

Sublingual Immunotherapy Dosing Regimens: What Is Ideal?



Jay J. Jin, MD, PhD^a, James T. Li, MD, PhD^a, Ludger Klimek, MD^b, and Oliver Pfaar, MD^{b,c} Rochester, Minn; Wiesbaden and Mannheim, Germany

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: January 1, 2017. Credit may be obtained for these courses until December 31, 2017.

Copyright Statement: Copyright © 2017-2019. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.0 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Jay J. Jin, MD, PhD, James T. Li, MD, PhD, Ludger Klimek, MD, and Oliver Pfaar, MD

Learning objectives:

1. To recognize the differences in dosing regimens of sublingual immunotherapy products.

2. To describe both immediate and long-term effects of sublingual immunotherapy in allergic airways disease.

3. To understand inherent limitations when comparing products containing allergen extracts.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: J. T. Li is employed by Mayo Clinic. L. Klimek has received research support from ALK-Abelló, Allergopharma, Bencard, Biomay, HAL, GlaxoSmithKline, LETI, Lofarma, Novartis, and Roxall; is on the Meda (Germany) and Novartis (Switzerland) boards; has received consultancy fees from ALK-Abelló, Allergopharma, Bionorica, Boehringer Ingelheim, GlaxoSmithKline, Lofarma, Novartis, Meda Pharmaceuticals, Merck Sharp & Dohme, Phadia/ThermoFisher, and Optima; has received lecture fees from ALK-Abelló, Allergopharma, Bionorica, Boehringer Ingelheim, GlaxoSmithKline, Lofarma, Novartis, and Meda; and has received payment for manuscript preparation from Meda and Bionorica. O. Pfaar has received consultancy fees from HAL-Allergy, Allergy Therapeutics, Bencard, Novartis, LETI, MEDA, ALK-Abelló, Allergopharma, Anergis, Biotech Tools s.a., Sanofi, Mobile Chamber Experts (a GA2LEN Partner), Pohl-Boskamp, Stallergenes, and Lofarma; has received research support from ALK-Abelló, Allergopharma, Allergy Therapeutics, Lofarma, Novartis, LETI, Biomay, Nuvo, Circassia, Biotech Tools s.a., Stallergenes, HAL-Allergy, and Bencard; has received lecture fees (including service to speakers bureaus) from HAL-Allergy, Bencard, Novartis, LETI, MEDA, ALK-Abelló, Allergopharma, Lofarma, and Stallergenes; has received payment for the development of educational presentations from Allergopharma, Novartis, ALK-Abelló, and Stallergenes; and has received travel support from HAL-Allergy. J. J. Jin declares no relevant conflicts of interest.

^aDivision of Allergic Diseases, Mayo Clinic, Rochester, Minn

^bCenter for Rhinology and Allergology, Wiesbaden, Germany

^cDepartment of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Conflicts of interest: J. T. Li is employed by Mayo Clinic. L. Klimek has received research support from ALK-Abelló, Allergopharma, Bencard, Biomay, HAL, GlaxoSmithKline, LETI, Lofarma, Novartis, and Roxall; is on the Meda (Germany) and Novartis (Switzerland) boards; has received consultancy fees from ALK-Abelló, Allergopharma, Bionorica, Boehringer Ingelheim, GlaxoSmithKline, Lofarma, Novartis, Meda Pharmaceuticals, Merck Sharp & Dohme, Phadia/ThermoFisher, and Optima; has received lecture fees from ALK-Abelló, Allergopharma, Bionorica, Boehringer Ingelheim, GlaxoSmithKline, Lofarma, Novartis, and Meda; and has received payment for manuscript preparation from Meda and Bionorica. O. Pfaar has received consultancy fees from HAL-Allergy, Allergy Therapeutics, Bencard, Novartis, LETI, MEDA, ALK-Abelló, Allergopharma, Anergis, Biotech Tools s.a., Sanofi, Mobile Chamber Experts (a GA2LEN Partner), Pohl-Boskamp, Stallergenes, and Lofarma; has received

research support from ALK-Abelló, Allergopharma, Allergy Therapeutics, Lofarma, Novartis, LETI, Biomay, Nuvo, Circassia, Biotech Tools s.a., Stallergenes, HAL-Allergy, and Bencard; has received lecture fees (including service to speakers bureaus) from HAL-Allergy, Bencard, Novartis, LETI, MEDA, ALK-Abelló, Allergopharma, Lofarma, and Stallergenes; has received payment for the development of educational presentations from Allergopharma, Novartis, ALK-Abelló, and Stallergenes; and has received travel support from HAL-Allergy. J. J. Jin declares no relevant conflicts of interest.

Received for publication May 31, 2016; revised September 1, 2016; accepted for publication September 13, 2016.

Corresponding author: Jay J. Jin, MD, PhD, Division of Allergic Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: Jin.Jay@mayo.edu. 2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2016.09.027>

Sublingual immunotherapy (SLIT) is a treatment for allergic respiratory diseases that has demonstrated efficacy and safety. Several formulations of SLIT are now available worldwide for treatment of allergic rhinitis (AR). Grass tablets containing 15 to 25 µg of group 5 major allergen reduced combined AR symptoms and medication use by 23% to 41% in 3 treatment years and 2 follow-up years. Ragweed pollen tablets (12 µg of *Ambrosia artemisiifolia* 1) and liquid extracts (50 µg of *Ambrosia artemisiifolia* 1) reduced combined AR symptoms and medication use by 26% and 43%, respectively. House dust mite tablets containing 300 index of reactivity (16 µg of *Dermatophagoides pteronyssinus* 1 and 68 µg of *Dermatophagoides farinae* 1) reduced AR symptoms by 17.9% and 17.0% in 1 treatment year and 1 follow-up year, respectively. A different house dust mite tablet (12 standardized quality house dust mite) was able to reduce the risk of asthma exacerbation compared with placebo (hazard ratio, 0.69; 95% CI, 0.50-0.96). Most adverse events were local and mild to moderate in severity. For SLIT products reviewed herein, effective doses range from 1.12 to 84 µg of major allergen(s). However, allergen content is not uniformly standardized, can be expressed in arbitrary or proprietary units (depending on the manufacturer), and assays for determination of allergen content are highly variable. Thus, results from one study of a given product cannot be extrapolated to other products. Despite these limitations, this Clinical Management Review aims to provide practitioners with relevant information on the dosing of selected SLIT formulations in the treatment of allergic respiratory disease. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1-10)

Key words: Sublingual immunotherapy; Allergic rhinitis; Allergic rhinoconjunctivitis; Asthma; Dosing

The efficacy of sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis (AR) has been demonstrated in numerous randomized, double-blind, placebo-controlled trials (RDBPCTs) and systematic reviews with meta-analyses.¹⁻³ Select open studies have also demonstrated benefit for asthma symptoms and even indicated prevention of new asthma diagnoses in patients treated with SLIT.⁴⁻⁷ Although a few cases of anaphylaxis have been reported because of SLIT, most adverse reactions have been localized and self-resolving with minimal, if any, lasting harm to the patient.^{3,8-11}

Based on the increasing utilization of SLIT, its demonstrated efficacy, and favorable safety profile, the World Allergy Organization, the European Association of Allergy and Clinical Immunology, as well as the American Academy of Allergy, Asthma, and Immunology jointly with the American College of Allergy, Asthma, and Immunology have released several position statements, consensus statements, and guidelines regarding the use of SLIT for the treatment of allergic respiratory disease.^{3,12-15}

This review aimed to provide current information on dosing, dose-response (where available), dosing schedule, and duration of therapy as it relates to key clinical outcomes with selected SLIT formulations. This information should help allergy practitioners understand the basis for SLIT dosing in the clinical management of allergic respiratory diseases.

