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Sublingual Immunotherapy: A Guide for Primary Care

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INTRODUCTION

Allergen immunotherapy (AIT), the only potential disease-modifying treatment for allergic disease, has been used for more than a century.[1] Hankin et al showed significant reduction in pharmacy, outpatient, and inpatient resources in the 6 months following vs the 6 months preceding AIT in Medicaid-enrolled children with allergic rhinitis (AR).[2] A 2013 analysis showed sustained cost reduction over 18 months in patients with AR treated with AIT compared with matched control subjects not treated with AIT.[3] The overall cost savings were 38% with AIT, which was similar to the cost savings observed in adults.

AIT is underused, partly because of the lack of familiarity of nonallergy/immunology-trained health care providers, and partly because of safety concerns (primarily anaphylaxis risk) associated with its subcutaneous administration.[1] These safety concerns, as well as practical and logistic considerations associated with administration of subcutaneous immunotherapy (SCIT), spurred interest in the use of sublingual immunotherapy (SLIT), which can be self-administered, does not require injections, and carries a much lower risk of anaphylaxis compared with SCIT.[4] While SLIT has been used outside the United States for decades, the US Food and Drug Administration (FDA) has recently approved 4 SLIT allergen extract products (tablets) for treatment of the symptoms and morbidity associated with grass pollen, ragweed, or house dust mite AR, with or without conjunctivitis.

Grass and ragweed allergens are among the most common aeroallergens and characteristically cause seasonal allergic rhinoconjunctivitis (ARC) and/or seasonal allergic asthma. On the other hand, cat dander, cockroach, or dust mite allergens cause symptoms year-round and are associated with perennial AR and/or allergic asthma.[4]

Medical management of seasonal and perennial nasal allergic disease typically involves allergen avoidance and use of pharmacotherapeutic agents such as nonsedating oral antihistamines, intranasal antihistamines, intranasal cromolyn and, most importantly, intranasal corticosteroids.[5] Required daily use for efficacy raises concerns regarding long-term adherence, safety, and cost. Allergic asthma control with long-term use of inhaled steroids and long-acting bronchodilators also poses risks.[4]

Since allergic disease is an immunologic, systemic disorder with local manifestations, it is not surprising that treatment with immunotherapy can modify the underlying natural history of the disease, resulting in long-term efficacy (ie, immune tolerance) after termination of treatment.[6,7] Unlike pharmacotherapy, AIT can also reduce the incidence of subsequent asthma in patients with AR and reduce sensitization to new allergens.[8]

AIT is most beneficial for patients with moderate-to-severe intermittent or persistent symptoms of AR or ARC, particularly those whose symptoms are not responsive to pharmacotherapy and environmental control measures.[1]

Mechanisms of SCIT and SLIT

Whether by the subcutaneous or sublingual route, administration of AIT leads to very early decrease in susceptibility of mast cells and basophils to degranulation (ie, rapid desensitization), possibly due to upregulation of histamine type 2 receptors and decreased effector cell function.[9] This is followed by generation of allergen-specific regulatory T cells and suppression of allergen-specific Th1 and Th2 cells, and, after several months, a significant decrease in the allergen-specific IgE/IgG4 ratio and a decrease in tissue mast cell and eosinophil numbers and release of mediators.[6]

Allergen extracts administered sublingually are taken up by dendritic cells in the oral mucosa and presented to T cells in the draining lymph nodes, likely resulting in activation of regulatory T cells and downregulation of mucosal mast cells.[10] The low level of effector cells such as mast cells, basophils, and eosinophils within the oral and sublingual mucosa

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is believed to be an important factor in the lower rates of adverse systemic allergic reactions observed with SLIT compared with SCIT.[10]

Subcutaneous immunotherapy

SCIT has been shown to be highly effective in reducing both symptoms and use of medications in patients with seasonal AR and ARC with or without asthma.[4,11] However, subcutaneous administration can be associated with systemic allergic reactions, including, rarely, anaphylaxis and death.[1,5] Therefore, SCIT must be administered in a setting with immediate access to resuscitative measures.

