

Clinical Applications of Sublingual Immunotherapy



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KEYWORDS

- Sublingual immunotherapy • Allergic rhinitis • Allergic asthma • Asthma
- Atopic dermatitis • Food allergy • Allergy • Immunotherapy

KEY POINTS

- Sublingual immunotherapy (SLIT) reduces symptoms and medication use in allergic rhinitis. Literature suggests that SLIT efficacy may persist for up to 8 years following a 4-year course of treatment.
- SLIT reduces the risk of moderate/severe allergic asthma exacerbations and is indicated in patients who remain symptomatic. Uncontrolled asthma is a contraindication for SLIT.
- Although additional studies are needed, SLIT is effective for some food allergies.
- In appropriately selected patients, SLIT safety profile is excellent. Anaphylaxis does occur, but at an estimated rate of 1 case per 100 million doses, the risk is exceedingly small.

INTRODUCTION

Approximately 25% of the population of the United States has an allergic disease, encompassing rhinitis, conjunctivitis, asthma, atopic dermatitis, urticaria, and food allergy.¹ Allergic rhinitis (AR) is the most common chronic childhood disease and the fifth most common overall; it is responsible for \$3.4 billion in direct medical costs annually.^{2,3} Asthma is also very common, with 7.8% of the US population and 300 million people worldwide affected.⁴

Allergy prevalence is increasing. The rates of AR, peanut allergy, and asthma have nearly doubled between 1980 and 2000.¹ The World Health Organization expects 100 million new asthma diagnoses in the next 10 years.⁴ The hygiene hypothesis, recently retitled the microflora, biodiversity, or microbiome hypothesis, refers to microbiome disruption in childhood by antibiotic use as well as lifestyle, diet, and birth practice

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changes, leading to an increased risk of allergic disease.^{5–7} This hypothesis, coupled with worldwide development, are commonly implicated for rising allergy prevalence.⁸

More than one-third of patients with allergic syndromes remain undiagnosed or do not receive appropriate therapy.¹ Both physician-related and patient-related causes are implicated. Physicians often overlook allergy screening or overestimate the degree of control achieved with current therapy. Therefore, therapies are not escalated when treatment fails.¹ Often, patients do not seek medical care for AR. More than 50% of patients with uncontrolled AR symptoms had not seen a physician in the past year for treatment. Those who do seek care wait until symptoms are “intolerable.”⁹ Further, almost half of patients receiving specialist care report nonadherence.¹ Some patients avoid treatment due to medication cost or side effects, as well as unfounded concerns about the habit-forming nature of medications. The least common reason is lack of efficacy.⁹

In general, patients desire therapies that treat the root cause of their disease and provide lasting relief. Immunotherapy is the only disease-modifying and durable therapy for allergic disease. However, only 5% of eligible patients are offered allergy immunotherapy (AIT).¹

AIT induces allergen tolerance by initially producing a population of CD4⁺CD25⁺ T lymphocytes (regulatory T cells) that secrete inhibitory cytokines (interleukin-10 and/or transforming growth factor- β). These cytokines decrease antigen-specific production of immunoglobulin (Ig)E by B cells; reduce proinflammatory cytokine release from mast cells, eosinophils, and T cells; and lead to tolerance of T cells by inhibiting the CD28 costimulatory pathway. Long-term AIT leads to a shift from a T_H2 to a T_H1 cytokine response.¹⁰

AIT was first described in 1900 for hay fever and used an oral ragweed extract.¹¹ Subcutaneous immunotherapy (SCIT) has traditionally been the favored route of AIT administration in the United States. However, following 26 SCIT-related anaphylaxis deaths in the United Kingdom, there was increased interest in alternative IT routes with improved safety profiles.¹² Aqueous allergen extracts are not currently approved by the US Food and Drug Administration (FDA) for sublingual immunotherapy (SLIT), but they are often used off-label by US practitioners. This review summarizes SLIT efficacy and safety for the treatment of several allergic diseases and provides tips for the practical implementation of SLIT.

SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC RHINITIS

AR is a IgE-mediated type I hypersensitivity reaction causing inflammation of the nasal mucosa with exposure to an inciting trigger. Characteristic symptoms include nasal congestion, rhinorrhea, and sneezing.² An estimated 500 million people worldwide have AR.^{8,13} AR treatments include antihistamines, corticosteroids, leukotriene receptor antagonists, and AIT (SCIT and SLIT), among others. Only AIT alters the natural course of the disease.²

Indications and Contraindications

The American Academy of Otolaryngology–Head and Neck Surgery recommends “...immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate relief of symptoms with pharmacologic therapy....”² Many patients undergo empiric pharmacotherapy with intranasal corticosteroids, second-generation oral H₁-antihistamines, and/or intranasal H₁-antihistamines initially.²

Skin or in vitro allergy testing is often next undertaken in patients with AR. If results of allergy testing are positive, indicating type I IgE-mediated reactivity, an association

between positive test allergens and symptom pattern should be confirmed and patients may be screened for suitability for AIT. Absolute contraindications to SLIT include history of severe local or systemic reaction to SLIT; severe, uncontrolled, or unstable asthma; current beta-blocker use (although some consider this a relative contraindication); hypersensitivity to an inactive ingredient in the SLIT preparation; and a history of eosinophilic esophagitis. Other considerations include patient compliance, other immunologic diseases, comorbidities, and cost (Table 1).^{2,14–18} AIT can be continued in patients who become pregnant. Recent literature also suggests AIT may be safely initiated in pregnant patients.¹⁹ Pediatric patients are candidates for AIT. SLIT studies included children as young as 4 years.²⁰

Efficacy

Multiple large-scale systematic reviews and meta-analyses, including a Cochrane review of 60 double-blinded randomized controlled trials (DBRCTs), demonstrate SLIT efficacy for AR in adults and children (Table 2).^{16,17,21,22} The Cochrane review found a significant reduction in symptoms (standardized mean difference [SMD] -0.49 ; 95% confidence interval (CI) -0.64 to -0.34 , $P < .00001$) and medication requirements (SMD -0.32 ; 95% CI -0.43 to -0.21 , $P < .00001$) in participants receiving SLIT versus placebo.¹⁶ A more recent systematic review of 63 DBRCTs, considering an additional 11 studies not included in the Cochrane review, noted a moderate strength of evidence supporting SLIT for AR (rhinitis/rhinoconjunctivitis), with 4 studies demonstrating statistically significant improvements in disease-specific quality of life using validated instruments.¹⁷

The progression from atopic dermatitis (AD) to AR to allergic asthma (AA) is referred to as the “allergic march.”² Some studies assert that AIT prevents the progression of AR to asthma. A 2013 systematic review of AIT for asthma and AR in pediatric patients included 3 studies that evaluated the prevention of asthma with SLIT.²⁰ Two studies showed decreased new asthma diagnoses in patients with AR treated with SLIT versus placebo.^{23,24} One study showed children receiving conventional AR treatment were 3.8 times (95% CI 1.5–10.0) more likely to develop asthma versus those receiving SLIT for 3 years.²⁴ Another study evaluating SLIT treatment for 2 years, however, showed no difference in the number of patients with asthma at 8 years of follow-up.²⁵

Four SLIT tablet formulations are currently approved by the US FDA for AR treatment. Timothy Grass Pollen Allergen Extract (Grastek; Merck), House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract Tablet for Sublingual Use (Odactra; Merck, Kenilworth, NJ, USA), a 5-grass tablet

Table 1
Indications, contraindications, and additional considerations to initiation of sublingual immunotherapy (SLIT)

Indications	Contraindications	Additional Considerations
• Failure of avoidance measures and pharmacotherapy • Evidence of immunoglobulin E-mediated disease via skin or in vitro testing • Association between reactive antigens and symptoms	• History of severe local or systemic reaction to SLIT • Severe, uncontrolled, or unstable asthma • History of eosinophilic esophagitis • Current use of β-blockers • Hypersensitivity to an inactive ingredient in the SLIT preparation	• Other immunologic disease • Social factors (eg, cost, concerns about patient adherence)

