of the maintenance vial with lesser volume, 0.5 mL of the maintenance solution will be combined with 2 mL of 50% glycerin in a separate treatment vial, giving a total volume of 2.5 mL.

Subsequent maintenance vials for continuation of SLIT should be created in the same manner as the initial maintenance vial.

Dosing schedule

Dose escalation

The purpose of performing a short-dose escalation in this dosing recommendation is to identify patients who might have excessive local adverse symptoms at doses below the targeted maintenance dose. The escalation is not performed to allow incremental changes in the immune system to reduce the risk of severe/anaphylactic reaction. With the short dose escalation recommended, one can identify a potential dose that causes local side effects that are bothersome, and the targeted maintenance dose can then be lowered to the last tolerated amount. The escalation is not a requirement, and it is common practice for patients to be started on the targeted maintenance dose, instead of escalating the dose. This is different than the purpose of slow-dose escalation with injection immunotherapy, in which the goal is to increase the amount of antigen given over time to allow for favorable changes in the immune system as the antigen amount is increased. With injection immunotherapy, starting immunotherapy at the targeted maintenance dose carries a significant risk of severe/anaphylactic reaction.

The initial dose from the escalation vial (Vial #1) is 1 drop on day 1. Each subsequent day an additional drop is added to the dose amount until 7 drops are delivered on day 7 (Table 3). The drops are held under the tongue for 2 minutes and then swallowed. After reaching 7 drops, the escalation vial is discarded and the same escalation scheduled is followed for the maintenance vial (Vial #2). Once a dose of 7 drops is achieved, the patient has reached maintenance dosing.

If during the course of escalation the patient encounters excessive local reactions or abdominal discomfort, it is an option to use the last tolerated dose amount as maintenance for approximately 3 months before trying to escalate to the targeted dose again.

Maintenance dosing

There are several options for delivering the maintenance dose. The calculations for the desired maintenance dose for each antigen are based on delivering a targeted 0.3 mL of maintenance solution daily. One option is to continue 7 drops daily from the treatment vials used for escalation.

TABLE 3. Dose escalation schedule

Vial #1	Dose
Day 1	1 drop
Day 2	2 drops
Day 3	3 drops
Day 4	4 drops
Day 5	5 drops
Day 6	6 drops
Day 7	7 drops
Vial #2	
Day 8	1 drop
Day 9	2 drops
Day 10	3 drops
Day 11	4 drops
Day 12	5 drops
Day 13	6 drops
Day 14	7 drops

Although the amount of solution administered per drop differs for individual dropper vials, it is acceptable to consider that 7 drops delivered from the “average” dropper vial will deliver close to the targeted amount.

Another option for maintenance delivery is to deliver measured volumes. There are 2 main options for delivering a measured 0.3-mL dose. The least expensive option is to distribute 1-mL TB syringes with the needles removed to the patients. The syringes can be washed and reused. The patient can be taught to stick the tip of the syringe into the vial to withdraw 0.3 mL, and then deliver this into the sublingual area. Another option is to use commercially available metered-pump sublingual vials. Various companies offer different options. The patient should be instructed on how many pumps to deliver with each dose, depending on the amount of solution that is delivered with each pump. The volume delivered with each pump may be different for different commercially available vials, so the physician should determine the number of pumps necessary based on the manufacturer’s determination of the volume delivered per pump for each product.

Whatever delivery method used, the goal is to deliver approximately 0.3 mL of solution per dose.

Duration of immunotherapy

As with subcutaneous immunotherapy, it is commonly believed that if significant improvement is realized with SLIT, the treatment should be continued for 3 to 5 years. It is thought that this duration of immunotherapy is necessary to better solidify the positive immunologic changes of immunotherapy long term after immunotherapy is stopped.

Once a patient has finished a 3-year to 5-year SLIT treatment program, it is generally accepted that immunotherapy can be abruptly stopped without any need for tapering. The patient can then be monitored over time for symptom control. If the patient demonstrates a clear, persistent worsening of allergy symptoms over time off immunotherapy, one can give consideration to restarting immunotherapy.