The discomfort of injections and inconvenience of office visits for SCIT also contribute to underuse of SCIT as a therapeutic option and to low adherence among patients.[1,12] A 2014 survey of patients' experience with AIT showed that, among patients treated with SCIT (n=456) or SLIT (n=34), only 61.8% and 52.9%, respectively, completed the recommended number of doses.[12] Although it might have been expected that adherence with SLIT would be higher than with SCIT because of the convenience of treatment at home, personal experience shows that adherence with SLIT also declines over time, as is generally the case with medication adherence. This indicates the importance of supporting patient self-management at each visit.

Sublingual immunotherapy

Overview of available products

In 2014, the FDA approved 3 sublingual tablets, 1 containing 5 grass pollen extracts (Oralair) and another containing 1 grass (Timothy) pollen extract (Grastek). The third product (Ragwitek) contains a short ragweed pollen extract. Oralair is indicated for the treatment of grass pollen-induced AR with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the 5 grass species contained in the product: Sweet Vernal grass, orchardgrass, perennial ryegrass, Timothy, and Kentucky bluegrass. In contrast, Grastek is limited to treatment of people with positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens.[13,14] There is low cross-allergenicity among the 5 grass species in the 5-grass pollen product and several of the southern grasses (particularly Bermuda grass).

The short ragweed pollen product Ragwitek is indicated for the treatment of short ragweed pollen-induced AR, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen.[15] A fourth SLIT product (Odactra) was approved by the FDA in March 2017 for house dust mite-induced AR, with or without conjunctivitis.[16] Several studies indicate that it improves AR in patients with AR and asthma symptoms, with efficacy that is maintained during treatment-free follow-up.[17-20]

The approved minimum age for use is 5, 10, 18, and 18 years of age, respectively, for Grastek, Oralair, Ragwitek, and Odactra.[13-16] All are approved for use in adults through 65 years of age.

Efficacy and impact on natural history of allergy

For AR, rhinoconjunctivitis, and asthma, numerous double-blind, placebo-controlled trials, as well as several meta-analyses and systematic reviews, have confirmed that SLIT is effective in reducing symptom scores and medication use, improving quality of life, inducing favorable changes in specific immunologic markers, and modifying the course of the condition over time (**TABLE 1**).[21-30] Several randomized, double-blind studies demonstrated that 3 years of continuous treatment with the 1- or 5-grass pollen SLIT products resulted in clinical and immunologic benefits that were sustained for at least 2 subsequent years.[18,19]

The efficacy of SLIT has been compared to either pharmacotherapy or SCIT for management of ARC. A pooled analysis indirectly compared the treatment effect of SLIT (N=3094 in Timothy grass SLIT tablet trials; N=58 in ragweed SLIT tablet trials) vs pharmacotherapies (montelukast, N=6799; desloratadine, N=445; or mometasone furoate nasal spray, N=2140) for seasonal and perennial AR.[31] Improvement in total nasal symptom scores (TNSSs) relative to placebo in seasonal AR was numerically greater with SLIT than with montelukast and desloratadine (16.3% and 17.1% in the Timothy grass and ragweed trials, respectively, vs 5.4% and 8.5% in the montelukast and desloratadine trials, respectively), and was nearly as great as with mometasone furoate nasal spray (22.2%). Similar outcomes were reported in a meta-analysis indirectly comparing results from 28 pharmacotherapy trials and 10 grass pollen SLIT trials (total number of patients, N=21,223).[32] Grass pollen SLIT tablets had a greater mean relative clinical impact (based on reported posttreatment or season-long nasal or total symptom score) than second-generation antihistamines and montelukast, and the same mean relative clinical impact as nasal corticosteroids.[32]

Comparing the efficacy of SCIT with SLIT is difficult because of heterogeneity of allergen composition, dose, duration, and patient selection, particularly among older studies.[8,33-38] A 2015 network meta-analysis of 37 studies comparing grass pollen SCIT and SLIT tablets demonstrated comparable reduction in ARC symptoms and supplemental medication use during the first pollen season.[38]

TABLE 1 Randomized, double-blind, placebo-controlled trials of SLIT tablets for grass and ragweed pollen

