Medical Policy Manual Medicine, Policy No. 121

Sublingual Immunotherapy as a Technique of Allergen Specific Therapy

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Sublingual immunotherapy (SLIT) is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. It is proposed as a more convenient alternative delivery route for treating a variety of allergic disorders.

MEDICAL POLICY CRITERIA

Sublingual liquid allergen extracts or non- U.S. Food and Drug Administration (FDA) approved sublingual tablets are considered **investigational** as a technique of allergy immunotherapy.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Allergy and Sensitivity Tests of Uncertain Efficacy, Laboratory, Policy No. 1
2. Medication Policy Manual, Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

Allergen-specific immunotherapy involves administering well-characterized allergen extracts, the potencies of which are measured and compared with a reference standard. An initial induction or build-up phase progressively increases the allergen dose; this is followed by multiple years of maintenance injections at the highest dose. Allergen-specific immunotherapy has been used to treat a variety of conditions including insect allergy, allergic rhinitis, and asthma.

Subcutaneous injection of allergen-specific immunotherapy (SCIT) is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, the use of sublingual immunotherapy (SLIT) allergen extract tablets is the most prominent. SLIT targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue for one to several minutes and then swallowed or spit out.

REGULATORY STATUS

Several injectable liquid allergen extracts have been approved by the U.S. Food and Drug Administration (FDA) as a treatment for a variety of allergy disorders. (http://www.fda.gov/BiologicsBloodVaccines/Allergenics/default.htm

The FDA has approved several sublingual allergen extract tablets, which can be found at the following path: http://www.fda.gov/BiologicsBloodVaccines/Allergenics/default.htm. Enter the drug name in the search bar. Not all sublingual allergen extract tablets are FDA-approved.

No liquid allergy extracts are currently approved by the FDA for use sublingually.

EVIDENCE SUMMARY

SUBLINGUAL IMMUNOTHERAPY COMPARED WITH PLACEBO

Systematic Reviews

A 2020 Cochrane systematic review (SR) evaluated the efficacy and safety of sublingual immunotherapy (SLIT) compared with placebo or standard care for adults and children with asthma.[1] Parallel randomized controlled trials (RCTs) with any blinding or of any duration that evaluated sublingual immunotherapy and a placebo or as an adjunct to standard asthma management were included. Primary outcomes were asthma exacerbations requiring a visit to the emergency department (ED) or admission to hospital, validated measures of quality of life, and all-cause serious adverse events (SAEs). In addition, asthma symptom scores, exacerbations requiring systemic corticosteroids, response to provocation tests, and dose of inhaled corticosteroids (ICS) were analyzed as secondary outcomes. Sixty-six studies were included in the review consisting mostly of double-blind and placebo-controlled trials that varied in duration from one day to three years. Participants had mild or intermittent asthma, often with comorbid allergic rhinitis. Data were not available for analysis from 16 studies and an additional six studies could only be included in a post hoc analysis of all adverse events. High risk of performance or detection bias (or both) was present in about one quarter of the studies and attrition was high or unknown in around half of the studies. The primary outcomes targeted in the review were not reported in most studies; only two small studies reported exacerbations requiring an ED or hospital visit. The pooled estimate from those studies

suggest SLIT may reduce exacerbations compared with placebo or usual care, however the evidence is very uncertain (OR 0.35, 95% confidence interval (CI) 0.10 to 1.20; n = 108; very low-certainty evidence). Analysis by risk difference suggests no more than 1 in 100 people taking SLIT will have a serious adverse event (RD -0.0004, 95% CI -0.0072 to 0.0064; participants = 4810; studies=29; moderate-certainty evidence) indicating there is not an increased risk of serious adverse events with the treatment compared to placebo or usual care. While more people taking SLIT had adverse events of any kind compared with control (OR 1.99, 95% CI 1.49 to 2.67; high-certainty evidence; participants = 4251; studies = 27), these events were usually reported to be transient and mild. Measurement of asthma symptom and medication scores was commonly done with non-validated scales, which precluded meaningful meta-analysis, however, a general trend of SLIT benefit over placebo for secondary outcomes was observed. The authors of this comprehensive literature review concluded “the evidence for important outcomes such as exacerbations and quality of life remains too limited to draw clinically useful conclusions about the efficacy of SLIT for people with asthma.” A 2020 SR by Chen assessing the effect of SLIT on house dust mite-induced allergic rhinitis only included studies conducted in children aged 4 to 18 years.[2] The review included 16 placebo-controlled trials (N=1,929) of SLIT drops or tablets for 6 to 24 months. Pooled outcomes included nasal symptom, medication, and ocular symptom scores. The review did not report discontinuation rates. Nasal symptom scores, reported in 16 studies, were significantly lower with SLIT versus placebo (SMD -1.73, 95% CI -2.62 to -0.84), but heterogeneity was very high (I2=98%). Total medication scores were also significantly lower with SLIT versus placebo based on evidence from 11 studies (SMD -1.21, 95% CI -1.75 to -0.67), but again heterogeneity was high (I2=94%). For both outcomes, the review found evidence of publication bias, but even after adjustment for bias, SLIT was more effective than placebo for both outcomes, p=0.02 and p<0.0001, respectively. Ocular symptom scores were only reported in six of the studies. When data were pooled there was no clear difference between SLIT and placebo (p=0.31), however subgroup analysis found SLIT tablets (SMD -0.28, 95% CI -0.42 to -0.14) more effective than SLIT drops (SMD 0.13, 95% CI -0.20 to 0.60), relative to placebo.

