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Review

# Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012

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ABSTRACT

**Objective:** To perform a structured analysis of the latest scientific evidence obtained for the clinical efficacy of sublingual immunotherapy (SLIT) in children.

**Data Sources:** PubMed, Embase, reference lists from reviews, and personal databases were reviewed for original articles on clinical trials with SLIT in patients younger than 18 years published from January 1, 2009, through December 31, 2012, using broad search and medical subject heading terms.

**Study Selections:** Clinical trials, irrespective of their design, of SLIT in the treatment of respiratory and food allergy in patients 18 years or younger were selected. Clinical outcomes (symptom scores, medication use, provocation tests, pulmonary function tests, skin prick tests, and adverse events) and immunologic changes were tabulated. Quality of each trial and total quality of compounded evidence was analyzed with the Grading of Recommendations Assessment, Development and Evaluation system.

**Results:** Of 56 articles, 29 met the inclusion criteria. New evidence is robust for the precoseasonal tablet and drop grass pollen SLIT efficacy in allergic rhinitis and scarce for seasonal asthma. Some evidence for *Alternaria* SLIT efficacy is appearing. For house dust mite (HDM) SLIT in asthma, there is high-quality evidence for medication reduction while maintaining symptom control; evidence for HDM SLIT efficacy in allergic rhinitis is of moderate-low quality. There is moderate evidence for efficacy of dual grass pollen–HDM SLIT after 12 months of treatment and 1 year after discontinuation. Specific provocation test results (nasal, skin) improve with grass pollen and HDM SLIT but nonspecific bronchial provocation testing does not. Food oral immunotherapy is more promising than food SLIT. Possible new surrogate markers have been reported. No anaphylaxis was found among 2469 treated children.

**Conclusion:** Evidence for efficacy of SLIT in children with respiratory or food allergy is growing.



## Introduction

Allergen immunotherapy (AIT) is still the only treatment directed at correcting the deviated immune response, which has been found to be the cause of allergy. Moreover, because of its mechanisms of action, AIT is the only therapy that modifies the natural history of the disease. Several studies have reported on the preventive effect of immunotherapy in children with allergic rhinitis (AR) because it appears to reduce the development of new allergic sensitizations and/or new-onset asthma.[1,2] Today, clear humoral, cellular, and tissue level changes have been documented with AIT,[3–5] and its clinical efficacy leads to economic savings after 6 months of treatment.[6] In 2011, the centenary of subcutaneous immunotherapy (SCIT) was celebrated[7,8]; concurrently, it was 25 years ago that the first double-blind, placebo-controlled (DBPC) trial with SLIT was published.[9] This alternative, less traumatic, and safer route of administration seems especially suitable for children, and after the first big conclusive trials in adults,[10,11] many pediatric SLIT trials were conducted, and pediatric SLIT was appraised in several meta-analyses and reviews.[12–16] However, published meta-analyses generally only include a selection of trials based on their design.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[17] has been introduced as a method to support health policy decision making built on clinical recommendations as a result of analysis of different aspects, one of which is the quality of evidence coming from research. As such, the GRADE system developed tools to define the scientific quality of

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clinical trials, taking into account internal and external validation, including the risk of bias. In GRADE all clinical trials, irrespective of their design, are considered and their quality of evidence is established according to defined parameters (eTable 1).[18] Since 2004, the GRADE system has been adapted by many specialties as a useful tool for the formulation of guidelines.

In this review, we analyze all clinical trials published on pediatric SLIT since the World Allergy Organization position paper was published in 2009,[19] assess their scientific quality with GRADE, and integrate this evidence on clinical aspects of SLIT in children.

## Methods

### *Search Strategy*

Literature searches were conducted in PubMed and Embase (D.L.L., H.V.B., M.B.) to identify original articles on clinical trials with SLIT in children published between January 1, 2009, and December 31, 2012, and written in English or Spanish. Search terms and limits were all combinations of *desensitization*, *immunologic* (medical subject heading [MeSH] terms) OR *allergen immunotherapy* AND *administration, sublingual* (MeSH terms) AND 2009/01/01-2012/11/15 AND (Randomized) (Controlled) (Clinical Trial) AND (English OR Spanish) AND the MeSH terms *humans*, *infant* OR *child,* OR *adolescent*. We identified additional articles by manually searching references from the obtained articles, review articles, and the authors' own literature database. Study design was not a restriction; only full-text articles were included.