ALLERGEN CONTENT VARIABILITY

Numerous SLIT products available worldwide come with specific dosing recommendations that have been adapted from the treatment protocols used in the RDBPCTs. The

recommended dosing regimen of each product is different due to various factors inherent to the extract itself and clinical trial design in which it was tested. Many European allergen extract manufacturers continue to use in-house reference assays, which are not universally accepted. An analysis of SLIT products from European and US manufacturers revealed approximately 7- to 200-fold differences in major allergen concentrations of house dust mite (HDM), timothy grass, cat, and ragweed products. These concentrations were determined by ELISA and expressed in US dosing units. Reference standards from the United States were used for comparison. Notably, the assay used to determine major allergen content and the laboratory in which such determinations were performed can also lead to variable estimates of major allergen concentration.¹⁶

Given this variability, the EAACI Immunotherapy Interest Group task force has identified a specific need for standardization of extract concentrations as well as clinical trial design to develop the best understanding of dose-response relationships and efficacy of SLIT.^{17,18} The remainder of this review will highlight dose ranging studies of selected products and other clinical studies that have demonstrated efficacy and safety of currently available or investigational SLIT formulations.

DOSE, MAJOR ALLERGEN CONTENT, UNITS, EFFICACY, AND SAFETY

Grass pollen

Several sublingual formulations of grass pollen extracts have been used in RDBPCTs including single-grass tablets, 5-grass tablets, and 5-grass liquid drops.

Single-grass pollen

A single-grass pollen tablet (Grazax/Grastek, ALK-Abelló, Horsholm, Denmark/Merck & Co, Whitehouse Station, NJ) is manufactured in a single dosage form containing 2800 bio-equivalent allergy units (BAUs) of group 5 major allergen from *Phleum pratense* (Phl p 5; Tables I and II).²² BAU is a US Food and Drug Administration (FDA)-defined standardized unit of potency for grass and cat extracts based on intradermal testing. A reference standard determined by the FDA Center for Biologics Evaluation and Research is used for comparison. An extract is labeled to contain 100,000 BAUs/mL when the intradermal application induces a wheal size of 50 mm on adding 2 perpendicular diameters. The potency of all grass and cat allergen extracts produced by US manufacturers is reported in BAUs.^{23,24} The manufacturer estimates that the 2800 BAU tablet contains 15 µg of Phl p 5, but the method by which this was determined is not specified. This tablet contains allergen extracted from a single-grass species and relies on the observation from subcutaneous immunotherapy that immunotherapy with a representative major allergen from a single-grass species can improve symptoms from sensitivity to other cross-reactive species.²⁵ A post hoc analysis of 6 studies using this single-grass tablet found improvements in symptom and medication scores in patients who were monosensitized to timothy grass as well as those who were polysensitized to other grasses.²⁶

A dose ranging study for the single-grass pollen tablet used maintenance doses of 2,500, 25,000, and 75,000 standardized quality-tablet (SQ-T; 0.5, 5, and 15 µg of Phl p 5, respectively) and included adults from age 18 to 65 years with AR and allergic rhinoconjunctivitis (ARC) attributable to grass pollen.²⁷ The method by which the actual allergen content was measured was

Abbreviations used

<i>AadSS</i> -Average adjusted symptom score
<i>Amb a 1-U</i> -Ambrosia artemisiifolia 1-unit
<i>AR</i> -Allergic rhinitis
<i>ARC</i> -Allergic rhinoconjunctivitis
<i>AUN</i> -Allergy unit native
<i>BAU</i> -Bioequivalent allergy unit
<i>Der f</i> -Dermatophagoides farinae
<i>Der p</i> -Dermatophagoides pteronyssinus
<i>FDA</i> -Food and Drug Administration
<i>HDM</i> -House dust mite
<i>IR</i> -Index of reactivity
<i>RDBPCT</i> -Randomized, double-blind, placebo-controlled trial
<i>RTSS</i> -Rhinoconjunctivitis total symptom score
<i>SLIT</i> -Sublingual immunotherapy
<i>SQ</i> -Standardized quality
<i>SQ-T</i> -Standardized quality-tablet
<i>TCRS</i> -Total combined rhinitis score
<i>TEAE</i> -Treatment-emergent adverse event

not reported. SQ refers to a manufacturer's in-house standardization assay and is a proprietary trademark used to designate that a product has undergone extensive quality control. A later study summarizing the efficacy and safety of these tablets equated the 2,500, 25,000, and 75,000 SQ-T doses to 93, 933, and 2,800 BAUs, respectively. No details were provided on how these equivalences were determined.²⁸ In the dose ranging study, the tablet was started at least 8 weeks in advance of the grass season and continued for 24 weeks. The intention-to-treat analysis revealed an average reduction of 16% in rhinoconjunctivitis symptoms score and an average reduction of 28% in medication use score over the entire pollen season in patients receiving the 75,000 SQ-T dose compared with placebo. The 2,500 and 25,000 SQ-T doses did not demonstrate any statistically significant difference from placebo in terms of efficacy compared with placebo. The frequency of patients experiencing adverse events with possible or probable relation to treatment was similar among the 3 doses and only the number of mild adverse events increased with increasing doses (68%, 78%, and 85%, respectively). The frequency of patients having severe adverse events was similar (9%, 11%, and 12%, respectively). In the 25,000 SQ-T group, one reaction (uvula edema) was classified as a drug-related serious adverse event. However, treatment of this reaction or withdrawal of the patient from the study was not necessary. Notably, no life-threatening systemic reactions or deaths occurred in any group.²⁷

Subsequent studies using the 2800 BAU single-grass tablet have shown single-season, multiple season, and posttreatment efficacy in patients with AR and ARC attributable to grass pollen.^{19,29-32}

In children aged 5 to 16 years, the 2800 BAU dose resulted in median rhinoconjunctivitis symptom score and medication score reductions of 24% and 34%, respectively, in the treatment group versus the placebo group.²⁹ Median asthma symptom scores were reduced by 64% in the treatment group compared with the placebo group. The adverse event frequency was similar between the treatment and placebo groups. However, the frequency of treatment-related symptoms, including oral pruritus (32% vs 2%), throat irritation (10% vs 2%), swollen lip (7% vs 0%), and cough (5% vs 2%), was higher in the treatment group.

The largest North American trial of the 2800 BAU single-grass tablet involving more than 1501 patients aged 5 to 65 years also demonstrated comparable efficacy and safety of this dose over a single grass season.³¹ The median total combined score (taking into account symptoms and rescue medication use) was reduced by 23% in the treated group versus the placebo group over the entire grass season.