A meta-analysis by Yang (2018) evaluated the use of sublingual immunotherapy (SLIT) to treat allergic conjunctivitis or allergic rhinoconjunctivitis in pediatric patients, specifically looking for SLIT’s effectiveness for relieving eye symptoms.[3] Thirteen randomized clinical trials were identified, which included a total of 1,592 pediatric patients. Overall, the trials showed that allergic conjunctivitis symptoms were significantly reduced by SLIT (standardized mean difference [SMD] -0.21, 95% CI -0.41 to -0.01, p=0.04, I^2=55%). However, on a subgroup analysis of the different SLIT modalities, ocular symptoms improved with tablets (p<0.001) but not drops (p=0.47); in addition, SLIT significantly reduced pollen-induced allergic conjunctivitis (p<0.001) but not mite-induced (p=0.34). The investigators stated that the meta-analysis was limited by variations in the baseline severity of patients’ conjunctivitis, the ocular scoring systems used, and in the SLIT therapeutic regimens, as well as the small sample sizes (n<30) of 46% of the studies.

A meta-analysis of placebo-controlled randomized trial by Feng (2017a) evaluated the efficacy and safety of SLIT use in pollen-induced allergic rhinitis in children ages 3 to 18 years.[4] Of the 26 eligible RCTs (published 1990 to 2016), 14 (1,475 patients) studied symptom reduction and 12 (1,196 patients) examined medication use. Only the subgroup analysis evaluated the use of SLIT for the population of interest, thereby rendering the overall results of the meta-analysis beyond the scope of this evidence review. Nasal symptom and medication scores were assessed using mean differences and standardized mean differences (SMD). Although the

meta-analysis overall demonstrated a significant reduction in symptoms and medication use for pediatric patients, the subgroup analysis found that that SLIT was effective for grass pollen-induced allergic rhinitis only. Overall, oral pruritus was the most common adverse effect in children who were receiving SLIT. Although the study addressed heterogeneity and potential of bias overall, these were not specifically reported for the studies included in the subgroup analysis.

Feng (2017b) also conducted a meta-analysis of 25 placebo-controlled RCTs (published from 1990 to 2016) on the efficacy of SLIT for dust mite-induced allergic rhinitis.[5] Most trials were double-blinded and deemed to be of high quality. All studies compared the intervention to placebo for a period that ranged from 6 to 36 months. In total, there were 3,674 randomized patients, and the largest trial included 992 participants. There were 12 pediatric trials, with ages ranging from 3 to 18 years. The RCTs included participants from Europe (13 studies, n=2,845 patients), Eastern Asia (five studies, n=590 patients), Western Asia (five studies, n=149 patients), Oceania (one study, n=30 patients), and Africa (one study, n=60 patients). Of 23 studies that reported discontinuation rates, 539 (14.6%) participants dropped out due to the following: adverse effects (3.0%), loss to follow-up (2.0%), noncompliance (1.9%), and poor efficacy (0.9%). Primary end points were symptom scores and medication use. Symptom scores varied by type, including rhinitis symptoms only, rhinoconjunctivitis symptoms, or rhinoconjunctivitis and asthma symptoms. Overall, there was a significant reduction in symptoms in the SLIT group relative to placebo (SMD 1.23, 95% CI 1.74 to 0.73, p<0.001). A subgroup analysis of trials using different modalities (drops n=19, tablets n=6) found a significant reduction in symptom scores with the use of tablets (SMD -1.81, 95% CI -2.94 to -0.68, p=0.002) relative to drops (SMD -1.06, 95% CI -1.67 to -0.44, p<0.001).