### *Study Selection*

In the first phase of screening, 3 reviewers (D.L.L., M.B. and H.V.B.) independently examined the titles and abstracts of the search results. The second phase of screening was based on full-text articles, which were obtained and assessed for inclusion with the predetermined selection criteria: AIT administered sublingually to children (0-18 years old) with confirmed allergic disease and language of publication. Only those trials were incorporated that reported clinical data and/or safety data and/or immunologic findings as outcome measures. Trials recruiting both adults and children were only included if the pediatric data were presented separately or if more than 50% of the active group were younger than 18 years.

### *Data Collection and Analysis*

The data from the full-text articles were extracted independently by at least 2 reviewers per article (D.L.L., C.B.C., H.V.B., M.B.). Disagreement, if any, was resolved by discussion. Data on design, outcomes, and immunologic changes were abstracted in extraction tables (Table 1 and Table 2) and into the GRADE quality assessment sheet (eTable 1), as described in previous publications.[18,51,52] Two of the authors independently performed GRADE quality assessment of the studies (D.L.L., E.C.). Information on safety was captured in a descriptive way. We tried to follow the World Allergy Organization grading system of systemic adverse events[53] in classifying these, whenever possible.

## Results

### *Retrieved Articles*

Fifty-six articles were identified as possible candidates for review (eTable 2). Of these, 22 were excluded because of age limits; 4 studies that included adults were kept in the analysis, because most participants were children.[38,39,47,49] Five further articles were excluded because of administration route,[54] publication type,[55] and outcome measures outside the scope of this review.[56–58] In all, 29 articles on SLIT in children will be analyzed in this review article. Two manuscripts were on the same trial[24,29]; thus, 28 clinical trials are reviewed.

Twenty-five articles reported clinical data (Table 1), pulmonary function test (PFT) results, specific and nonspecific bronchial challenge test results, and/or skin prick test (SPT) results (Table 2). Three trials studied exclusively safety data,[48–50] and 1 trial studied only immunologic outcomes[21] because the clinical results of this latter trial had been published previously.[22] Sixteen other articles reported some provocation testing or immunologic outcomes (Table 2).

### *Design and Quality of the Studies*

Thirteen trials had a DBPC design. One trial was double-blind, double-dummy with 2 active and 1 placebo arms. Six were randomized controlled trials (RCTs) and 3 were randomized trials with both groups receiving active treatment and no control group. One was an open controlled trial. The rest had an observational design.

The possible quality of the trials was analyzed with the GRADE system (eTable 1). Nine articles (8 studies) were assigned the maximum GRADE score of 4 for the whole trial or part of it, and 9 had a score of moderate quality (grade score of G3), leaving the rest with low or very low quality.

### *Allergen Extracts*

The allergen extracts were preparations from European allergen manufacturers in 25 of the 28 studies analyzed (10 from ALK-Abelló, 8 from Stallergènes, 2 from Lofarma, and 2 from Allergopharma). In 2 DBPC trials[26,44] and in 1 RCT[45] an aqueous extract was used from a US manufacturer (Greer Laboratories, Lenoir, North Carolina); 2 of these studies were with food allergens.

Fourteen trials administered pollen SLIT (11 grass, 3 tree) and 1 house dust mite (HDM) SLIT, including 1 trial with dual grass pollen–HDM immunotherapy.[26] *Alternaria*, peanut, milk, and mixed allergens were administered in one trial each.

SLIT allergen extracts are preparations in liquid form in 24 trials; in all but one[43] a glycerinated natural allergen was given. Four studies used SLIT grass tablets, one of them being an allergoid.[32] No adjuvant extracts were used in the reviewed trials.