Table 2
Meta-analyses and systematic reviews of the efficacy of SLIT for AR

Citation	Included Studies	n	Results	Conclusion
Radulovic et al, ¹⁶ 2010	49	4589	Symptoms: SMD −0.49 95% CI −0.64 to −0.34 $P < .00001$ Medication Use: SMD −0.32 95% CI −0.43 to −0.21 $P < .00001$	"Sublingual immunotherapy is now established as a viable alternative to allergen injection immunotherapy, with a significantly lower risk profile and, on the basis of meta-analyses, little difference in overall efficacy."
Lin et al, ¹⁷ 2013	36	2985	• 94% of studies demonstrated greater improvement in the SLIT groups vs placebo. • Medium risk of bias. • Magnitude of association was moderate or strong in 14 studies (39%).	"...moderate strength in the evidence to support the use of sublingual immunotherapy for allergic rhinitis and asthma."
Devillier et al, ²¹ 2014	38	21,223	• Five-grass pollen SLIT tablets: Weighted mean RCI on symptom scores, (range) −29.6% (−23% to −37%) • Timothy pollen SLIT tablets: RCI −19.2% (−6% to −29%) • Nasal corticosteroids: RCI −23.5% (−7% to −54%) • Azelastine-fluticasone combination (MP29-02): RCI −17.1% (−15% to −20%) • H1-antihistamines: RCI −15.0% (−3% to −26%) • Montelukast RCI −6.5% (−3% to −10%)	"...grass pollen SLIT tablets [were] associated with a greater [RCI] than that provided by second-generation H1-antihistamines and a leukotriene receptor antagonist..."
Di Bona et al, ²² 2015	13	4659	Symptoms: SMD −0.28 95% CI, −0.37 to −0.19 $P < .001$ Medication Use: SMD −0.24 95% CI, −0.31 to −0.17 $P < .001$	"...small benefit of the grass pollen sublingual tablets in reducing symptoms and in decreasing the use of symptomatic medication...in patients with [seasonal allergic rhinoconjunctivitis]."

Abbreviations: CI, confidence interval; RCI, relative clinical impact; SLIT, sublingual immunotherapy; SMD, standardized mean difference.

(Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract [Oralair; Stallergenes-Greer, Cambridge, MA, USA]), and Short Ragweed Pollen Allergen Extract (Ragwitek; Merck). Prescribing information and indications for these medications are slightly varied ([Table 3](#)).^{26–29}

Durability

The reduction in AR symptoms begins from several weeks to 1 year after SLIT initiation.² Treatment effect may persist up to 8 years following SLIT completion, based on one study.³⁰ Although symptoms may return, a 15-year longitudinal study compared SLIT treatment length (3, 4, or 5 years) and showed a 4-year treatment course to be optimal. This study also showed a second SLIT course had prompt clinical impact after attenuation of the first course's benefit.³⁰

Safety

A primary concern for patients and physicians with any treatment is safety. This concern is particularly heightened with AIT, as anaphylaxis and death have occurred with SCIT. Systemic reactions (SRs), such as urticaria, wheezing, and anaphylaxis, occur in 0.06% to 0.9% of patients undergoing SCIT.² There is 1 death per 2.5 million injections of SCIT.¹⁰

The SLIT safety profile is much higher compared with SCIT. No deaths have occurred with SLIT and SRs are less common, occurring in 0.056% of patients.^{2,13,15–17,20,22} Anaphylaxis rarely occurs with SLIT. Before initiation of therapy, many practitioners prescribe an epinephrine autoinjector. Education on anaphylaxis symptoms and epinephrine autoinjector use must be provided. The first dose of SLIT is administered in the physician's office and the patient is observed for SRs.