Di Bona (2015) published a meta-analysis of studies on FDA-approved grass pollen SLIT tablets.[6] Thirteen studies met reviewers' inclusion criteria, which were placebo-controlled RCTs on grass pollen SLIT in patients with a clinical history of seasonal allergic rhinoconjunctivitis and reported a symptom score or medication score. A small but significant reduction in symptoms (SMD -0.28, 95% CI -0.37 to -0.19, p<0.001) and in decreasing the use of symptomatic medication (antihistamines and corticosteroids) (SMD -0.24, 95% CI -0.31 to -0.17, p<0.001) were reported. Adverse events were reported in 1,384 of 2,259 patients (61.3%) receiving SLIT and in 477 of 2,279 patients (20.9%) receiving placebo. Seven patients in the SLIT group reported treatment-related adverse events requiring epinephrine. Findings were similar in an analysis excluding the five studies at high or moderate risk of bias. However, the reviewers concluded that "due to the low magnitude of the benefit, the convenience and easy administration do not seem to be sufficient reasons for the choice of SLIT."

Liao (2015) published a systematic review and meta-analysis of studies on dust mite SLIT for treating children with asthma.[7] The authors identified 11 RCTs and prospective controlled studies evaluating SLIT in patients less than18 years old with asthma and reporting clinical outcomes. Nine studies compared SLIT to placebo and two trials compared SLIT to pharmacotherapy, and these studies were not analyzed separately, by comparator group. Findings of the meta-analysis were mixed. A pooled analysis of eight studies reporting an asthma symptom score found that the score decreased significantly more in the SLIT groups than the control groups (standardized score difference [SSD] -1.20, 95% CI -2.07 to -0.33, p=0.007). A pooled analysis of three studies reporting medication scores did not find significant differences between groups in change in medication usage (SSD -0.52, 95% CI -1.753 to 0.713, p=0.408). Group also did not differ significantly in an analysis of change in specific *Dermatophagoides pteronyssinus* IgE levels before and after treatment (SSD 0.430, 95% CI -

0.045 to 0.905, p=0.076). Limitations of this review include: high levels of heterogeneity among included studies for all analyses, most of the studies had small study populations, and a publication bias for specific *D pteronyssinus* IgE levels.

Maloney (2015) performed a meta-analysis on the safety data from eight placebo-controlled trials on Grastek.[8] There were 4,195 patients in the pooled study population, 3,314 adults and 881 children and adolescents. A total of 2,115 were treated with grass SLIT tablets. Eight (0.4%) SLIT-treated patients experienced a mild or moderate systemic allergic reaction, no serious systemic allergic reactions were reported. Sixteen (1.6%) SLIT-treated patients reported treatment-related severe local allergic swellings. These comprised mouth edema, oropharyngeal swelling, palatal edema, pharyngeal edema, tongue edema, swollen tongue, throat tightness, and laryngeal edema. However, since the numbers of treatment related adverse events reported were rare, statistical analyses were not able to be performed. Large-scale postmarketing surveillance will be necessary to provide more conclusive evidence of the safety of grass SLIT-tablet in patients with asthma.

A Cochrane review conducted by Romantsik (2014)[9] assessed the successful desensitization and development of tolerance to egg protein and the safety of egg oral (OIT) and SLIT in children and adults with a mediated egg allergy as compared to a placebo treatment. Eighty-three studies were included in the review, including four RCTs. Thirty-nine percent of participants were able to tolerate a full serving of egg compared to 11.9% of the controls. Sixty nine percent of participants presented with mild-to-severe adverse effects during OIT, with five requiring epinephrine. The authors noted several limitations to the studies included in the systematic review, which include: small sample sizes, a non-standardization of protocols between studies, and a low quality of evidence.