### *Clinical Outcomes*

In most trials AR or rhinoconjunctivitis was the leading allergic disease, with some of the included patients also having mild asthma. In 5 trials the principal disease was allergic asthma, caused by HDM (n = 3), grass (n = 1), or tree pollen (n = 1), with this latter being a safety study.[50] Table 1 depicts details of all clinical trials performed from January 1, 2009, through December 31, 2012. In the right column differences found between active and placebo (control) groups are stated, with the corresponding statistical significance as reported in the articles. In some studies only intragroup differences were reported, comparing data before and after SLIT. The study order is according to the allergen administered, the allergic disease primarily treated (rhinitis or asthma), and the study quality. Findings of the studies are then discussed, adding quality of evidence to them (eg, G2, meaning GRADE score 2). Publications with only safety data are presented at the bottom of Table 1, and outcomes of provocation testing, SPT results, and immunologic responses can be found in Table 2. From 2009-2012 there were no studies published on preventive or pharmacoeconomic effects of SLIT in children.

### *Symptom and Medication Scores: Seasonal Allergens*

Four high-quality trials (G4) show a reduction in symptoms and medication score with grass pollen SLIT. Three of these 4 trials were

**Table 1**
Clinical efficacy of SLIT in children: update (2009-2012)

| Source | Q score | Age range, y | Active/ placebo (control), No. | Dropout, No. | Allergen, drops or tablet | Duration | Dose, μg, dosing frequency | Dose vs SCIT | Disease | Manufacturer | Statistically significant differences | No statistically significant differences |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pollen** | | | | | | | | | | | | |
| Blaiss et al,[20] 2011 | 4 | 5-17 | 175/169 | 33/29 | Grass, tablet | 6 m | 15 μg of Phl p 5 daily | NS | RC (A) | ALK | SLIT vs placebo: Daily symptom (25%), daily medication (81%), and total scores (26%) and QoL improved 18% ($P < .04$). | SLIT-placebo: Asthma symptom score |
| Nieminen et al,[21] 2010 (subgroup of study by Valovirta et al,[22] 2006) | 4 | 5-15 | 10 Low, 10 high, 10 placebo | | Birch-alder-hazel mix, drops | 2 y | 24,000 SQ U/wk (3.6 μg group 1), 200,000 SQ U/wk (30 μg of group 1) | 0.5 and 4.5 | RC (A) | ALK | Mechanistic study: see mechanistic table | |
| Stelmach et al,[23] 2012 | 4 | 6-18 | 20 Continuous, 20 precoseasonal, 20 placebo | 1/3/2 | Grass, drops | 2 y | 10 μg of group 5 daily continuously: for 2 y; precoseasonal: 2 for 6 mo | NS | RC (A) | Stallergènes | Both active groups vs placebo: significant improvement in medication and symptom scores. Precoseasonal group vs placebo: significant reduction in medication score | |
| | 3 | | | | | | | | | | | Medication score continuous group: Asthma symptoms |
| Wahn et al,[24] 2009 | 4 | 4-17 | 139/139 | 8/4 | 6-grass, tablet | 8 m | 25 μg of group 5 daily, tablets | 30 | R (A) | Stallergènes | SLIT vs placebo: improved total and individual rhinitis sympt ($P = .01$) and medication ($P = .0064$) scores. Fewer days with medication intake ($P = .015$) | |
| Bufe et al,[25] 2009 | 4 | 5-16 | 126/127 | 12/7 | Phleum pratense, tablet | 6 m | 15 μg of Phl p 5 daily | 30 | R (A) | ALK | Active vs placebo: Significant reduction in RC symptoms score (−24%), asthma score (−64%), randomized controlled medications (−34%), and well days (+28%). All $P < .03$. | |
| Swamy et al,[26] 2012 | 3 | 5-58 | 20/10 | 0/0 | Dual grass and HDM, drops | 12 m | 15 μg of Phl p 1 | 1-2.8 for each dose | RC | Greer | Active-placebo: Rhinocon junctivitis symptom score, medication score and combined score reduced at 12 and 24 m (12 m after treatment discontinuation) ($P < .001$) | |
| Wahn et al,[27] 2012 | 3 | 4-12 | 158/49 | 26/2 | 6-grass drops | 8mo | 40 μg of group 5 daily | NS | RC (A) | All manufacturers | SLIT vs placebo: Change in pre-post treatment higher for symptom-medication, symptom, and medication scores. SLIT higher rate of positive response (≥40% decrease of the AUC of the SMS). | SLIT vs placebo: Mean number of well days |