Local reactions, such as pruritus and/or oral cavity edema, are common with SLIT. These local reactions are typically minor, nondistressing, self-limited, and viewed by patients as an inconvenience. Rarely, they lead to cessation of treatment.¹⁶

SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC ASTHMA

Asthma is a chronic inflammatory disease of the airways with expiratory airflow limitation. Symptoms include wheezing, coughing, chest tightness, and shortness of breath. The most common asthma phenotype is AA, with symptoms triggered by allergen

Table 3
Prescribing information for Food and Drug Administration–approved sublingual immunotherapy tablets for allergic rhinitis

Medication	Indications	Contraindications	Notes	
Grastek ²⁶	• Allergic rhinitis • Documented allergy with positive skin testing	5–65 y	• Severe, unstable, or uncontrolled asthma • History of severe local/systemic reaction to sublingual immunotherapy	Also indicated for pollens cross-reactive with Timothy Grass
Odactra ²⁷	OR Specific immunoglobulin E antibodies to allergen contained in tablet	18–65 y		Approved by the Food and Drug Administration, March 2017
Oralair ²⁸		10–65 y	• Eosinophilic esophagitis • Hypersensitivity to inactive ingredients in tablets	Requires 2-step escalation in children
Ragwitek ²⁹		18–65 y		

exposure. AA often presents in childhood and is associated with personal or family history of eczema, AR, or food allergy.⁵ Eight percent of adults and 9% of children in the United States have asthma; approximately 300 million people worldwide have the disease.³¹

Indications and Contraindications

The 2017 update of the Global Strategy for Asthma Management and Prevention by the Global Initiative for Asthma now recommends consideration of SLIT in adults with AA, AR, and house dust mite (HDM) sensitivity who have asthma exacerbations despite inhaled corticosteroid treatment. These patients should have a forced expiratory volume in 1 second (FEV₁) that is 80% of predicted or better.⁵ The American Academy of Allergy, Asthma and Immunology has broader indications for the use of AIT in AA (Box 1).¹⁰

Indications and contraindications when considering appropriate candidates for SLIT for AA are similar to those for AR (see Table 1). The contraindication regarding poorly controlled asthma is particularly important in this population, as patients with severe or uncontrolled asthma undergoing SCIT have an increased risk of SRs and death during anaphylaxis.¹⁰

Efficacy

Several meta-analyses and systematic reviews of SLIT for the treatment of AA have been performed (Table 4).^{32–35} Three of these articles report a statistically significant reduction in asthma symptoms.^{32–34} There was, however, a considerable degree of heterogeneity among studies. A 2015 Cochrane Review included 52 studies on SLIT for AA. Unfortunately, data from these studies were determined insufficient for a robust meta-analysis and did not report findings for areas of clinical interest such as exacerbation prevalence, quality of life, asthma symptoms, and medication use.³⁵

New studies of SLIT efficacy for AA not included in these meta-analyses are now being released. The MITRA trial, a DBRCT with 834 European participants, investigated the efficacy of an HDM SLIT tablet for HDM-related AA. This study showed the addition of HDM SLIT reduced the risk of moderate or severe asthma exacerbation (hazard ratio [HR] 0.69; 95% CI 0.50–0.96, $P = .03$).³⁶ An HDM SLIT tablet is approved for HDM-related AA and AR in 11 European countries. A 12 standardized quality (SQ)-HDM SLIT tablet (Odactra) was approved by the FDA on March 1, 2017, for

Box 1

American Academy of Allergy, Asthma and Immunology indications for allergy immunotherapy in patients with specific immunoglobulin E antibodies to clinically relevant antigens

Indication

- Patient preference
- Inadequate response to avoidance measures
- Burdensome medication requirements
- Adverse effects of medications
- Coexisting allergic rhinitis and asthma
- Possible prevention of asthma in patients with allergic rhinitis

Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1 Suppl):S13; with permission.

Table 4
Meta-analyses and systematic reviews of the efficacy of sublingual immunotherapy for allergic asthma

Citation	Included Studies	n	Results	Conclusion
Penagos et al, ³² 2008	9	441	Symptoms: SMD -1.14 95% CI -2.10 to -0.18 $P = .02$ Medication use: SMD -1.63 95% CI -2.83 to -0.44 $P = .007$	"SLIT with standardized extracts reduces both symptom scores and rescue medication use in children with allergic asthma compared with placebo."
Compalati et al, ³³ 2009	9	476	Symptoms: SMD -0.95 95% CI -1.74 to -0.15 $P = .02$	"Promising evidence of efficacy for SLIT in...patients suffering from AR and AA, are herein shown. These findings suggest that more data are needed, derived from large population-based high-quality studies, and corroborated by objective outcomes, mainly for AA."
Tao et al, ³⁴ 2014	16	794	Symptoms: SMD -0.74 95% CI -1.26 to -0.22 $P = .006$ Medication use: SMD -0.78 95% CI -1.45 to -0.11 $P = .02$	"SLIT is safe and clinically effective in reducing symptoms and medication use for allergic asthma."
Normansell et al, ³⁵ 2015	52	5077	"[W]e were able to perform a very limited meta-analysis...Use of largely unvalidated symptom and medication scores also impeded quantitative synthesis of findings."	"This finding supports continued use of SLIT for people with other respiratory allergies, such as allergic rhinitis, who may also have well-controlled mild to moderate asthma."