Devillier (2014) published a systematic review with meta-analyses of SLIT and pharmacotherapy for seasonal allergic rhinitis. Only well-powered (≥100 patients in the smaller treatment arm), placebo-controlled, randomized trials were included (28 pharmacotherapy trials and 10 SLIT trials, total number of patients 21,223). Studies evaluated children and adults. Because of methodologic heterogeneity across trials (e.g., in symptom scales used), results from individual trials were standardized relative to placebo effects to permit meta-analysis. Pooled percentage improvements in symptom scores were 30% for five-grass pollen SLIT, 24% for nasal corticosteroids, 19% for timothy pollen SLIT, 17% for combination azelastinefluticasone,15% for H1 antihistamines, and 7% for montelukast.[10]

Lin (2013a) conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on allergen-specific therapy for treating allergic rhinoconjunctivitis and/or asthma.[11] The authors identified 60 studies comparing SLIT to placebo or another intervention. (Studies that used SCIT as the comparator were evaluated separately; see section below on SLIT compared with SCIT). Over two-thirds of the studies (71%) compared SLIT to placebo, 14% compared SLIT to pharmacotherapy or rescue medication, and 15% compared SLIT to another intervention. Most studies (66%) evaluated seasonal allergens, 31% evaluated perennial allergens, and the remainder addressed both types of allergens. About half of studies used only one allergen, and the other half used multiple allergens. Only 22% of the studies were rated as having a low risk of bias. Most (68%) were considered to have a moderate risk of bias and 14% to have a high risk of bias. The authors did not pool study findings because of heterogeneity among studies, including types and sources of allergen extracts, treatment duration, and outcome scoring systems used. The review concluded that there was high-grade evidence that SLIT improved asthma symptoms

compared with placebo or another intervention (13 RCTs) and moderate-grade evidence that SLIT improved rhinitis/rhinoconjunctivitis symptoms compared with placebo or another intervention (35 RCTs). There was moderate-grade evidence that SLIT improved other outcomes in this population, for example, decreased medication use and increased quality of life.

Lin (2013b) also published the findings of the systematic review in a peer-reviewed journal.[12] The review focused on studies comparing SLIT to placebo, pharmacotherapy, or another SLIT regimen and did not address SCIT. Like the AHRQ review, study findings were not pooled. The authors noted that high-quality studies are needed to determine optimal dosing strategies.

A 2013 systematic review and meta-analyses by the U.K. National Health Service evaluated the effectiveness of SCIT and SLIT for seasonal allergic rhinitis.[13] Literature was searched to April 2011, and 28 placebo-controlled RCTs were included (17 SCIT and 11 SLIT). Statistically significant moderate effect sizes for improvements in symptom scores, medication scores, combined symptom and medication scores, and quality of life measures favored active treatment. However, due to substantial heterogeneity in outcome measures, standardized mean differences were used for meta-analyses, rendering conclusions about clinical significance of the results uncertain. Meta-analysis of nine SLIT studies in children yielded statistically significant results for symptom scores but not for medication scores.

A 2013 systematic review with meta-analyses evaluated SLIT for allergic asthma,[14] including 16 double-blind, placebo-controlled RCTs. Statistically significant reductions in symptom scores (SMD 0.74, p=0.006) and medication scores (SMD 0.78, p=0.02) favored SLIT. The relative risk of adverse events was 2.23 (p=0.01). Authors concluded that SLIT reduced symptoms and medication use for allergic asthma, but subgroup analysis failed to identify a disproportionate benefit of SLIT in any specific group of asthmatics. The strength of the review was limited by the quality of the RCTs included in the analysis and the heterogeneity of study allergens, doses, treatment duration, and the reporting of outcomes and safety data.

An additional 2013 systematic review of SCIT and SLIT in pediatric asthma and rhinoconjunctivitis was conducted.[15] Literature was searched through May 2012, and 34 RCTs were included. For SLIT, strength of evidence was high that SLIT improves asthma symptoms and moderate that SLIT improves rhinitis and conjunctivitis symptoms and decreases medication usage compared with placebo. Local adverse reactions were frequent. Several limitations were noted by authors. The authors reported considerable heterogeneity in the study allergens, dosages, dose units, duration of treatment, and in reporting and scoring of outcomes and safety data, thus heterogeneity precluded quantitative pooling of the data. The interpretation of RCTs was limited by the quality of the studies that were included in the review. Further, several studies had moderate or high risk of bias because they did not specify whether allocation schemes were concealed or if the intervention was concealed from the participants and outcome assessors, or did not clarify the role of industry support or sponsors. The majority of SCIT studies were limited to a single allergen and cannot be generalized to the use of multiple allergen regimens. SLIT studies included in the review used multiple allergens, and therefore the results are not generalizable to single-allergen regimens. Safety data were variably reported and only reflect observed reports from RCTs.