In a long-term efficacy trial, adults aged 18 to 65 years were treated with the 2800 BAU dose daily for 3 consecutive years.¹⁹ In each of the 3 treatment years and in the 2 follow-up years without treatment, the average combined symptom and medication scores showed relative reductions of 27% to 41% in the treatment group versus the placebo group. Rhinoconjunctivitis quality of life questionnaire responses at the peak of the grass seasons also showed statistically significant relative reductions of 25% to 32% in each of the 5 years of the study. The authors report that no treatment-related serious adverse events or severe systemic allergic reactions were reported during the 5 years. The most common adverse symptoms reported were oral pruritus (44% treated vs 4% placebo), mouth edema (19% vs 1%), throat irritation (13% vs 2%), and ear pruritus (12% vs 1%). Most of these occurred on the first or second day of treatment and lasted for 5 to 10 minutes after the tablet was taken.

5-Grass pollen

A 5-grass pollen tablet (Oralair, Stallergenes S.A., Antony, France) is manufactured in 2 dosage forms: 100 index of reactivity (IR) and 300 IR tablets containing group 5 major allergens from sweet vernal (*Anthoxanthum odoratum*), orchard (*Dactylis glomerata*), perennial rye (*Lolium perenne*), timothy (*Phleum pratense*), and Kentucky blue grass (*Poa pratensis*) species (Tables I and II).³³ IR is the manufacturer's in-house measure of standardization. An extract contains 100 IR when a 7-mm wheal develops on skin prick testing in 30 sensitized subjects.³⁴ There is no method by which to convert from IR to other standardized units. The manufacturer estimates that the 100 IR dose is equivalent to 3000 BAUs and the 300 IR dose is equivalent to 9000 BAUs, but no basis for this equivalence estimate is provided.³³ Presumably, these determinations were made according to US FDA standards because this product is marketed in the United States and therefore must abide by allergen extract potency labeling guidelines.²⁴ The 300 IR maintenance tablet is estimated to contain 25 µg of the major group 5 allergens, but the method by which this determination was made is not specified.³⁴

A dose ranging study for the 5-grass tablet compared placebo, 100 IR, 300 IR, and 500 IR maintenance doses in adults aged 18 to 45 years with AR and ARC attributable to grass pollen.^{35,36} In this study, treatment was started 4 months in advance of the grass pollen season and continued until the end of the grass pollen season. The median rhinoconjunctivitis total symptom score (RTSS) improved by 37.0% and 35.1% in the 300 and 500 IR groups, respectively. The 100 IR group demonstrated no statistically significant change in median RTSS compared with placebo. Between the 300 IR and 500 IR doses, the scores for the individual components of the RTSS (sneezing, runny nose, itchy nose, watery eyes, and nasal congestion) were similar. The proportion of patients who experienced a treatment-emergent adverse event (TEAE) was 48.7%, 68.8%, 62.6%, and 64.4% in the placebo, 100 IR, 300 IR, and 500 IR groups, respectively. The frequency of mild (100 IR, 52.2%; 300 IR, 47.7%; 500 IR, 48.8%), moderate (31.8%, 33.5%, 36.3%), and severe (6.4%,

TABLE I. Dosing of SLIT tablets

Category	Allergen				
	Single-grass tablet	5-Grass tablet	Ragweed tablet	HDM tablet	HDM tablet
Product	Grazax/Grastek	Oralair	Ragwitek	Actair*	Acarizax*
Indication	Age 5-65 y with AR or ARC due to grass pollen confirmed by skin prick test or specific-IgE antibody to timothy grass or cross-reactive species	Age 10-65 y with AR or ARC due to grass pollen confirmed by skin prick test or specific-IgE antibody to any of 5 grass species†	Age 18-65 y with AR or ARC due to short ragweed confirmed by skin prick test or specific-IgE antibody to short ragweed	Age 12 y and older with AR or ARC due to HDM	Age 18-65 y with AR due to HDM confirmed by skin prick test or specific-IgE antibody to HDM or AR and asthma due to HDM not well controlled by ICS
Schedule	12 wk before and during grass season or continuous for 3 y	16 wk before and during grass season; can repeat for 3 y	12 wk before and during ragweed season	Continuous for 1 y	Continuous up to 18 mo
Maintenance dose	2800 BAU daily	300 IR daily	12 Amb a 1-U daily	300 IR daily	12 SQ-HDM
Major allergen content	15 µg Phl p 5‡	25 µg group 5 major allergens from 5 grasses ³⁴	12 µg Amb a 1 ⁴¹	16 µg Der p 1, 68 µg Der f 1 ²¹	15 µg Der p 1 and Der f 1, 15 µg Der p 2 and Der f 2 ⁵⁴
Build-up	No	Age 10-17 y: day 1, 100 IR; day 2, 200 IR; day 3, 300 IR	No	All patients: day 1, 100 IR; day 2, 200 IR; day 3, 300 IR	No

*Not approved by the US FDA.

†Five grass species: sweet vernal (*Anthoxanthum odoratum*), orchard (*Dactylis glomerata*), perennial rye (*Lolium perenne*), timothy (*Phleum pratense*), Kentucky blue grass (*Poa pratensis*).

‡Estimated by manufacturer.

TABLE II. Selected dosing regimens demonstrating long-term effects of SLIT

Product	Maintenance dosing regimen	Treatment duration	Posttreatment outcome
Single-grass tablet (Grastek)	2800 BAU tablet daily, 12 wk before grass season then continuous	3 y	Reduced symptom-medication score lasting 2 y ¹⁹
5-Grass tablet (Oralair)	300 IR tablet daily, 4 mo before and during grass season	3 y	Reduced symptoms-medication score lasting 2 y ²⁰
5-Grass tablet (Oralair)	300 IR tablet daily, 2 mo before and during grass season	3 y	Reduced symptom-medication score lasting 1 y (not significant from placebo in second year) ²⁰
Grass liquid extract	5 drops of 25 BU/mL, 5 times per week during grass season	3 y	Odds ratio of 3.8 (95% CI, 1.5-10.0) for new asthma in control group vs treatment group ⁴
HDM tablet (Actair)	300 IR tablet daily, continuous	1 y	Reduced symptom-medication score lasting 1 y (not evaluated beyond 1 y) ²¹
HDM liquid extract	5 drops of 10,000 RAST units/mL, 3 times per week	3, 4, or 5 y	Reduced symptom-medication scores lasting 7 or 8 y Fewer patients had new allergic sensitizations Persistently higher methacholine PD ₂₀ doses lasting 5 y ⁶

BU, Biologic unit; PD₂₀, provocative dose of methacholine causing 20% reduction in FEV₁; RAST, radioallergosorbent test.