Study	Age range (y)	A/P	Dropouts (A/P)	Product tested	Duration	Disease	Results
Durham, 2006[21]	18-65	569/286	44/21	TGPAE	8 wks before and during grass pollen season	Grass pollen–induced RCA	Reduction in RC score for symptoms (16%) and medication use (28%) vs placebo (*P*=.0710, *P*=.0470). Better RC QOL scores (17%, *P*=0.006) and increased number of well days (18%, *P*=.041). One drug-related serious adverse event (uvular edema); did not require treatment and did not lead to withdrawal. No life-threatening systemic reactions or deaths.
Nelson 2011[22]	18-65	213/225	38/33	TGPAE	16 wks before and during grass pollen season	Grass pollen–induced RCA with or w/out asthma	Improved TCS by 20% (*P*=.005), DSS by 18% (*P* =.02), and RQLQ(S) scores by 17% (*P*=.02). DMS were improved by 26% (*P*=.08) No treatment-related serious AEs or reports of anaphylactic shock/respiratory compromise.
Maloney 2014[23]	5-65	1501 total (A + P)	NS	TGPAE	NS	Grass pollen–induced RCA with or w/out asthma	Improvements (*P*≤0.001) vs placebo of 23% in entire-season TCS, 29% in peak-season TCS, 20% in entire-season DSS, 35% in entire-season DMS; 12% in peak-season RC QOL questionnaire (*P*=.027). No serious treatment-related AEs or anaphylactic shock
Durham 2012[24]	18-65	137/104	NS	TGPAE	4-8 mos before and during grass pollen season continued for 3 seasons; 2-y blinded follow-up	Grass pollen–induced RCA	SLIT vs placebo: Mean RC DSS was reduced by 25%-36% (*P* ≤.004) over the 5 grass pollen seasons covered. RCV DMS was reduced by 20%-45% (*P*≤.022 for seasons 1-4; *P* =.114 for season 5). Weighted RC combined score was reduced by 27%-41% (*P*≤.003). Percentage of days with severe symptoms during the peak grass pollen exposure was lower in all seasons in the active group than in the placebo group (relative differences of 49% to 63% (*P*<.0001). No treatment-related serious AEs or events of severe systemic allergic reactions.
Cox 2012[25]	18-65	233/240	26/17	5-GPAE	6-mo preseasonal and coseasonal treatment and 2-wk follow-up	Grass pollen–induced RCA	The mean daily combined score over the pollen period was significantly lower w/SLIT vs placebo (LSM difference, -0.13; 95% CI, -0.19 to -0.06; *P*=.0003; relative reduction, 28.2%; 95% CI, -13.0% to -43.4%). There were no reports of anaphylaxis, and no actively treated participant received epinephrine.
Didier 2007[26]	18-45	472/156	59/10	5-GPAE	4 mos prior to pollen season and continued throughout season	Grass pollen–induced RCA	Significantly reduced mean RC TSS (3.58 ± 3.0, *P*=.0001; and 3.74 ± 3.1, *P*=.0006 for 300-IR and 500-IR doses) vs placebo (4.93 ± 3.2). No serious systemic events or anaphylactic shock were observed.

CONTINUED

TABLE 1 Randomized, double-blind, placebo-controlled trials of SLIT tablets for grass and ragweed pollen *(Continued)*

Study	Age range (y)	A/P	Dropouts (A/P)	Product tested	Duration	Disease	Results
Didier 2011[27]	18-50	414/219	117/56	5-GPAE	Either 2 or 4 mos before and then during grass pollen season for 3 consecutive seasons	Grass pollen–induced RCA	Mean AAdSS was reduced by 37.7% and 34.8% at season 3 in the 2- and 4-month preseasonal and coseasonal active treatment groups, respectively, vs placebo (P<.0001 for both). 1 severe local reaction and 1 angioedema during first year, resulting in study discontinuation.
Wahn 2009[28]	5-17	139/139	8/4	5-GPAE	4 mos before estimated pollen season and continued throughout season	Grass pollen–induced RCA	The 300-IR group showed a mean improvement for the RTSS of 28.0% over that seen with placebo (P=.001) and a median improvement of 39.3%. AEs were generally mild or moderate in intensity and expected. No serious side effects were reported.
Creticos 2013[29]	18-50	586/198	140/38	SRPAE	52 wks of daily SLIT	Short ragweed–induced RCA	During peak season, low, medium, and high doses of SLIT reduced TCS by 9% (-0.76; P=.22), 19% (-1.58; P=.01), and 24% (-2.04; P=.002) compared with placebo. No systemic allergic reactions occurred.
Nolte 2013[30]	18-50	377/188	100/42	SRPAE	12 wks before and during entire ragweed season and thereafter up to 52 wks	Short ragweed–induced RCA	During peak season, the low and high ragweed AIT doses showed 21% (-1.76 score; P=.004) and 27% (-2.24 score; P<.001) improvement in TCS vs placebo. No systemic allergic reactions were reported. One patient in the treatment group received epinephrine at an emergency facility for sensation of localized pharyngeal edema.