Several additional systematic reviews and meta-analyses were conducted prior to 2013 and similarly concluded that methodological flaws preclude definitive conclusions regarding the efficacy of SLIT with placebo.[16-22]

Randomized Controlled Trials

Nolte (2020) published the results of a multisite industry-sponsored RCT evaluating the efficacy and safety of ragweed SLIT in 1025 children aged 5 to 17 with ragweed pollen-induced allergic rhinitis with or without conjunctivitis (AR/C).[23] Participants were randomized 1:1 to daily ragweed SLIT or placebo for up to 28 weeks. The primary end point was the average total combined score (TCS; sum of rhinoconjunctivitis daily symptom score [DSS] and daily medication score [DMS]) during peak ragweed pollen season (RPS). Relative TCS (95% CI) improvements with ragweed SLIT versus placebo were -38.3% (-46.0% to -29.7%; p<0.001) during peak RPS and -32.4% (-40.7% to -23.3%; p<0.001) during the entire RPS. DSS and DMS during peak RPS improved with SLIT versus placebo by -35.4% (-43.2% to -26.1%; p<0.001) and -47.7% (-59.8% to -32.5%; p<0.001), respectively. No events of anaphylaxis, airway compromise, or severe treatment-related systemic allergic reactions were reported.

The results of a phase III RCT of SLIT in 1476 participants (312 adolescents aged ≥12 and 1164 adults) with moderate to severe house dust mite (HDM)-induced allergic rhinitis was published by Demoly in 2020.[24] Participants received approximately 12 months of treatment with placebo or the sublingual tablet. Significant improvements in combined scores and prespecified secondary end points were observed in the treatment over the placebo group during the four weeks following the treatment period. Treatment-related adverse events (mainly mild or moderate local reactions) were reported for 51.0% of the patients in the treatment group and 14.9% in the placebo group. The study was sponsored and funded by industry (Stallergenes Greer) and mitigation of the risk of conflict of interest was not addressed in the publication. Long term outcomes were not reported.

A multi-center, placebo-controlled trial by Liu (2019) evaluated SLIT for atopic dermatitis in mite-sensitized patients in China.[25] The 239 patients in the study were randomized to either placebo or one of three treatment groups: high-dose, medium-dose, or low-dose. SLIT efficacy was assessed with the SCORAD index, the dermatology quality of life index (DLQI), skin lesion area, and use of other medications for symptoms. By the end of the 36-week trial, 48 patients (20%) had dropped out. All groups had improvements in SCORAD index scores during the study. Statistical significance for the trend between groups was not reported, except for the score at the fourth visit, which was reported to be significantly decreased in the high- and medium-dose groups compared with placebo. P-values were not reported for many of the outcomes.

Tanaka (2019) published a double-blinded RCT assessing the efficacy and safety of SLIT in Japanese patients with allergic asthma.[26] For this trial 826 patients were randomized to receive a low- or high-dose of house dust mite SLIT, or placebo, and treatment lasted up to 19 months. The primary outcome of the study was the time from randomization to the first asthma exacerbation with reduction in inhaled corticosteroid dose. No statistically significant difference was seen between groups for the primary or other efficacy endpoints.

A double-blinded, placebo-controlled randomized trial by Scadding (2017) enrolled 106 adults with moderate-to-severe seasonal allergic rhinitis at a single center to determine whether two years of SLIT improved symptoms at the three-year follow-up, one year after discontinuation of treatment.[27] Patients were randomized to SLIT with placebo, SCIT with placebo, or double-placebo, and 92 patients completed the study overall. Nasal response challenge at three-year follow-up, measured by total nasal symptom scores (TNSS) within 10 hours of the challenge,

was the primary end point. Secondary end points included change in peak nasal inspiratory flow (PNIF) after challenge, seasonal weekly visual analog scale (VAS), seasonal weekly rhinitis quality of life (MiniRQLQ), end of season global rhinitis severity score, seasonal medication use, and early and late skin responses to intradermal allergen. Although the intention-to-treat (ITT) population included all randomized patients, only those with an evaluable endpoint were included in the analysis (modified ITT). The reported between-group difference was -0.18 (95% CI -1.25 to 0.90, p=0.75), adjusted for baseline, demonstrating no statistically significant improvement in the primary outcome compared with placebo. There was no benefit from SLIT or SCIT compared to placebo for PNIF, VAS, MiniRQLQ, or the global rhinitis severity score.