5.2%, 6.3%) TEAE was similar between the 100, 300, and 500 IR treatment groups. The most common adverse symptoms of oral pruritus (placebo, 5.1%; 100 IR, 19.7%; 300 IR, 25.8%; 500 IR, 25.6%), headache (13.5%, 14.6%, 14.2%, 8.8%), throat irritation (3.2%, 11.5%, 9.0%, 14.4%), and nasopharyngitis (7.1%, 10.2%, 8.4%, 7.5%) were also more frequent in the treatment groups compared with the placebo group, but similar between the 3 treatment groups. The median duration of oral pruritus was reported as 1, 12, 12.5, and 5 days. Systemic reactions with possible, probable, or certain relation to the sublingual treatment included 8 episodes of rhinitis (2 in the 100 IR group, 4 in the 300 IR group, and 2 in the 500 IR group) and 2 episodes of urticaria (both in the 100 IR group). No serious

TEAE or anaphylactic shock occurred during this study. On the basis of efficacy and safety outcomes, the authors concluded that 300 IR was the optimal maintenance dose because it had similar efficacy outcomes but slightly better safety outcomes compared with the 500 IR maintenance dose.³⁶

In the complementary analysis of subgroups of this trial, Malling et al³⁵ used the data and patient characteristics to identify subgroups that might demonstrate better outcomes with the 300 IR maintenance dose of the 5-grass pollen tablet. This analysis revealed no difference in efficacy or safety outcomes for patients with higher specific IgE levels (≥ 17.5 kU/L), higher RTSSs (≥ 15), or bigger wheal diameters (≥ 10.5 mm) compared with the overall study population.³⁵

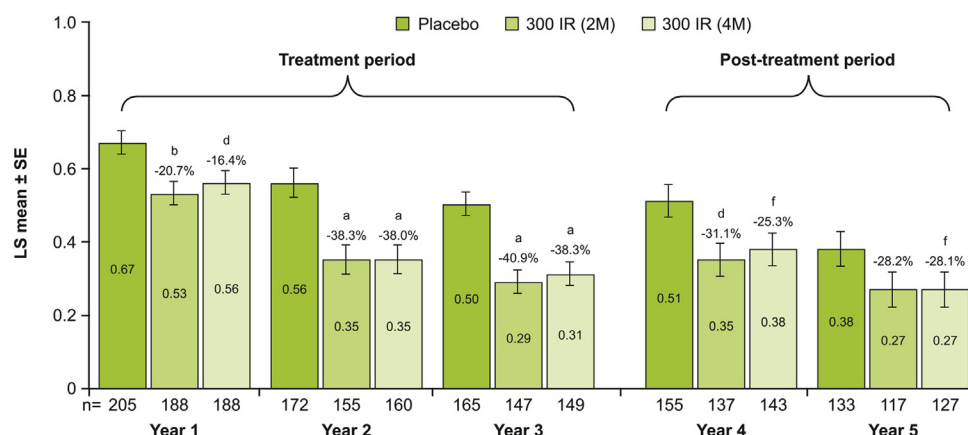


FIGURE 1. Daily combined score reductions with 300 IR 5-grass tablet started 2 months (2M) or 4 months (4M) in advance of the grass season over 3 treatment years and 2 posttreatment years. Repeated-measures analysis of covariance of the DCS per year of the study: a, $P < .0001$; b, $P < .0005$; c, $P < .001$; d, $P < .005$; e, $P < .01$; f, $P < .05$ for comparison (5-grass tablet) versus placebo. DCS, Daily combined score; LS, least squares; SE, standard error. (Reproduced with permission from Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. Clin Transl Allergy 2015;5:12.²⁰)

Subsequent to the dose ranging study, several clinical trials demonstrated the efficacy and safety of the 5-grass pollen 300 IR tablet maintenance dose in single season and long-term outcomes in patients with AR and ARC attributable to grass pollen.^{20,37-39}

In a multicenter, multinational, RDBPCT, Wahn et al³⁹ compared the 300 IR dose to placebo in children aged 5 to 17 years with AR and ARC attributable to grass pollen. In the intention-to-treat analysis, the median RTSS improved by 39.3% in the 300 IR treatment group compared with the placebo group over a single grass pollen season. The 300 IR treatment group had a higher frequency of TEAE (54.0%) compared with the placebo group (20.1%). Oral pruritus (32.4%), mouth edema (12.9%), and throat irritation (7.9%) occurred more frequently in children taking the 300 IR tablet.³⁹

A multicenter, US-based, RDBPCT was conducted in adults aged 18 to 65 years using the 300 IR 5-grass tablet (started 4 months in advance of the grass pollen season and continued through the season). The combined score (taking into account the RTSS and rescue medication score) was improved in the 300 IR treatment group with a mean relative reduction of 28.2%. Interestingly, a prespecified subgroup analysis of patients with serum specific IgE level of less than 0.1 kU/L to timothy grass demonstrated no difference in combined score between the 300 IR treatment group and the placebo group. The drug-related TEAE frequency was higher in the treatment group (54.9%) versus the placebo group (22.5%), but no deaths, serious allergic reactions, or epinephrine use was reported.³⁷

Long-term efficacy of the daily 300 IR dose of the 5-grass tablet was demonstrated in a multinational, multicenter, RDBPCT over a 5-year time period and included adults aged 18 to 50 years with AR and ARC attributable to grass pollen. The 2 treatment arms were started on the 300 IR dose 2 months or 4 months in advance of the grass season and compared with a placebo group. Treatment was continued through the grass pollen season. These schedules were repeated in 3 consecutive years and outcomes were followed in 2 posttreatment years. Both

treatment groups showed reductions in combined symptom and medication scores during the 3 treatment periods (years 1 to 3). In the first posttreatment year, both groups showed significant mean relative reductions in the daily combined score in comparison to placebo (−31.1% in the 2-month preseasonal group; −25.3% in the 4-month preseasonal group). In the second posttreatment year, only the 4-month preseasonal group continued to have a statistically significant reduction in mean combined score compared with placebo (−28.1%) (Figure 1).²⁰

A study using an environmental exposure chamber and investigating clinical effects of the 300 IR 5-grass pollen tablet found statistically significant reductions in average RTSS (average of RTSS from 16 time points where symptoms scores were collected during each challenge) starting at 1 month and persisting to the 4-month (final) time point.⁴⁰

Other grass pollen formulations

A 5-grass liquid extract with a single maintenance dose of 5 drops of 25 BU/mL (0.5 µg/mL) of group 5 major allergens from orchard (*Dactylis glomerata*), perennial rye (*Lolium perenne*), meadow fescue (*Festuca pratensis*), timothy (*Phleum pratense*), and Kentucky blue grass (*Poa pratensis*) (ALK-Abelló, Horsham, Denmark) was used in children with ARC due to grass pollen with no history of asthma.⁴ The allergen concentration was standardized by a radioallergosorbent test inhibition assay using a manufacturer's in-house reference standard. Treatment was repeated in 3 consecutive grass pollen seasons. At the end of the study period, the control group with standard symptomatic therapy only had a higher relative risk of 3.8 (95% CI, 1.5-10.0) for developing asthma compared with the treatment group (Table II).