| Pajno et al,[28] 2011 | 3 | 8-16 | 40 Continuous, 40 coseasonal | 3/5 | Grass drops | CONT3yrs COS: 3x4m | 8 μg of group 5, 5 times per week | NS | RA | Stallergènes | Continuous vs coseasonal: first year: Symptom plus medication, symptom, chest symptom and medication scores improved more in continuous SLIT groups. | Third year: no difference in clinical outcomes between continuous vs coseasonal SLIT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Halken et al,[29] 2010 (additional data from the study by Wahn et al,[24] 2009) | 3 | 5-17 | 278 Total: 131 SLIT, 135 placebo | ? | Grass tablet | 6m | 25 μg of Phl p 5 daily (300 IR) | | RC | Stallergènes | Active-placebo: Total symptom score reduced at whole and peak pollen season. Nasal and ocular symptoms reduced. Less rescue medication during whole and peak pollen season. | |
| Panzner et al,[30] 2011 (open extension of previous DBPC 12-month trial by Panzner et al,[31] 2008) | 2.5 | Mean, 17.6 | 26 SLIT, 25 supralingual | 8 | 6-Grass, drops | 12 m (+24 m open) | 11.2 μg of group 5 3 times per week | Total: 20 times | R | Sevapharma | Pre-post treatment supralingual and SLIT: symptom, medication, and combined score reduced year by year. | SLIT vs supralingual: trend for more symptom and medication reduction in SLIT (NS) |
| Agostinis et al,[32] 2009 | | 4-16 | 20 SLIT, 20 control | 0/0 | Grass, tablet | Precoseasonal for 2 y | 1,000 AU drops 5 times week | NS | R (A) | Lofarma | SLIT vs control: VAS improved after first and second year (both $P < .05$). SLIT pre-post treatment: reduction in sympt ($P < .05$) | Control pre-post treatment: no reduction in symptoms |
| Ahmadiafshar et al,[33] 2012 | 0 | 5-18 | 12 SLIT, 12 placebo | 2/2 | Lolium, drops | 6 m | 900 IR 3 times per week | 100? | RC | Stallergènes | SLIT pre-post treatment: reduction in symptoms ($P < .05$) and medication score ($P < .05$) | SLIT vs placebo: not reported. |
| Stelmach et al,[34] 2009 | 2 | 6-17 | 20 SLIT, 15 placebo | 5/10 | Grass, drops | Precoseasonal for 2 y | 10 μg of group 5 grass drops daily | NS | A | Stallergènes | SLIT vs placebo: asthma symptoms ($P < .002$), nasal sympt ($P < .04$), nasal and asthma symptoms, asthma medication and nasal, asthma, and medication scores (both $P < .001$) | SLIT vs placebo: ocular symptoms, total asthma, nose, and eye symptoms |
| **HDM** | | | | | | | | | | | | |
| Yonekura et al,[35] 2010 | 3 | 7-15 | 20/11 | 1/2 | Mite, drops | 1 y | 0.5 μg of Der f 1 once a week | 20 | RC | TOR | Active-placebo: week 30: reduced symptom score. Initial (weeks 0-3) to end (weeks 37-40) active group: Decrease in symptoms and symptom-medication score | Active-placebo: combined symptom-medication score |
| De Bot et al,[36] 2012 | 2 | 6-18 | 126/125 | 15/17 | Mite, drops | 2 y | 2.03 μg of Der p 1 2 times per week; total cumulative dose (2 y): 435 μg | NS | RC | ART | | Total nasal symptom score, QoL, medication score, well days |
| Han et al,[37] 2012 | 1 | 6-18 and ≥18 | 54 Children/22 adults | 0/0[b] | HDM, drops | 1 y | Pangramin SLIT: 6 μg/mL of Der 1 and Der 2 | NS | R | ALK | Pre-post treatment pediatric group: improvement in total symptom score and in each rhinitis symptom ($P < .05$). Medication use reduced, but no statistical calculations made. | Pediatric vs adult patients: no difference in symptom (NS), med score trend more improvement in pediatric group ($P = .06$) |
| Lee et al,[38] 2011 | 1 | Mean, 14.7 (range, 4-53) | 70 Mono-sensitized, 64 poly-sensitized | NS | HDM, drops | 12 m (first 30 d = up-dose) | 5 drops of 1,000 STU/mL of Der p and Der f 3 times per week | NS | R | ALK | Mono- and polysensitized symptom and medication scores: all improved | No difference between mono- and polysensitized in any variable |
| Trebuchon et al,[39] 2012 | 1 | 5-18 (n = 735) (1289 patients total) | | | HDM, drops | ≥2 y | Variable, most 300 IR daily | NS | 70% R, 50% A | Stallergènes, some ALK | More descriptive study of how SLIT is given, dosing schedules, duration, etc. Treatment (very) effective, according to physician: 82%. Reduction in asthma medication: 26% stopped taking ICSs | |