Changing sublingual dosing

A physician may have patients who are already on SLIT doses different than the dosing recommendations included in this review. There is not sufficient literature to make an evidence-based recommendation on whether or how to switch a patient to a different SLIT dose. The authors agree that a practical approach is to assess the current clinical response of the patient. If the patient has had sufficient success with the current SLIT dose, then it would be reasonable to continue that dose. If the patient has not achieved the desired level of improvement, and the current dose is below the dose listed in these recommendations, the physician has the option to increase the dose to see if better clinical improvement can be obtained. If the dose is going to be increased, it is reasonable to follow the short escalation schedule in these recommendations to make sure there are no unacceptable reactions to the higher doses.

Multiantigen SLIT

The vast majority of published immunotherapy trials for subcutaneous and SLIT involve the use of single-antigen therapy. Despite the paucity of clinical trials assessing multiantigen immunotherapy, it is common practice for physicians to offer patients multiantigen immunotherapy, both in injection form and with SLIT. There is insufficient published literature to make an evidence-based recommendation on the practice of multiantigen SLIT. It is the opinion of the authors that it is reasonable practice, based on common practice in the physician communities, to offer multiantigen SLIT. From a practical standpoint, the number of antigens that can be included in a single vial is limited by the volume of the vial. When mixing the treatment vials, the

practitioner would add the appropriate amount of stock concentrate solution for each antigen being treated, and then a sufficient amount of 50% glycerin diluent would be added to end up with a 10-mL treatment vial. If the amount of stock antigen needed to treat multiple antigens exceeded 10 mL, even without the addition of glycerin diluent, then the antigens would need to be separated into separate vials to accommodate the necessary volume of stock concentrate. There is insufficient literature to direct whether doses from multiple sublingual vials should be administered at the same time or separated. The authors are aware of physicians who recommend taking both doses at the same time, whereas others recommend separating dosing (such as 1 vial dosed in the morning, and 1 vial dosed in the evening). Those who support separating the doses cite concerns of possible diluting effects of 1 dose with the other, whereas those proposing dosing at the same time often cite concerns that multiple daily doses may reduce compliance with regular SLIT administration.

Summary

SLIT has been extensively studied over the last 25 years. It has been widely accepted that SLIT is a reasonable alternative method for delivering immunotherapy to appropriately selected patients. Multiple surveys suggest that many physicians who want to offer SLIT as part of their immunotherapy practice are reluctant to mix the SLIT vials themselves. This is likely because of a lack of published dosing recommendations. The purpose of this SLIT dosing evidence-based review is to provide physicians with practical dosing recommendations based on the best available published data. As with subcutaneous immunotherapy, it is important to realize that dose-response studies are not available for most antigens; therefore, dosing recommendations are based on extrapolation of data from the antigens that have been studied, as well as expert opinion. As more information becomes available over time, dosing recommendations may change. It is important for physicians to continue to monitor the literature to keep up to date with current dosing recommendations.

References

- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 Suppl): S1–S55.
- Lin SY, Erekesima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013;309:1278–1288.
- Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66:740–752.
- Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy*. 1986;16:483–491.
- Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103:451–459; quiz 459–461, 495.
- Sikora JM, Tankersley MS; ACAAI Immunotherapy and Diagnostics Committee. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. *Ann Allergy Asthma Immunol*. 2013;110:194–197.e4.
- Ryan MW, Marple BF, Leatherman B, et al. Current practice trends in allergy: results of a United States survey of otolaryngologists, allergist-immunologists, and primary care physicians. *Int Forum Allergy Rhinol*. 2014;4:789–795.
- Leatherman B, Skoner DP, Hadley JA, et al. The Allergies, Immunotherapy, and Rhinoconjunctivitis (AIRS) survey: provider practices and beliefs about allergen immunotherapy. *Int Forum Allergy Rhinol*. 2014;4:779–788.
- Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999;318:593–596.
- Marcucci F, Sensi L, Di Cara G, et al. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sublingual immunotherapy. *Pediatr Allergy Immunol*. 2005;16:519–526.
- Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol*. 2014;133:1608–1614.e6.
- Ippoliti F, De Santis W, Volterrani A, et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol*. 2003;14: 216–221.
- Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol*. 2006;17:408–415.
- Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med*. 2006;100:1374–1383.
- O'Hehir RE, Gardner LM, de Leon MP, et al. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional

- regulatory T cells. *Am J Respir Crit Care Med*. 2009;180:936–947.
16. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy*. 2000;55:842–849.
 17. Tonnel AB, Scherpereel A, Douay B, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy*. 2004;59:491–497.
 18. Wang DH, Chen L, Cheng L, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope*. 2013;123:1334–1340.
 19. Yonekura S, Okamoto Y, Sakurai D, et al. Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children. *Allergol Int*. 2010;59:381–388.
 20. Aydogan M, Eifan AO, Keles S, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. *Respir Med*. 2013;107:1322–1329.
 21. Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol*. 2001;32:49–55.
 22. Bousquet J, Scheinmann P, Guinneepein MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy*. 1999;54:249–260.
 23. Bush RK, Swenson C, Fahlberg B, et al. House dust mite sublingual immunotherapy: results of a US trial. *J Allergy Clin Immunol*. 2011;127:974–981.e7.
 24. de Bot CM, Moed H, Berger MY, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol*. 2012;23:150–158.
 25. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy*. 2000;55:369–375.
 26. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol*. 1997;8:21–27.
 27. Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol*. 2007;18:47–57.
 28. Tseng SH, Fu LS, Nong BR, Weng JD, Shyr SD. Changes in serum specific IgG4 and IgG4/IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. *Asian Pac J Allergy Immunol*. 2008;26(2–3):105–112.
 29. Cortellini G, Spadolini I, Patella V, et al. Sublingual immunotherapy for *Alternaria*-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2010;105:382–386.
 30. Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to *Alternaria alternata*: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. *Curr Med Res Opin*. 2010;26:2801–2806.
 31. Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol*. 1993;92:229–236.
 32. Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, Fernandez-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. *Allergy*. 2007;62:810–817.
 33. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. 2009;124:150–156.e5.
 34. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergen immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol*. 2011;127:64–71.e4.
 35. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol*. 2009;123:167–173.e7.
 36. Dahl R, Kapp A, Colombo G, et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol*. 2008;121:512–518.e2.
 37. 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.
 38. Durham SR, Emminger W, Kapp A, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol*. 2010;125:131–138.e7.
 39. 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.
 40. Frolund L, Durham SR, Calderon M, et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy*. 2010;65:753–757.
 41. Lima MT, Wilson D, Pitkin L, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy*. 2002;32:507–514.
 42. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol*. 2014;112:146–153.e2.
 43. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol*. 2011;127:72–80.e2.
 44. Rak S, Yang WH, Pedersen MR, Durham SR. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: a double-blind, randomised study. *Qual Life Res*. 2007;16:191–201.
 45. Panzner P, Petras M, Sykora T, Lesna I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med*. 2008;102:1296–1304.
 46. Rolinck-Werninghaus C, Wolf H, Liebke C, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy*. 2004;59:1285–1293.
 47. Wuthrich B, Bucher C, Jorg W, et al. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Invest Allergol Clin Immunol*. 2003;13:145–148.
 48. de Blay F, Barnig C, Kanny G, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol*. 2007;99:453–461.
 49. Pradaliere A, Basset D, Claudel A, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy*. 1999;54:819–828.
 50. Roder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol*. 2007;119:892–898.
 51. Andre C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol*. 2003;131:111–118.
 52. Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2014;133:751–758.
 53. Creticos PS, ER, Couroux P, et al. A randomized, double-blind, placebo controlled parallel trial of standardized short ragweed sublingual allergy immunotherapy liquid (SAIL) extract in adult subjects with ragweed-induced allergic rhinoconjunctivitis [Poster #519]. Poster presented at: Annual Meeting of the American Academy of Allergy Asthma and Immunology; February 22–26, 2013; San Antonio, TX.
 54. Nayak AS, Atiee GJ, Dige E, Maloney J, Nolte H. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. *Allergy Asthma Proc*. 2012;33:404–410.
 55. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol*. 2014;113:93–100.e3.
 56. Nolte H, Hebert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol*. 2013;110:450–456.e4.
 57. Piconi S, Trabattoni D, Rainone V, et al. Immunological effects of sublingual immunotherapy: clinical efficacy is associated with modulation of programmed cell death ligand 1, IL-10, and IgG4. *J Immunol*. 2010;185:7723–7730.
 58. Skoner D, Gentile D, Bush R, Fasano MB, McLaughlin A, Esch RE. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol*. 2010;125:660–666.e4.
 59. D'Ambrosio FP, Ricciardi L, Isola S, et al. Rush sublingual immunotherapy in *Parietaria* allergic patients. *Allergol Immunopathol (Madr)*. 1996;24:146–151.
 60. La Rosa M, Ranno C, Andre C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):425–432.
 61. Pajno GB, Passalacqua G, Vita D, Caminiti L, Parmiani S, Barberio G. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with *Parietaria*-induced respiratory allergy: a randomized controlled trial. *Allergy*. 2004;59:883–887.
 62. Passalacqua G, Albano M, Riccio A, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: A double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 1999;104:964–968.
 63. Purello D, D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy*. 1999;54:968–973.
 64. Khinchi MS, Poulsen LK, Carat F, Andre 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.
 65. Voltolini S, Troise C, Incorvaia C, et al. Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study. *Curr Med Res Opin*. 2010;26:37–40.
 66. Horak F, Stubner P, Berger UE, Marks B, Toth J, Jager S. Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study. *J Invest Allergol Clin Immunol*. 1998;8:165–171.
 67. Kerkvliet E, Peekel I, Van Tuyn J, Sleijster H, Van Den Hout R. Amount of major allergen Bet v 1 and allergen activity in different European products for sublingual immunotherapy. *Allergy*. 2011;66(Suppl 94):622.
 68. Kinaciyan T, Jahn-Schmid B, Radakovics A, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol*. 2007;119:937–943.
 69. Marogna M, Colombo F, Spadolini I, et al. Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J Invest Allergol Clin Immunol*. 2010;20:146–152.
 70. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study. *J Allergy Clin Immunol*. 2005;115:1184–1188.

71. Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol.* 2007;98:274–280.
72. Mauro M, Russello M, Incorvaia C, D'Ingianna E, Gazzola G. Efficacy and safety of subcutaneous and sublingual immunotherapy in birch pollinosis. *J Allergy Clin Immunol.* 2004;113:S108.
73. Fujimura T, Yonekura S, Horiguchi S, et al. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clin Immunol.* 2011;139:65–74.
74. Makino Y, Noguchi E, Takahashi N, et al. Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2010;126:1163–1169.e5.
75. Ventura MT, Carretta A, Tummo RA, Buquicchio R, Arsieni A, Murgia N. Clinical data and inflammation parameters in patients with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy. *Int J Immunopathol Pharmacol.* 2009;22:403–413.
76. Vervloet D, Birnbaum J, Laurent P, et al. Safety and efficacy of *Juniperus ashei* sublingual-swallow ultrarush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol.* 2007;142:239–246.
77. Vourdas D, Syrigou E, Potamianou P, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy.* 1998;53:662–672.
78. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol.* 2006;117:1021–1035.
79. Leatherman BD, Owen S, Parker M, et al. Sublingual immunotherapy: past, present, paradigm for the future? A review of the literature. *Otolaryngol Head Neck Surg.* 2007;136(3 Suppl):S1–S20.
80. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy.* 2009;64(Suppl 91):1–59.
81. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy.* 2012;67:302–311.
82. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy.* 2005;60:133.
83. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. *Allergy.* 1999;54:1110–1113.
84. Lombardi C, Gargioni S, Melchiorre A, et al. Safety of sublingual immunotherapy with monomeric allergoid in adults: multicenter post-marketing surveillance study. *Allergy.* 2001;56:989–992.
85. Larenas-Linnemann D, Cox LS. European allergen extract units and potency: review of available information. *Ann Allergy Asthma Immunol.* 2008;100:137–145.
86. Larenas-Linnemann D, Esch R, Plunkett G, et al. Maintenance dosing for sublingual immunotherapy by prominent European allergen manufacturers expressed in bioequivalent allergy units. *Ann Allergy Asthma Immunol.* 2011;107:448–458.e3.
87. Larenas-Linnemann DE. Sublingual immunotherapy: dosing in relation to clinical and immunological efficacy. *Allergy Asthma Proc.* 2008;29(2):130–139.
88. American Academy of Otolaryngology: Compounding Allergenic Extracts. 2014. <http://www.aaof.org/pr.aspx?CAT=20>. Accessed May 24, 2015.
89. Cox L. Sublingual immunotherapy for aeroallergens: status in the United States. *Allergy Asthma Proc.* 2014;35:34–42.