Ragweed pollen

A SLIT tablet containing short ragweed pollen (Ragwitek, Merck & Co.) is manufactured in a single dosage form containing 12 *Ambrosia artemisiifolia* 1-unit (Amb a 1-U; Table I).⁴¹ Amb a 1-U is a standardized unit of potency used by the FDA for

the determination of potency of ragweed extracts and is equivalent to 1 µg of Amb a 1. This unit of standardization was adopted before the adoption of the BAU. For purposes of conversion, approximately $350 \pm 20\%$ Amb a 1-units are equivalent to 100,000 BAU/mL.²³

A dose ranging and safety study compared tablets containing 3, 6, 12, 24, 50, and 100 Amb a 1-U in adults aged 18 to 50 years with ARC due to ragweed. The highest dose that was well tolerated was the 12 Amb a 1-U dose.⁴² Two patients in the 24 Amb a 1-U group reported 10 severe treatment-related events characterized by chest discomfort, dysphagia, oral pruritus, allergic conjunctivitis, mouth edema, and swollen tongue. One patient in the 50 Amb a 1-U group reported conjunctivitis and periorbital edema. These severe reactions occurred on the first day of treatment. No serious events or anaphylactic shock occurred. Recruitment to the 50 Amb a 1-U dose group was discontinued because of adverse events and no patients were enrolled at the 100 Amb a 1-U dose.⁴²

In a subsequent study, Creticos et al⁴³ assessed the efficacy and safety of 1.5, 6, and 12 Amb a 1-U doses in adults. The 1.5, 6, and 12 Amb a 1-U ragweed tablets were started 16 weeks in advance of the ragweed season and continued for 52 weeks. The total combined score (taking into account both symptoms and medication use) were reduced by 12%, 18%, and 27%, respectively, in the 3 treatment groups compared with placebo over the entire ragweed pollen season.⁴³ In a study by Nolte et al,⁴⁴ 6 and 12 Amb a 1-U doses were started 12 weeks in advance of the ragweed season and continued for 52 weeks. The mean total combined scores (over the entire ragweed pollen season) were reduced by 16% and 26% in the 6 and 12 Amb a 1-U dose groups, respectively, compared with placebo.⁴⁴ A pooled analysis of safety and tolerability over 52 weeks reported TEAE in 68.4%, 75.5%, 76.9%, and 80.6% in the placebo, 1.5, 6, and 12 Amb a 1-U groups, respectively. The specific treatment-related adverse events included throat irritation, ear pruritus, oral pruritus, and swollen tongue, which were typically more common in the treatment groups than in the placebo groups. No serious treatment-related adverse events were reported in any group.⁴⁵ Based on the efficacy and safety outcomes, 12 Amb a 1-U was considered the optimal dose.^{41,43}

Ragweed SLIT using a liquid extract has also been shown to improve symptom and medication scores in a large RDBPCT in North America.⁴⁶ This study used a glycerinated liquid formulation of ragweed extract (Greer Laboratories, Inc, Lenoir, NC) containing approximately 50 Amb a 1-U in the maintenance dose. Treatment was started 8 to 16 weeks in advance of ragweed season and continued until the end of the season. In the intention-to-treat analysis, mean total combined score was reduced by 43% in the treatment group versus the placebo group. From a safety standpoint, oral mucosal symptoms (10% vs 5%), nasopharyngitis (6% vs 4%), and gastrointestinal symptoms (8% vs 6%) were more common in the treatment group versus the placebo group, but no treatment-related serious local or systemic adverse events were observed.⁴⁶ Another study used this same liquid extract with maintenance doses of 4.8 and 48 Amb a 1-U after a single day, rapid up-titration to the maximum tolerate dose followed by daily administration starting 8 to 10 weeks before the ragweed season.⁴⁷ The primary outcomes of symptom and medication favored the 2 treatment groups over placebo, but the improvement was not statistically significant. However, in an analysis of covariance correcting for preseasonal symptoms, the 48 Amb a-1 U group

demonstrated significantly improved symptom and medication scores over placebo.

Notably, the ragweed SLIT liquid extract demonstrated safety and efficacy at doses up to 50 Amb a 1-U, but the tablet formulation caused severe treatment-related events at the 24 and 50 Amb a 1-U doses. Thus, there may be differences in potency between liquid extracts and sublingual tablets.

House dust mite

The World Allergy Organization 2013 position paper update on SLIT includes 84 RDBPCTs using HDM formulations.³ This section will focus on the dosing regimens reported in recent studies demonstrating the efficacy and safety of HDM SLIT.

A dose ranging study of a sublingual tablet containing a mixture of major allergens from *Dermatophagoides farinae* (Der f) and *Dermatophagoides pteronyssinus* (Der p) compared 100, 200, 300, 400, and 500 IR doses (Stallergenes S.A.). This study found that a short-dose escalation regimen to achieve 500 IR daily doses was better tolerated than starting at 500 IR without dose escalation.⁴⁸ A subsequent study assessed the efficacy and safety of 300 and 500 IR doses compared with placebo in adults aged 18 to 50 years with AR due to HDM.²¹ The 300 IR tablet was estimated to contain 16 µg of Der p 1 and 68 µg of Der f 1 by ELISA (Indoor Biotechnologies, Charlottesville, Va). In this study, treatment was continued for 1 year and outcomes assessed during the treatment year and in a follow-up year (without treatment). The 300 IR and 500 IR groups had statistically significant reductions in the primary outcome of average-adjusted symptom score (AAdSS). The relative reductions in AAdSS in the treatment year compared with placebo were 17.9% for the 300 IR group and 20.2% for the 500 IR group. Notably, a significant treatment effect was found beginning 4 months after the initiation of the SLIT treatment. In the follow-up year (treatment free), relative reductions of 17.0% in AAdSS in the 300 IR group and 19.1% in the 500 IR group compared with placebo were demonstrated. The most commonly reported adverse events were oral pruritus (300 IR, 30.0%; 500 IR, 25.4%), throat irritation (300 IR, 24.7%; 500 IR, 21.3%), and mouth edema (300 IR, 12.4%; 500 IR, 16.6%).²¹ A 300 IR HDM SLIT tablet (Actair, Stallergenes S.A.) has been approved for use in Japan and Australia in patients aged 12 years and older with AR due to HDM. Similar to the 300 IR 5-grass pollen tablet, a brief dose escalation of 100 IR per day for 2 days is recommended for all patients (Tables I and II).⁴⁹

A series of studies using a different HDM SLIT tablet (Acarizax, ALK-Abelló) identified a tolerable dose and demonstrated efficacy for AR and allergic asthma.⁵⁰ In phase I studies, a 12 developmental unit dose was identified as tolerable.⁵¹ Developmental unit is a measure of potency based on a manufacturer's in-house reference standard for HDM extracts⁵² and is the same as standardized quality (SQ) HDM, which is the nomenclature used in Europe for this tablet.^{52,53} This tablet was found to contain approximately 15 µg of Der f 1 and Der p 1 and 15 µg of Der f 2 and Der p 2 by radial immunodiffusion and ELISA.⁵⁴ In an environmental exposure chamber study, Nolte et al⁵² found statistically significant improvements in total nasal symptom scores starting at 16 weeks for the 6 SQ-HDM dose and 8 weeks for the 12 SQ-HDM dose compared with placebo. By the 24-week study end point, total nasal symptom score (primary end point) had improved by 48.6% in the 12 SQ-