(continued on next page)

**Table 1** (*continued*)

| Source | Q score | Age range, y | Active/ placebo (control), No. | Dropout, No. | Allergen, drops or tablet | Duration | Dose, μg, dosing frequency | Dose vs SCIT | Disease | Manufacturer | Statistically significant differences | No statistically significant differences |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Keles et al,[40] 2011 | 3/4 | 5-12 | 15/15/15/15 SCIT/ SLIT/build-up SCIT→ then SLIT/pharma-ceutical group | 4/2/1/3 | HDM SCIT: alum adsorbed, SLIT drops | 18 m | SCIT: 13 μg of Der p and Der f 1 time per mo; SLIT: 0.75 μg of Der p and Der f 1 3 times per week | 0.75 | A (and R) | ALK | Active vs pharmaceutical group: SCIT→SLIT: all clinical parameters improved at 12 mo, half of them already at 4 mo. SCIT: all but rhinitis score improved at 12 mo. SLIT: only asthma medication score at 12 mo improved. Within group: Asthma medication and asthma attacks: SCIT and SCIT→SLIT reduced at 4, 12, and 18 mo compared with baseline. SLIT: reduced at 12 mo. | SLIT vs pharmaceutical group: none improved = GRADE 3, underpowered. (except asthma medication score). Pharmaceutical group: not one clinical parameter improved. |
| Eifan et al,[41] 2010 | 4 | 5-10y | 16 SLIT, 16 SCIT, 16 PHARMA | 1/2 | HDM SCIT: alum adsorbed, SLIT drops | 12 m | Dosing calculations in article do not check (SLIT: 3.8 μg of Der p and Der f 1 3 times per week; SCIT: 22.2 μg of Der p and Der f once per month) | 2.2? | A (R) | ALK | SLIT and SCIT vs pharmaceutical group: total rhinitis symptom, asthma symptom, medication, and VAS scores | |
| | 3 | | | | | | | | | | | SLIT vs SCIT: no difference in total rhinitis symptom, asthma symptom, medication, or VAS score |
| Yukselen et al,[42] 2012 | 3.5 | Mean (SD), 10 (3) | 11/10/11 Double-blind, double-dummy: SLIT/ SCIT/placebo | 1/0/1 | Mite, drops | 1 y (+1 y observation) | Der p and Der f: SLIT: 1,000 TU/ mL: 28 drops 3 times per week; SCIT: 3,368 TU every 4 weeks | 4.2 | A and R | AllerPhar | SCIT vs SLIT: SCIT significantly more reduction in asthma symptoms. SCIT vs placebo: rhinitis symptoms, asthma symptoms, total symptoms, rhinitis medication, asthma medication scores improved. VAS score: significant reduction for both rhinitis and asthma. SLIT and SCIT vs baseline year: both improved in almost all clinical parameters | |
| | 2.5 | | | | | | | | | | | SLIT vs placebo: NS for all clinical parameters. NS for VAS rhinitis and asthma. SCIT vs SCIT: rhinitis symptoms, rhinitis medication, and asthma medication (NS) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marogna et al,[43] 2011 | 2 (3 for metacholine challenge of SLIT with passive smoke, versus SLIT without passive smoke) | 5-17 | 34 SLIT, 34 CET, 50%-50%: cigarette[a] | 3/4 | HDM, drops or tablets not specified | 36 m | 1,000 AU once per week | ? | A (intermittent) and R | Lofarma | SLIT vs CET in passive smokers: Methacholine challenge greatly improved (GRADE 3). SLIT nonsmoking: clinical scores, nasal corticosteroids, B2 use, and PFT results all improved. SLIT smoking: all show a trend to improvement, but only $MEF_{25}$ was statistically significantly increased. CET and smoking: all parameters get worse. | CET and nonsmokers: clinical and PFTs |