The largest pediatric trial to date by Valovirta (2017) assessed the impact of SLIT on grass pollen allergic rhinoconjunctivitis (ARC) symptoms, medication use, immunologic markers, and notably, the onset of asthma.[28] The five-year double-blind, placebo-controlled trial with two years of follow-up was conducted at 101 sites in 11 European countries and enrolled 812 children ages 5 to 12 with a history of allergic rhinoconjunctivitis (mean, 3.4 years). Of those randomized, 608 (75%) completed the trial. There was no difference in time to onset of asthma (primary end point) between the SLIT group (n=398) and placebo (n=414). However, there was a 71% relative risk reduction in asthma symptoms and asthma medication use for the entire trial period and for the two-year follow-up period (OR=0.28, p<0.001). Assessment of secondary end points are as follows. During the three years of treatment and two follow-up years, the SLIT group had a 22% to 30% reduction in ARC symptoms when compared with placebo (p<0.002). VAS scores revealed a 22% reduction in symptoms for the SLIT group compared with placebo (p=0.005). The SLIT group also had a 27% reduction in medication use relative to placebo (p<0.001). The most frequently reported adverse effects were nasopharyngitis, allergic conjunctivitis, oral pruritus, cough, and gastroenteritis. Compared to placebo, a higher proportion of children in the intervention group dropped out due to adverse effects. However, the study identified no new safety concerns.

A small randomized trial by Kinaciyan (2017) compared two SLIT formulations, “rMal d 1” and “rBet v 1”, with placebo in a total of 60 patients (20 per group).[29] Participants received daily SLIT or placebo for 16 weeks. Sublingual allergen challenges, skin prick tests with recombinant allergens, and allergen-specific IgE and IgG4 measurements where performed at baseline and after treatment. The rMal d 1 group had reduced rMal d 1 oral and cutaneous reactions compared to placebo (p=0.007 and p=0.022, respectively). The authors reported no systemic, only local adverse events.

Fleischer (2013) reported on the first phase of an RCT in which forty subjects were randomized to daily peanut or placebo SLIT, and given the option to cross-over at 44 weeks.[30] At week 44, 14 (70%) in the SLIT group were considered responders compared with three (15%) in the placebo group. Seventeen patients in the placebo group crossed over to receive high-dose SLIT and seven (44%) were considered responders after 44 weeks. The initial phase reported that subjects with a peanut allergy were more responsive to SLIT when compared to placebo. Due to the high drop-out rate (>50%), it was not possible to conclude whether longer treatment, beyond 68 weeks. In addition, there was a lack of a placebo group available for the final analyses, due to cross-over. Burks (2015) reported the second phase (open-label) outcomes from this multicenter trial, including 40 patients (20 per group) with a peanut allergy.[31] All subjects in the treated group were to receive up to a total of 164 weeks (three years) of active peanut SLIT. At three years, SLIT was discontinued for eight weeks, followed by another 10-g oral food challenge and an open feeding of peanut butter to assess

sustained unresponsiveness. Approximately 98% of the 18,165 doses were tolerated without adverse reactions beyond the oropharynx, with no severe symptoms or uses of epinephrine.

Narisety (2014) published a randomized double-blind placebo-controlled study of children which examined SLIT versus oral immunotherapy (OIT) for the treatment of a peanut allergy.[32] There were four arms to the study including 21 subjects which were randomized to receive either SLIT or placebo, or OIT or placebo. The results indicated the OIT group increased their challenge threshold to the allergen after 12 months when compared to the SLIT group. Although adverse reactions were noted to be generally mild with both SLIT and OIT, they were more commonly found in OIT subjects which included moderate reaction and doses requiring medication. This study was limited by the 24% drop out rate of an already small sample, and the four additional subjects who were unresponsive to either SLIT or OIT at completion of the study.

Creticos (2014) determined the efficacy and tolerability of standardized glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allergic rhinoconjunctivitis (ARC).[33] The phase 3, randomized, placebo-controlled included subjects (age range, 18-55 years) with or without asthma and were selected based on ARC symptom severity and erythema skin prick reaction to short ragweed. Subjects self-administered the maximum tolerated dose of RW-SAIL (n=218) or placebo (n=211) daily beginning approximately 8 to 16 weeks before and through the end of the ragweed pollen season. The primary end point was subject-assessed total combined daily rhinoconjunctivitis symptom and medication scores (TCS). During the entire season, there was a 43% decrease in TCS in subjects treated with RW-SAIL compared with placebo. Similar decreases were observed in TCS between the two groups during peak season (42%) and in daily symptom scores during the entire (42%) and peak (41%) seasons. The occurrence of adverse events was similar between the treatment groups; most were mild in severity. Treatment-related oromucosal local application site reactions occurred early and were transient and self-limited. No anaphylaxis occurred. This study was limited by the implementation of self-reported questionnaires for the reporting of primary outcomes that may contribute to recall bias.