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; CI, confidence interval; SLIT, sublingual immunotherapy; SMD, standardized mean difference.

the treatment of HDM-associated AR, but it has not been approved for use in AA in the United States.

Durability

Studies of the efficacy of SLIT for the treatment of AA are continuing. As such, there are limited studies of the long-term durability of this treatment. One open, parallel group trial of HDM SLIT for 4 to 5 years versus standard therapy in children ($n = 60$) has been published.³⁷ This study found significant reductions in asthma diagnoses at the end of SLIT therapy. These reductions persisted for 5 years after the cessation

of therapy (8.5% vs 96%, $P = .001$). Additionally, patients who underwent SLIT had a higher peak expiratory flow rate 5 years after the cessation of therapy versus controls. Although this study further supports the use of SLIT for AA, additional randomized controlled trials are needed to further evaluate the durability of the therapy.

Safety

Like SLIT for AR, SLIT for AA has a high safety profile. The previously mentioned Cochrane review analyzed results from 22 studies with 2560 patients and found, “no more than one in 100 [patients] are likely to suffer [a severe adverse event] as a result of treatment with SLIT (risk difference [RD] 0.0012, 95% CI -0.0077 – 0.0102 ; moderate-quality evidence).”³⁸

The primary safety concern in SLIT for the treatment of AA is the potential to induce bronchospasm and hypoxia. Appropriate selection of patients with partly controlled asthma is the solution; that is, patients may have asthma exacerbations and symptoms but their asthma is not considered uncontrolled. The 7-item Asthma Control Questionnaire (ACQ) can be used in adults and children to identify patients with partly controlled asthma.⁵ Patients respond on a 7-point scale, and the overall score is the mean of the responses (0, totally controlled; 6, severely uncontrolled). Patients who score between 1.0 and 1.5 on the ACQ are partly controlled.³⁹

One of the ACQ's 7 items is the FEV₁. Even if the ACQ is not used, patients with AA being considered for SLIT should undergo pulmonary function testing. SLIT should not be initiated in patients with an FEV₁ less than 70% of predicted, as this indicates poor control. In summary, patients with partly controlled asthma, defined as an ACQ of between 1.0 and 1.5 (or other measure of control) and an FEV₁ greater than or equal to 70% of predicted may be considered possible candidates for SLIT.⁵

SUBLINGUAL IMMUNOTHERAPY FOR ATOPIC DERMATITIS

Patients with AR and AA often present with other allergic disorders. AD, sometimes referred to as eczema or atopic eczema, is a chronic inflammatory condition that often begins as a skin rash and progress to skin redness, drying, scaling, and itching. It most frequently presents in infants and children. It can persist into adulthood, or can less commonly begin in adulthood. SLIT as a possible treatment for AD has been investigated, but results are inconclusive.

A 2011 study randomized patients with HDM-related AD to receive pharmacotherapy plus HDM SLIT drops or pharmacotherapy alone. Treatment was considered effective if a subject's Severity Scoring of Atopic Dermatitis index decreased by 60% or more. Effectiveness in the SLIT group was 77.78% versus 53.85% for controls ($\chi^2 = 12.73$, $P < .05$). Daily medication use score was lower in the treatment group at 6 and 12 months as compared with the control group ($P < .01$).⁴⁰ However, a Cochrane review of AIT (4 SLIT trials, 6 SCIT trials) for the treatment of AD (733 participants) found limited, low-quality evidence that AIT is effective for AD treatment. Additional trials using high-quality allergens, patient-reported outcome measures, and low-bias study design are needed to further investigate SLIT for AD.⁴¹

SUBLINGUAL IMMUNOTHERAPY FOR FOOD ALLERGY

IgE-mediated food allergies often present as urticaria, vomiting, wheezing, or anaphylaxis following ingestion of an allergen-containing product. The prevalence of food allergies is increasing, as is their severity.⁴² The leading food allergen resulting in anaphylaxis and death is peanut. In the past decade, the prevalence of peanut allergy

has doubled in Western countries to between 1.4% and 3%.⁴³ AIT for food allergy is being studied as a potential treatment.