| **Other Allergens** | | | | | | | | | | | | |
| Kim et al,[44] 2011 | 4 | 1-11 | 11/7 | 0/0 | Peanut, drops | 12 m | 2000 $\mu$g daily (8 pumps) | | Peanut allergy | Greer | DBPC food challenge: ingestion of median cumulative dose of peanut protein SLIT 1,710 mg; placebo: 85 mg ($P < .011$). | |
| Keet et al,[45] 2012 | 4 | 6-11 | 10 SLIT, SLIT start then: 10 high-dose OIT, 10 low-dose OIT | 0/1/1 | Milk protein drops | 14 m | SLIT, 7 mg; high-dose OIT, 2,000 mg; low-dose OIT, 1,000 mg of milk protein daily | NS | Cow milk allergy | Greer | DBPC food challenge passed by more OIT patients vs SLIT alone (1 SLIT, 6 SLIT and low-dose OIT, 8 SLIT and high-dose OIT) | Regained hyperreactivity after 6-wk milk avoidance: 3 of 6 desensitized low-dose OIT patients, 3 of 8 high-dose OIT patients |
| Acquistapace et al,[46] 2009 | 0-1 | 6-18 | 90 SLIT/81 controls | NA | Several, drops | 2 y | Varied | NS | RC (A) | ALK (SLIT) | SLIT vs controls: reduced symptoms, medication score, and new sensitizations | SLIT vs control: asthma symptoms |
| Pozzan et al,[47] 2010 | 2 | 10-65 | 34 SLIT/18 controls | 1/0 | *Alternaria* drops | 36 m | 1 vial of SLIT once daily | NS | R (A) | ALK | Results of pediatric group not separated: Primary outcome: active vs control: symptom score reduced by VAS ($P = .0002$); ICS dose reduced ($P < .01$). Active pre-post: medication score significantly reduced in SLIT but not control group. | Active vs control: No medication score reduced |
| **Trials With Only Safety Data** | | | | | | | | | | | | |
| Seidenberg 2009[48] SAFETY | 1 | 5-17 | 193 SLIT | 10 (+50 <4-m treatment) | Grass and/or tree, drops | 4 m | Started with ultrarush up-dosing: 30-90-150-300 IR each 30 min ($\mu$g?) | Final dose approximately 30 times the SCIT dose | RC (A) | Stallergènes | During up-dosing: 60 patients (31%) reported 117 predominantly mild and local AEs, which resolved within 150 min. During maintenance: 562 AEs; most frequent local AEs were oral pruritus, burning sensation, lip or tongue swelling, and GI symptoms; the most frequent systemic AEs were RC and A. One clinically significant asthma event in an 11-year-old asthmatic boys: SLIT was resumed after 4 days | |
| Roger et al,[49] 2011 (total population, 218, 4-64 years old; safety trial) | 2 | 4-15 | 122 | None | HDM, drops | Up-dose | Every 30 min: 30-60-120-240 IR | | R and/or A | Stallergènes | 8 systemic reactions (3 moderate), all continued SLIT. Higher frequency of AEs in asthmatic patients. No difference in severity of AEs in patients younger than 15 y. | Slight increased frequency in AEs in patients younger than under 15 y (59.3% of AE were in pediatric patients, whereas only 53.7% of all patients were pediatric; NS) |
| Mösges et al,[50] 2010 (safety trial) | 4<br>2 | 6-14 | 27/27 | 0/0 | Tree pollen, drops | Up-dosing | 30-90-150-300 IR each 30 min ($\mu$g?) | | A | Stallergènes | | During up-dosing: active-placebo: serious AEs: no difference.<br>During up-dosing: Active-placebo: PFT change: no difference |