SUBLINGUAL IMMUNOTHERAPY COMPARED WITH SUBCUTANEOUS INJECTION OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Systematic Reviews

Tie (2022) published an updated systematic review of seven RCTs in patients with allergic rhinitis by failed to find a difference between SLIT or SCIT.[34] The authors also conducted an indirect comparison of trials evaluating SCIT versus placebo (n=13) or SLIT versus placebo (n=33), and found no significant differences between SCIT and SLIT.

Kim (2021) published a network meta-analysis comparing SCIT with SLIT in patients with a house dust mite allergy.[35] A total of 26 RCTs were included and ten studies with SLIT tablets found significant improvement in symptom scores with SLIT compared with placebo ($p<0.01$) while nine studies found improvement in medication score ($p<0.01$). The SCIT group had greater efficacy in the symptom score compared with SLIT tablets in network meta-analysis. Medication scores were also improved with SCIT. The analysis is limited by high levels of heterogeneity in the SLIT studies.

In a systematic review by Kim (2013), SCIT and SLIT in pediatric asthma and rhinoconjunctivitis were compared head to head.[15] The literature was searched through May 2012, and three RCTs of dust mite immunotherapy were included. Low strength of evidence supported SCIT over SLIT for improving asthma and rhinitis symptoms and for decreasing medication usage. Several limitations were cited by authors, including heterogeneity of studies, as described above.

Studies of SCIT and SLIT for allergic rhinitis published up to January 2012 were included in a recent systematic review by Calderon (2012).[36] The lack of consistency in the selection of primary outcome parameters represents a major problem when comparing the same therapeutic intervention. A main point of concern was the absence of validation data for those primary and secondary outcomes selected. In conclusion, the qualitative analysis of well powered studies confirms an urgent call from academics, regulatory agencies and the pharmaceutical industry for validated primary outcome parameters and standardized definitions.

Chelladurai (2013) subsequently reviewed head-to-head RCTs comparing SCIT and SLIT in adults and children.[37] Literature was searched through November 2012, and eight RCTs were included. Moderate-grade evidence supported the greater effectiveness of SCIT compared with SLIT for improving nasal and eye symptoms. Low-grade evidence supported greater effectiveness of SCIT compared with SLIT for improving asthma symptoms and combined rhinitis symptom and medication scores. Authors noted additional studies are required to strengthen this evidence base for clinical decision making. The strength of the review was limited by the quality of the RCTs included in the analysis and the heterogeneity of the reported study outcomes.

A systematic review with meta-analysis by Di Bona (2012)[16] included 22 placebo-controlled studies on SLIT and 14 on SCIT. The investigators identified a total of 960 adverse events (AEs) in patients who received SCIT (0.86 AE per patient) and 4,046 AEs in patients who received SLIT (2.13 AEs per patient). Most of the AEs were modest in severity. The authors did not report the total number of serious AEs. However, they stated that there were 12 episodes of anaphylaxis requiring epinephrine treatment in patients treated with SCIT and only one in patients treated with SLIT. There were also two reported episodes of anaphylaxis in patients treated with placebo in the SCIT studies.

Sieber (2011) published a systematic with meta-analysis of individual patient data from four observational studies on treatment of allergic rhinitis.[38] A total of 665 patients were treated with SLIT and 182 with SCIT. The median rhinitis symptom score decreased from 3.00 to 2.00 (range 1.00 to 4.00) in both treatment groups ($p<0.001$ for changes within-group). The median conjunctivitis symptom score decreased from 2.00 to 1.00 (range 0.00 to 3.00) in each group ($p<0.001$ for changes within-group). In addition, the median asthma symptom score decreased from 3.00 to 2.00 (range 1.00 to 4.00) in each group ($p<0.001$ for changes within-group). There were no significant differences in symptom scores when the SLIT group was compared to the SCIT group.

Randomized Controlled Trials

Few published randomized trials have compared SLIT and SCIT head-to-head.