A 2017 systematic review and meta-analysis of AIT for food allergy found it “effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy....”⁴² Although most included studies used oral immunotherapy, 4 RCTs using SLIT were included (**Table 5**).^{44–47} Pooled results revealed SLIT as effective for the treatment of food allergy (risk ratio [RR] 0.26, 95% CI 0.10–0.64, $P < .004$).

Based on these limited controlled studies, SLIT for food allergy appears to be safe in the populations tested. SRs were rare. Three of the 4 studies had no episodes of anaphylaxis requiring the use of epinephrine.^{44,45,47} One patient in the study by Fleischer and colleagues⁴⁶ experienced anaphylaxis requiring treatment with epinephrine. Between 0.2% and 2.9% of SLIT doses required treatment with oral antihistamines.^{44,46}

Citation	n	Allergen	Results	Conclusion
Enrique et al, ⁴⁴ 2005	23	Hazelnut	Change in mean quantity provoking objective symptoms: 2.29 g to 11.56 g, $P = .02$	“Our data confirm significant increases in tolerance to hazelnut after sublingual immunotherapy as assessed by double-blind, placebo-controlled food challenge, and good tolerance to this treatment.”
Fernández-Rivas et al, ⁴⁵ 2009	56	Peach	Change in dose needed to induce a local reaction: 9x higher Change in dose needed to induce a systemic reaction: 3x higher	“SLIT for peach allergy seems to be a promising therapeutic option that could modify the clinical reactivity of the patients to peach intake and the underlying immunologic response with a good tolerance.”
Kim et al, ⁴⁷ 2011	18	Peanut	The treatment group safely ingested 20 times more peanut protein than the placebo group (median 1710 vs 85 mg, $P = .011$)	“Peanut SLIT is able to safely induce clinical desensitization in children with peanut allergy, with evidence of immunologic changes suggesting a significant change in the allergic response.”
Fleischer et al, ⁴⁶ 2013	40	Peanut	SCD increased from 3.5 to 496 mg (median) after 44 wk. After 68 wk, median SCD increased to 996 mg.	“Peanut SLIT safely induced a modest level of desensitization in a majority of subjects compared with placebo. Longer duration of therapy showed statistically significant increases in the SCD.”

Abbreviations: SCD, successfully consumed dose; SLIT, sublingual immunotherapy.

Specific indications and durability data regarding SLIT for the treatment of food allergy are lacking, however. Additional studies with larger treatment groups and longer follow-up are needed to further standardize and evaluate this therapy.

PRACTICAL APPLICATIONS OF SUBLINGUAL IMMUNOTHERAPY IN CLINICAL PRACTICE
Allergy Testing

Skin testing is one option for allergy testing and can be used provided the patient does not have contraindications (ie, use of medications that interfere with testing [Table 6]), beta-blocker use, uncontrolled asthma, or dermatographism. Leukotriene receptor antagonists, selective serotonin reuptake inhibitors, proton pump inhibitors, and angiotensin-converting enzyme inhibitors do not impact skin testing.⁴⁸

Allergy skin testing may be performed via skin prick, intradermal dilution testing (IDT), and modified quantitative testing (MQT) also known as blended testing. IDT and MQT provide quantitative endpoints. Skin prick testing is a more qualitative method. Quantitative testing is not necessary if the patient knows that he or she will choose SLIT, as short escalation periods (nor no escalation) are used. In vitro laboratory testing for quantitative assessment of specific IgE is another option for allergy testing. The allergy testing panel is commonly made up of 10 to 30 antigens, with selection based on frequently encountered allergens in the local environment as well as individual medical history.