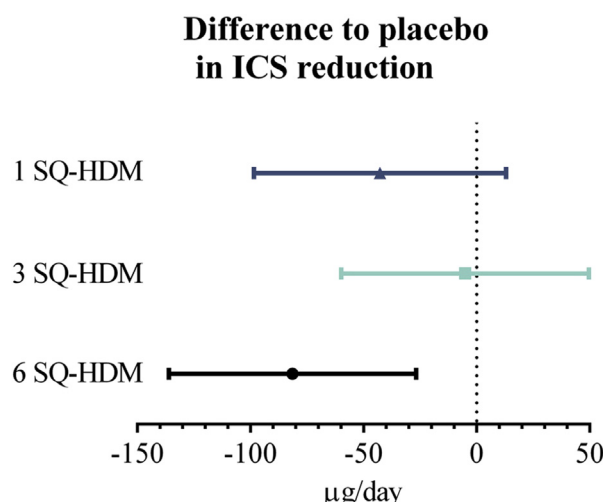


FIGURE 2. Reduced inhaled corticosteroid dose in those with moderate-to-severe asthma after 1 year of HDM SLIT. ICS, Inhaled corticosteroid. Each symbol represents the estimated adjusted mean difference (with 95% CIs) between active and placebo treatment in the change from baseline of the minimum ICS dose needed to maintain asthma control. (Reproduced with permission from Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-575.e7.⁵⁵)

HDM dose group and 26.6% in the 6 SQ-HDM dose group compared with placebo.⁵²

In a large, multinational, multi-center, RDBPCT, patients aged 14 years and older with both HDM AR and HDM-induced allergic asthma were recruited and randomized to placebo, 1, 3, or 6 SQ-HDM SLIT daily treatment groups for 1 year.^{53,55} For asthma, the primary end point was specified as reduction in inhaled corticosteroid dose at the end of the treatment period. On average, the 6 SQ-HDM group had a reduction of 81 µg/d in daily inhaled corticosteroid dose (from baseline), which was a statistically significant improvement compared with the placebo group (Figure 2). The 1 and 3 SQ-HDM groups did not demonstrate any statistically significant difference from placebo.⁵⁵ For AR, the composite end point was a sum of the daily rhinitis and medication use scores averaged over the last 4 weeks of the treatment period, termed the total combined rhinitis score (TCRS). A statistically significant reduction in TCRS was noted only in the 6 SQ-HDM group (28.8% relative improvement) versus placebo.⁵³ The overall frequency of adverse events was higher in the 3 and 6 SQ-HDM groups (67% and 66%, respectively) than in the placebo and 1 SQ-HDM groups (54% and 55%, respectively). However, most adverse events were local reactions at the application site and were mild to moderate in severity. The frequency of the most common adverse symptoms was higher in the higher dosage groups (Figure 3).^{53,55}

In a multinational, multi-center, phase III, RDBPCT of this HDM SLIT tablet, adults aged 18 to 65 years with moderate-to-severe HDM-induced AR with or without asthma and conjunctivitis were treated with placebo, 6, or 12 SQ-HDM for

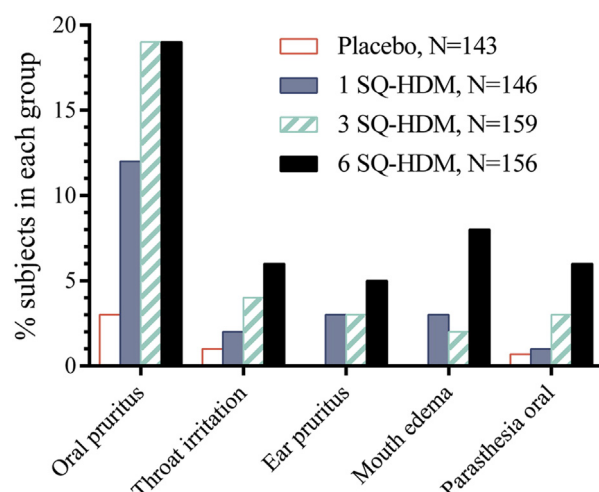


FIGURE 3. Relationship of HDM SLIT dose to most common adverse events reported in 5% or more subjects in any treatment group. (Reproduced with permission from Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-575.e7.⁵⁵)

1 year. Analysis of the full analysis set (adjusted means) demonstrated improvement in the mean TCRS by a relative difference of 18% for both the 6 and 12 SQ-HDM tablets compared with placebo. Individual symptoms of blocked nose improved similarly in the 6 and 12 SQ-HDM groups, but additional improvements in itchy nose, runny nose, and sneezing were statistically significant only in the 12 SQ-HDM group compared with placebo. Adverse event rates were higher in the treatment groups (63% and 67%) compared with placebo (46%), but most were mild or moderate in severity. The study authors did not specify whether these were treatment-emergent or treatment-related adverse reactions.⁵⁶

In a study examining asthma outcomes with HDM SLIT, Virchow et al⁵⁷ demonstrated a significantly reduced risk of moderate-to-severe asthma exacerbation in patients being treated with either 6 or 12 SQ-HDM SLIT tablets compared with placebo. Trial participants were aged 17 to 83 years and had both AR and allergic asthma secondary to HDM sensitization. Baseline FEV₁ measurements were greater than 70% of predicted. The trial included several treatment periods. In period 1, baseline data were recorded while switching to inhaled budesonide and a short acting beta agonist. In period 2, the daily SLIT tablet (placebo, 6, or 12 SQ-HDM) was started. This period lasted for 7 to 12 months. In period 3, SLIT was continued, but the dose of inhaled budesonide was decreased by 50%. In period 4, SLIT was continued and inhaled budesonide was discontinued completely in those participants who had not yet had an exacerbation of their asthma in one of the earlier periods. The primary outcome was time to first exacerbation during the periods when inhaled corticosteroid doses were reduced. In both the 6 SQ-HDM and 12 SQ-HDM groups, the risk of asthma exacerbation was significantly reduced compared to placebo during the study period (for the 6 SQ-HDM group: hazard ratio,

0.72 [95% CI, 0.52-0.99]; for the 12 SQ-HDM: hazard ratio, 0.69 [95% CI, 0.50-0.96]). The most frequent adverse events were oral pruritus, mouth edema, and tongue pruritus, which were more common in the treatment group.⁵⁷

In Europe and Australia, this HDM SLIT tablet has obtained approval for treatment of both AR and allergic asthma. The indication for treatment of allergic asthma is a first for a SLIT product.

Other HDM formulations

Long-term efficacy of HDM SLIT was demonstrated in one 10-year and another 15-year open-label, prospective studies of children with AR or asthma due to HDM and adults with AR due to HDM who were offered HDM SLIT with liquid drop formulations or usual medical care.^{6,58}

Di Rienzo et al⁵⁸ investigated a liquid extract maintenance dose containing 1.12 µg of group 1 and 0.56 µg of group 2 mite allergen taken twice weekly for 4 to 5 years. At the end of SLIT treatment, fewer children who received SLIT were using asthma medications (31 of 35 at trial onset; 4 of 35 at end of SLIT). These children also had improvement in asthma severity according to the Global Initiative for Asthma criteria. At baseline, 4 patients did not have asthma, 15 had intermittent, 6 had mild-persistent, and 10 had moderate asthma. At conclusion of SLIT, 31 patients did not have asthma, 2 had intermittent, and 1 each had mild-persistent and moderate asthma. Five years after the conclusion of SLIT treatment, these numbers remained essentially the same. In comparison, in the control group, the category of asthma severity and number of children using asthma medications remained stable throughout the study (2, no asthma; 14, intermittent; 4, mild-persistent; 5, moderate; 23 of 25 using medications at start, 24 of 25 using medications at end).⁵⁸