Narisety (2015) published a double-blind RCT comparing oral immunotherapy and SCIT in 21 children with peanut allergies.[32] Five (24%) children dropped out. Adverse events, generally

mild, were significantly more common in the oral immunotherapy group. Among the remaining 16 patients, those in the oral immunotherapy group had a significantly greater challenge threshold at 12 months than the SCIT group (p=0.01). However, only four patients (19%) had sustained unresponsiveness. Significant within-group changes in skin test results and peanut-specific IgE and IgG4 levels were found, with overall greater effects in the oral immunotherapy group. Although oral immunotherapy was more effective, this came at the price of increased adverse reactions. Long-term, open-label follow-up of an RCT included in the da Silva systematic review assessing the effect of SLIT on peanut allergy reported a similar proportion of patients with sustained unresponsiveness (10/48; 21%).[39]

Three RCTs comparing the efficacy of dust-mite specific SLIT and SCIT have been published by investigators in Turkey.[40-42] None of these studies found statistically significant differences between treatment with SLIT and SCIT in overall reduction of symptoms or medication use. For example, in one of the trials, Eifan (2010) published findings from a randomized, open-label trial of 48 children with asthma or rhinitis who had been sensitized to house dust mites.[40] Participants were randomized to receive treatment with SLIT (n=16), ASIT (n=16), or usual pharmacotherapy alone (n=16). As with the earlier trials, there was no significant difference in efficacy between the sublingual and subcutaneous immunotherapy groups. Compared to pharmacotherapy alone, both immunotherapy groups demonstrated significant reduction in rhinitis and asthma symptom scores and medication use scores.

A small 2013 RCT compared house dust mite (HDM)-SCIT and HDM-SLIT in children with rhinitis and asthma who were monosensitized to HDM.[43] Thirty children were randomized to receive one or two years of SCIT or SLIT. Symptom scores were improved after one year of SCIT and after two years of SLIT. The significance of this finding is uncertain given the small sample size.

These trials offer some evidence for similar efficacy of SLIT compared to SCIT. However, they are small and likely underpowered to detect meaningful differences between treatments and are therefore not sufficient evidence to establish equivalency of SLIT with SCIT.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY – HEAD AND NECK SURGERY FOUNDATION

In 2015, the American Academy of Otolaryngology – Head and Neck Surgery Foundation published evidence-based consensus guidelines on allergic rhinitis. Based on RCTs and systematic reviews, guideline developers recommended SLIT or SCIT “for patients with allergic rhinitis who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.” The purpose of the statement was “to increase the awareness of immunotherapy as a treatment for allergic rhinitis, promote its appropriate use, and reduce unnecessary or harmful variation in care.”[44]

In addition, the guidelines state that using any aqueous SLIT is considered an off-label use, and that there are no US practice guideline that address the dosing of aqueous SLIT, which is not standardized.

AMERICAN COLLEGE OF ALLERGY, ASTHMA AND IMMUNOLOGY (AAAAI) AND THE JOINT COUNCIL OF ALLERGY, ASTHMA AND IMMUNOLOGY

In 2017, a joint task force of AAAAI, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology issued updated practice parameters for allergen immunotherapy[45]. The document stated that RCTs of SLIT in individuals with allergic rhinitis and asthma have demonstrated significant improvement in symptoms. The authors noted that there were no FDA-approved extract formulations for a non-injection route of immunotherapy.

WORLD ALLERGY ORGANIZATION

In 2013, WAO updated its position paper on SLIT[46] stating the following:

- Grass-pollen SLIT is effective in seasonal allergic rhinitis in children 5 years of age or older and probably effective in children as young as 4 years of age.
- Grass or house dust mite SLIT may be used for allergic rhinitis in children with asthma, although more large randomized trials are needed.
- Although SLIT for latex allergy, atopic dermatitis, food allergy, and Hymenoptera venom is under investigation, more evidence is needed to support the use of SLIT for these indications.
- Patients eligible for SLIT should have a history of symptoms related to allergen exposure and a documented positive allergen-specific IgE test.
- SLIT may be considered as initial treatment, particularly for patients whose allergy is uncontrolled with optimal pharmacotherapy (ie, those who have severe chronic upper airway disease); patients intolerant of injections or adverse effects of pharmacotherapy; or patients who do not want to be on constant or long-term pharmacotherapy.
- Failure of pharmacotherapy is not an essential prerequisite for SLIT.

SUMMARY

There is not enough research to show that sublingual liquid allergen extracts or non- U.S. Food and Drug Administration (FDA) approved sublingual tablets can improve overall health outcomes for people with allergies. Therefore, sublingual liquid allergen extracts or non-U.S. FDA approved SLIT allergen extract tablets are considered investigational as a technique of allergy immunotherapy.

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CODES

NOTE: There are no specific CPT or HCPCS codes for sublingually administered immunotherapy.

Codes	Number	Description
CPT	95199	Unlisted allergy/clinical immunologic service or procedure
HCPCS	None	

Date of Origin: *June 2005*