Dosing

There is significant confusion regarding dosing with immunotherapy. Contributing to this confusion is the variety of proprietary dosing units used by manufacturers, such as bioequivalent allergy units, allergy units, and SQ units. Micrograms of major allergen is the most reliable method of reporting the antigen content in an SLIT dose and should be identified when reviewing literature, if reported by the investigators. Except for antigens included in FDA-approved SLIT tablets, the optimal dose for many SLIT antigens has not been precisely identified. In general, however, total monthly maintenance doses of SLIT are a mean 87 times (median 49 times) higher than monthly SCIT maintenance doses.¹⁸ Pediatric SLIT doses are generally equivalent to adult SLIT doses. The maximum tolerated dose, however, may be lower for younger or smaller children.⁴⁹

Table 6 Medications that inhibit skin-based allergy testing	
Medication	Maximum Days of Testing Suppression
1st-generation antihistamines	5
2nd-generation antihistamines	7
Antihistamine nasal sprays	1
Antihistamine eye drops	1
Tricyclic antidepressants	14
Benzodiazepines	7
Histamine-2 antihistamines (H ₂ blockers)	2
Topical corticosteroids (at testing site)	21

Data from AAOA Clinical Care Statement Workgroup. Compendium of Clinical Care Statements. AAOA Today, 2015. Available at <http://www.aaof.org/PDF/Clinical%20Statements/2015%20Clinical%20Care%20Statements%20Medicines%20to%20Avoid%20Before%20Allergy%20Skin%20Testing.pdf>.

Most randomized controlled trials of SLIT study a single antigen. Additionally, most large-scale SLIT studies were performed in Europe, where single-antigen AIT dosing is more common. In the United States, however, the mean number of antigens used for AIT is 10.¹⁴ Current data are limited as to the efficacy of multiantigen versus single-antigen SLIT, although this practice is commonly used in the United States.

Additional Considerations

Dosing and escalation protocols for SLIT vary widely. However, common themes are as follows: (1) SLIT dose is higher than SCIT dose, and (2) SLIT escalation is shorter than SCIT escalation. In some cases (ie, SLIT tablet dosing for adults), no escalation is used. The use of aqueous antigens is not currently approved by the FDA for SLIT application; use is off-label. If aqueous SLIT is used, the off-label nature of the treatment should be discussed with patients. Obtaining written informed consent for AIT is advocated, following a thorough discussion of the risks, benefits, and alternatives.

Following administration of the first dose in the clinician's office, SLIT is typically dosed at home. Thus, meticulous patient education is key. Patients should undergo thorough training regarding the appropriate method of taking SLIT doses, common side effects, and worrisome signs of systemic reaction or anaphylaxis. If an epinephrine autoinjector has been prescribed, patients (along with a family member or close friend) should be thoroughly educated on its use. Routine clinic follow-up to assess SLIT progress, symptom control, allergy medication use, and adherence to therapy is paramount.

Similar to SCIT, the allergy practitioner should be comfortable with his or her knowledge of SLIT before initiating this therapy in practice. Adding SLIT to a practice with no current allergy services or adding SLIT to an established SCIT practice requires planning, organization, and further study. With these considerations in mind, SLIT is a rewarding service for the provision of AIT.

SUMMARY

SLIT is effective for the treatment of AR and AA in adults and children, leading to significant reductions in symptoms and medication requirements. The effect of SLIT for AR is durable, with one study showing 8 years of benefit following a 4-year course of SLIT. The risk of moderate or severe exacerbations of AA is reduced with SLIT. Indications for SLIT use in AR have been published by the American Academy of Otolaryngology–Head and Neck Surgery and the World Health Organization. The Global Initiative for Asthma now includes SLIT in its stepwise approach to asthma treatment. A limited number of studies has shown that SLIT may have promise for the treatment of food allergy. SLIT has not, however, been demonstrated as effective for the treatment of AD based on current literature. SLIT has a higher safety profile as compared with SCIT. Although no deaths have occurred with SLIT, anaphylaxis rarely occurs. Appropriate patient selection, meticulous patient education, and routine follow-up are key for successful SLIT administration.

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