Abbreviations: AE, adverse event; AAdSS, average adjusted symptom score; AIT, allergy immunotherapy tablet; A/P, active/placebo; CI, confidence interval; DMS, daily medication score; DSS, daily symptom score; IR, index of reactivity; LSM, least-squares mean; NS, not stated; QOL, quality of life; RC, rhinoconjunctivitis; RCA, rhinoconjunctivitis/asthma; RQLQ(S), Standardized Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, Rhinoconjunctivitis Total Symptom Score (RTSS); SLIT, sublingual immunotherapy; SRPAE, short ragweed pollen allergen extract; TCS, total combined score; TGPAE, Timothy grass pollen allergen extract; 5-GPAE, 5-grass pollen allergen extract; TSS, total symptom score.

Safety

Based on more than 30 years of clinical use and more than 80 randomized, controlled trials, the safety profile of SLIT has been shown to be superior to SCIT.[39] No fatalities and few cases of anaphylaxis have been reported, with well over 1 million SLIT doses administered in clinical trials (as of 2006) and an estimated 1 billion doses administered worldwide between 2000 and 2012.[40]

Oral side effects (oral or ear pruritus, throat irritation, tongue pruritus, and mouth edema) are common with SLIT, affecting approximately 50% of patients, but typically last 10 days or less, and are infrequently (less than 5%) associated with discontinuation.[39] The occurrence and severity of adverse events declines in subsequent years of treatment. A low frequency of gastrointestinal side effects (eg, diarrhea, nausea, and abdominal pain) also may be observed.

Despite the extremely low incidence of systemic serious adverse reactions to SLIT, it is important to be familiar with potential factors that may increase the risk for its occurrence (**TABLE 2**).[40] Most important among these is severe, unstable, or uncontrolled asthma, which represents an absolute contraindication to SLIT (as well as to SCIT).[39] SLIT should also be avoided in patients with medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk for adverse reactions after epinephrine administration (eg, markedly compromised lung function, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension). SLIT may not be suitable for patients receiving medications that can potentiate or inhibit the effects of epinephrine (eg, beta-adrenergic blockers, alpha-adrenergic blockers, and tricyclic antidepressants).[13-15]

Key points for primary care providers

While best practices to guide the use of SLIT tablets are still evolving, some key points regarding patient management are summarized below.[41]

It is essential that patient sensitivity to the specific seasonal allergen is confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the specific pollen in order to guide appropriate therapy.[13-15] The in vitro, enzyme-linked immunosorbent assay (ELISA) test now recommended is an improvement over the radioallergosorbent test (RAST). SLIT is typically indicated for treatment of moderate to severe intermittent or persistent AR symptoms, particularly in patients who do not respond well to pharmacotherapy and environmental modification. These same considerations would likely be associated with perennial allergens.

Efficacy and safety of SLIT in children are similar to adults, and the 1- and 5-grass pollen products are indicated for children as young as 5 and 10 years old, respectively.[13,14,33]

Although patients with asthma were included in clinical trials of SLIT products, their asthma was well-controlled.[41] Therefore, caution should be used when initiating SLIT in patients with moderate-to-severe persistent and high-risk asthma, and SLIT should not be initiated or dosed at any time in patients with uncontrolled asthma. Other potential risk factors for SLIT-related anaphylaxis to be considered in patient selection for SLIT are listed in **TABLE 2**.[40]