In another (open-label) 15-year study of adults with AR to HDM, the maintenance dose was 5 drops 3 times per week from an extract containing 10,000 radioallergosorbent test units/mL (Anallergo, Florence, Italy). The mean cumulative dose per year was 390 µg of Der p1 and Der p2. The patients who opted for treatment with HDM SLIT were treated for 3 years, 4 years, or 5 years and were followed for 15 years. Each group demonstrated improvements in symptom and medication scores during the treatment phase, with successive years showing even greater improvements compared with the previous years. However, at 7 years posttreatment (for the 3-year treatment group) and at 8 years posttreatment (for the 4- and 5-year treatment groups), the effects of immunotherapy appeared to wane as symptoms recurred to more than 50% of the baseline values. HDM SLIT was then repeated and resulted in significant improvement in symptom and medication score over a shorter time frame compared with their first treatment period. The authors concluded that 4 years may be a reasonable time frame for continuing HDM SLIT for AR to achieve prolonged improvement in symptoms. Interestingly, new allergic sensitivities (as measured by skin prick testing) occurred in all control group patients, but only in 11% to 21% of the patients who underwent active treatment (Table II). The treated patients also demonstrated higher threshold doses for bronchial hyperresponsiveness to methacholine challenge during and after treatment compared with control subjects.⁶

A recent review compared the allergen content of 5 different HDM SLIT liquid extract formulations and found varying concentrations of Der p1 (0.6-14.5 µg/mL), Der f1 (0.2-12.4

µg/mL), and Der p2 plus Der f2 (0.2-1.5 µg/mL). A literature review conducted by the authors found little data on the efficacy of the specific products they examined.⁵⁹

Tree pollen

A dose ranging study using birch tree pollen SLIT liquid drops compared placebo, 3,333, 10,000, 20,000, and 40,000 allergy unit native (AUN)/mL (HAL-Allergy, Leiden, Netherlands) in patients with AR due to birch pollen.⁶⁰ Using a validated ELISA, it was estimated that the 10,000 AUN/mL dose contained 46.7 µg of the group 1 major allergen from birch tree (Bet v 1).^{3,61} The study medications were taken daily for 5 months outside of the tree pollen season. Mean symptoms scores after a titrated nasal provocation test were significantly reduced by 47.7% and 58.4% in the 20,000 AUN/mL and 40,000 AUN/mL groups in comparison to baseline.⁶⁰ Compared with the placebo arm, all treatment groups revealed more adverse reactions, but they were mainly mild and well controlled. A phase III trial using this formulation is currently underway (ClinicalTrials.gov NCT02231307).

A RDBPCT using a different birch pollen SLIT liquid (Stallargenes S.A., Antony, France) compared a 300 IR maintenance dose to placebo in adults with birch pollen ARC.⁶² No information was given on the major allergen content of this preparation. The maintenance dose was reached after daily dose escalations in the following manner: 1, 2, 4, 6, 8, 10, 30, 60, 120, 180, 240, and 300 IR/day. Treatment was started 4 months in advance of the pollen season, continued through the season, then stopped, and repeated in 2 consecutive years. Compared to the placebo group, the treatment group had reductions in AAdSS of 19.0% in the first year of treatment and 30.6% in the second year. No anaphylaxis was reported. The frequency of TEAEs were similar in the placebo (first year: 64.0%, second year: 48.6%) and treatment (first year: 70.7%, second year: 46.8%) groups. The most common specific symptom of oral pruritus affected 3.8% in the placebo group compared to 24.7% in the treatment group in year 1. By year 2, the frequency of oral pruritus decreased to 0.8% in the placebo group and 8.5% in the treatment group.⁶²

In a study of Japanese Cedar pollinosis, a 2000 Japanese allergy unit SLIT formulation was effective at lowering total nasal symptom and medication scores by 16% to 18% and 26% to 30% in the first and second year of treatment, respectively.⁶³ The SLIT arm was started 4 months before the pollen season with a daily up-titration schedule over 2 weeks to reach the maintenance dose of 2000 Japanese allergy unit by the beginning of the third week.

Cat dander

In an early phase experimental study, a 1400 BAU dose of cat allergen extract was tolerated as a daily dose for 8 weeks.⁶⁴ An RDBPCT using a liquid extract containing 0.51 µg/mL of the group 1 major cat allergen (Fel d1; total cumulative dose of 17.1 µg over the 1-year treatment period) demonstrated improvements in total symptom scores (including nasal, ocular, and respiratory symptoms) during a natural exposure challenge to cat.⁶⁵

Mold

A small RDBPCT using *Alternaria* extract in 26 patients with AR due to *Alternaria* found that 5 drops of a 10,000 radioallergosorbent test unit/mL SLIT formulation maintained for 10 months (cumulative dose of ~60 µg of Alt a 1) produced

reduced symptom and medication scores during the entire mold season.⁶⁶ The maintenance dose was taken every other day after a 15-day build-up. A 3-year study in 52 patients with AR to *Alternaria* showed improvements in patient-reported visual analog scale score and rescue medication use.⁶⁷

DOSING REGIMENS

SLIT maintenance doses are generally taken daily and require little to no dose escalation. Table 1 provides examples from selected SLIT tablets. In the studies described above, dosing frequency ranged from daily to every 3 days. The treatment strategies included both continuous and discontinuous regimens. For continuous regimens, the maintenance dose is taken daily throughout the year. This strategy was used in the studies of HDM tablets, single-grass tablet, and ragweed tablet. For discontinuous regimens, two common patterns can be described as “coseasonal” and “pre/coseasonal”. In a coseasonal strategy, SLIT is started at the beginning of the pollen season and then stopped at the end of the pollen season. In a pre/coseasonal strategy, SLIT is started before the relevant pollen season, continued through the season, and then stopped at the end of the pollen season. The coseasonal strategy was used in a study of a 5-grass liquid SLIT extract. The pre/coseasonal strategy was used for single-grass tablet, 5-grass tablet, birch liquid, and ragweed liquid SLIT formulations. The clinical outcomes for these SLIT formulations and dosing regimens can be reviewed in the relevant sections above. Because some SLIT products must be started before the beginning of the relevant pollen season, practitioners should be familiar with seasonal pollen variations in the locations most relevant to their patients.

CONCLUSIONS

The “ideal” dose for SLIT depends on a number of patient- and product-specific factors. It is important to recognize that the allergen content in the products discussed in this review are not standardized and are highly variable from product to product. Studies of various SLIT formulations have shown that effective doses range from 1.68 µg to 84 µg of major allergen(s). However, the methods for estimating major allergen content are not standardized and should be viewed with caution. Comparisons between products should also be approached carefully given this inherent variability. Despite these limitations, the data from some of the large, well-designed clinical trials reported in this review suggest that safe and effective doses can and have been established.