New-onset eosinophilic esophagitis has been reported to occur after initiation of SLIT and to be resolved after discontinuation of SLIT.[41] Therefore, a history of eosinophilic esophagitis is a contraindication to initiation of SLIT. Patients on SLIT should be counseled to report worsening dysphagia and/or heartburn.[13-15]

The 1-grass pollen and ragweed pollen SLIT products are approved for treatment initiation at least 12 weeks before, and the 5-grass pollen product 16 weeks before, the expected onset of each grass or ragweed pollen season. All 3 products are continued throughout the season and then stopped. It is unclear whether SLIT can be safely initiated during the pollen season (coseasonal initiation) because of a potential increased risk for systemic allergic reactions.[42] However, a systematic review that included 11 SLIT studies found no increase in adverse events of concern with coseasonal vs out-of-season initiation.[42] Evidence indicates that 3 years of treatment is necessary to modify the disease process and achieve lasting efficacy. In fact, SLIT administered either before and during the allergy season or continuously for 3 years has been shown to reduce symptoms and use of rescue medication for up to 2 to 3 years after discontinuation of therapy.[5,24,27,43,44]

The 1-grass pollen and ragweed pollen SLIT products are dosed once daily, with no increase in or induction of dose.[14,15]

TABLE 2 Potential risk factors for SLIT-associated anaphylaxis[40]

Overdose
Interruptions in dose regimen
Previous systemic reaction, including anaphylaxis, to SCIT or SLIT
Previous severe local reaction
Asthma (particularly if severe or uncontrolled)
Acute infection (eg, upper respiratory infection)
Fever
Oral infections or lesions (eg, ulcer, gingivitis, periodontitis, etc) due to SLIT
Gender (premenstrual status)
Young age
Emotional stress
Exercise
High pollen counts

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

Source: Adapted from: Calderon MA, Simons FER, Mailing H-J, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy*. 2012;67:302-311. © 2011 John Wiley & Sons A/S.

The 5-grass mixed pollen SLIT product is dosed once daily, with no increase in dose for adults 18 to 65 years of age.[13] For children 10 to 17 years of age, the dose is increased over the first 3 days to achieve the maintenance dose.

For initiation of SLIT-tablet therapy, the first dose is administered by the provider, followed by a 30-minute observation period to monitor for signs or symptoms of a severe systemic or local allergic reaction.[41] Epinephrine and other measures to treat anaphylaxis should be immediately available to the provider, and an epinephrine auto-injector should be prescribed for home use with instructions for when and how to use it. If the patient tolerates the first dose of SLIT, subsequent doses can be given at home. The patient should be instructed to remove the tablet from the blister pack with dry hands and to place it immediately under the tongue, allowing it to dissolve, and to avoid food or beverage for 5 minutes. Hands should be washed after handling the tablet.[13-15]

For mild-to-moderate oral adverse events and mild abdominal pain and nausea, antihistamine H1 and H2 blockers may be helpful.[41] Patients experiencing severe or recurrent symptoms should be instructed to contact the prescriber and consider stopping SLIT. To minimize the risk of serious harm, patients must be taught how to monitor for signs of rapidly progressing reactions, such as worsening laryngeal edema, urticaria, or shortness of breath, that may require epinephrine use.[41] Once suspected, anaphylaxis must be treated with an intramuscular injection of epinephrine, as death can occur

within minutes.[40] If SLIT is being administered to a child, the parent or other responsible adult must administer each dose and monitor the child for any serious allergic reaction.

Transitioning patients from SCIT to SLIT should be guided by the expertise of an allergy or immunology specialist. Concomitant administration of SCIT and SLIT has not been well-studied. Currently, there is no procedural terminology (CPT) code for billing purposes for SLIT administration.

Lastly, the cost of AIT varies widely. Data from 8 preferred provider organizations showed 60% to 80% coverage for SCIT, with weekly copays of $0 to $50 and deductibles from $0 to $7000.[45] Medicare had a flat rate of 80% coverage, costing the insurer $807.20 for a year of SCIT. The study also showed that the cost of SLIT ranged from $500 to $2100, depending on the allergy practice and the number of antigens treated. Another study showed that the total direct medical costs for SCIT were $32 per visit (range $13 to $61), with half accounted for by the cost of the extract.[46] Pre- and post-injection administrative tasks were the second largest driver of direct costs. ●

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