REFERENCES

- Lin SY, Ereksom N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278-88.
- Kim JM, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013;131:1155-67.
- Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organization J* 2014;7:6.
- Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;114:851-7.
- Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008;101:206-11.
- Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010;126:969-75.
- Schmitt J, Schwarz K, Stadler E, Wustenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015;136:1511-6.
- Wessel F, Chartier A, Meunier JP, Magnan A. Safety and tolerability of an SQ-standardized GRass ALlergy immunotherapy tablet (GRAZAX) in a real-life setting for three consecutive seasons—the GRAAL trial. *Clin Drug Investig* 2012;32:451-63.
- Park D, Daher N, Blaiss MS. Adult and pediatric clinical trials of sublingual immunotherapy in the USA. *Exp Rev Clin Immunol* 2012;8:557-64.
- Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011;66:740-52.
- Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy* 2011;41:1263-72.
- Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013;131:1288-1296.e3.
- Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;136:556-68.
- Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol* 2016;137:358-68.
- Li JT, Bernstein DI, Calderon MA, Casale TB, Cox L, Passalacqua G, et al. Sublingual grass and ragweed immunotherapy: clinical considerations—a PRACTALL consensus report. *J Allergy Clin Immunol* 2016;137:369-76.
- Larenas-Linnemann DE, Mosges R. Dosing of European sublingual immunotherapy maintenance solutions relative to monthly recommended dosing of subcutaneous immunotherapy. *Allergy Asthma Proc* 2016;37:50-6.
- Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on ‘dose-response relationship in allergen-specific immunotherapy’. *Allergy* 2011;66:1345-59.
- Demoly P, Calderon MA. Dosing and efficacy in specific immunotherapy. *Allergy* 2011;66:38-40.
- Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-725.e5.
- Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy* 2015;5:12.
- Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, 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.
- GRASTEK(R) (Timothy Grass Pollen Allergen Extract) tablet for sublingual use prescribing information. Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergens/UCM393184.pdf>. Accessed April 2, 2016.
- Lin SY, Ereksom N, Suarez-Cuervo C, Ramanathan M, Kim JM, Ward D, et al. Allergen-specific immunotherapy for the treatment of allergic rhinoconjunctivitis and/or asthma: comparative effectiveness review. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Available from: <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1428&pageaction=displayproduct>. Accessed November 9, 2016.
- Passalacqua G, Sastre J, Pfaar O, Wahn U, Demoly P. Comparison of allergenic extracts from different origins: the value of the FDA’s bioequivalent allergy unit (BAU). *Expert Rev Clin Immunol* 2016;12:733-9.
- Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127:S1-55.
- Nelson H, Blaiss M, Nolte H, Wurtz SO, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy* 2013;68:252-5.
- 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;117:802-9.
- Maloney J, Durham S, Skoner D, Dahl R, Bufe A, Bernstein D, et al. Safety of sublingual immunotherapy timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. *Allergy* 2015;70:302-9.

29. Bufer A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, 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.
30. 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.e1-2.
31. Maloney J, Bernstein DI, Nelson H, Creticos P, Hebert J, Noonan M, 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.
32. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, 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.
33. ORALAIR(R) (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) tablet for sublingual use prescribing information. Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergens/UCM391580.pdf>. Accessed April 2, 2016.
34. Demoly P, Passalacqua G, Calderon MA, Yalaoui T. Choosing the optimal dose in sublingual immunotherapy: rationale for the 300 index of reactivity dose. *Clin Translational Allergy* 2015;5:44.
35. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy* 2009;39:387-93.
36. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
37. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambrosio L, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol* 2012;130:1327-1334.e1.
38. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol* 2011;128:559-66.
39. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-166.e3.
40. Horak F, Ziegelmayer P, Ziegelmayer R, Lemell P, Devillier P, Montagut A, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol* 2009;124:471-7. 477.e1.
41. RAGWITEK(R) (Short Ragweed Pollen Allergen Extract) tablet for sublingual use prescribing information. Available from http://www.merck.com/product/usa/pi_circulars/r/ragwitek_pi.pdf. Accessed April 2, 2016.
42. Nayak AS, Atiee GJ, Dige E, Maloney J, Nolte H. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis [Erratum appears in *Allergy Asthma Proc* 2012;33:499.]. *Allergy Asthma Proc* 2012;33:404-10.
43. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol* 2013;131:1342-1349.e6.
44. Nolte H, Hebert J, Berman G, Gawchik S, White M, Kaur A, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet: efficacy and safety in North American adults. *Ann Allergy Asthma Immunol* 2013;110:450-6.
45. Nolte H, Amar N, Bernstein DI, Lanier BQ, Creticos P, Berman G, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol* 2014;113:93-100.e3.
46. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis [Erratum appears in *J Allergy Clin Immunol* 2014;133:1502.]. *J Allergy Clin Immunol* 2014;133:751-8.
47. 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;125:660-6. 666.e1-666.e4.
48. Demoly P, Meziane L, LeGall M, André C, Melac M. Safety and tolerability of house dust mite tablets in sublingual immunotherapy. *J Allergy Clin Immunol* 2008;121:S128.
49. Product information: ACTAIR 100 IR and 300 IR sublingual tablets. Available from: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01698-1>. Accessed April 2, 2016.
50. ACARIZAX(R) 12 SQ-HDM oral lyophilisate: product information. Available from: <http://www.csl.com.au/docs/924/920/20160802-ACARIZAX%20PI-v1-clean-registered%2001%20Aug%202016.0.pdf>. Accessed December 1, 2016.
51. Corzo JL, Carrillo T, Pedemonte C, Plaza Martin AM, Martin Hurtado S, Dige E, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. *J Invest Allergol Clin Immunol* 2014;24:154-61.
52. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol* 2015;135:1494-1501.e6.
53. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol* 2015;114:134-40.
54. Henmar H, Frisette S, Grosch K, Nielsen K, Smith G, Sonderkaer S, et al. Fractionation of source materials leads to a high reproducibility of the SQ house dust mite SLIT-tablets. *Int Arch Allergy Immunol* 2016;169:23-32.
55. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-575.e7.
56. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016;137:444-451.e8.
57. Virchow J, Backer V, Kuna P, Prieto L, Nolte H, Villessen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016;315:1715-25.
58. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;33:206-10.
59. Moreno Benitez F, Espinazo Romeu M, Letran Camacho A, Mas S, Garcia-Cozar FJ, Tabar AI. Variation in allergen content in sublingual allergen immunotherapy with house dust mites. *Allergy* 2015;70:1413-20.
60. Pfaar O, van Twuijver E, Boot JD, Opstelten DJ, Klimek L, van Ree R, et al. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. *Allergy* 2016;71:99-107.
61. Kerkvliet E, Peckel 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;66:622-3.
62. Worm M, Rak S, de Blay F, Malling HJ, Melac M, Cadic V, et al. Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study. *Clin Transl Allergy* 2014;4:7.
63. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2015;166:177-88.
64. Esch RE, Bush RK, Peden D, Lockey RF. Sublingual-oral administration of standardized allergenic extracts: phase I safety and dosing results. *Ann Allergy Asthma Immunol* 2008;100:475-81.
65. Álvarez-Cuesta E, Berges-Gimeno P, Mancebo EG, Fernández-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;62:810-7.
66. Cortellini G, Spadolini I, Patella V, Fabbri E, Santucci A, Severino M, et al. Sublingual immunotherapy for *Alternaria*-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol* 2010;105:382-6.
67. 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;26:2801-6.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.