Abbreviations: A, asthma; AE, adverse event; AUC, area under the curve; B2, $\beta_2$-agonist; CET, cetirizine; DBPC, double-blind, placebo-controlled; GI, gastrointestinal; HDM, house dust mite; ICS, inhaled corticosteroid; IR, index of reactivity; $MEF_{25}$, midexpiratory flow at 25% pulmonary capacity; NS, not stated or not applicable; OIT, oral immunotherapy; PFT, pulmonary function testing; Q, quality assessment according to Grading of Recommendations Assessment, Development and Evaluation; QoL, quality of life; R, rhinitis; RC, rhinoconjunctivitis; SAE, serious adverse event; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMS, symptom medication score; SQ, subcutaneous; VAS, visual analog scale.

[a]Parental passive smoke (at least 20 cigarettes per day).

[b]No dropouts mentioned and report of symptom scores on all included patients suggesting no one dropped out.

**Table 2**
Immunologic and provocation testing

| Source | Lung function | Inflammatory markers | Immunologic markers |
|---|---|---|---|
| **Pollen** | | | |
| Blaiss et al, 2011[20] | | | SLIT vs placebo: Phl p 5 specific IgG4 and IgE-blocking factor levels were higher at peak and end of the grass pollen season. |
| Bufe et al, 2009[25] | | | SLIT vs placebo: increase in IgG4 ($P < .001$) and in IgE blocking factor ($P < .001$). Seasonal IgE peak blunted in active (NS). |
| Nieminen et al, 2010[21] | | | Patients with elevated symptom and medication score: increase in allergen-induced PBMC mRNA IL-17 expression; a positive and dose-dependent correlation SMS and IL-17 production. High-dose group vs placebo at 2 y: increase in FOXP3 mRNA expression. FOXP3 mRNA changes correlate with IL-10 and TGF-$\beta$ mRNA. |
| Pajno et al, 2011[28] | | | First year: continuous SLIT: increase in grass IgE, second to third years: no change grass IgE Continuous: First to third years: increase in grass IgG4, first to second years: larger increase in grass IgG4 vs coseason, third year: no difference |
| Panzner et al, 2011[30] | | SLIT and supralingual before vs after treatment: both reduction in SPT ($P < .0001$). | SLIT vs supralingual: larger increase in specific IgG4 |
| Stelmach et al, 2009[34] | SLIT vs placebo: $FEV_1$ improved ($P = .005$), $FEF_{25\%-75\%}$ only trend | SLIT vs placebo: methacholine $PC_{20}$ trend for improvement ($P = .058$), nasal provocation test: no difference | SLIT vs placebo: no difference in specific IgE or total IgG4 |
| Stelmach et al, 2012[23] | No changes in morning PEF, $FEV_1$, and methacholine $PD_{20}$ within or among any of the 3 groups | Both active groups vs placebo: significant decrease in FeNO level comparable in both active groups | Peripheral blood: induction CD4CD25Foxp3-positive cells no difference between groups |
| Swamy et al, 2012[26] | | SLIT vs placebo: nasal provocation test (nasal disk challenge): $P < .0001$ for GP at 18 mo (6 mo after treatment) (HDM not performed). SLIT vs placebo at 12 mo: reduced SPT GP and HDM ($P < .05$) | SLIT vs placebo: specific IgE reduction and IgG4 increase (both $P < .05$) at 12, 18, and 24 m, no change in control Oak immunoglobulins. SLIT GP and HDM, pre-post treatment at 24 mo: Basophil activation after GP and HDM stimulation reduced pre-post treatment ($P < .0001$). No difference with Oak or in placebo group. Epigenetic modification of induced Treg cells in dual SLIT patients: decreased DNA methylation[a] in CD45RO1 memory Treg cells after 12-month dual SLIT ($P < .05$). Increase in Foxp3 transcript levels of memory Treg cells (DNA methylation was augmented and Foxp3 transcript reduced in allergic patients without SLIT compared with healthy controls.) Tolerant vs nontolerant dual SLIT patients: Already at baseline tolerant patients' memory Treg cells had increased expression of Foxp3 ($P < .05$), programmed cell death protein 1, and IL-10 (NS). Six months after treatment increased number memory or induced Treg cells in tolerant patients ($P < .05$). |
| Wahn et al, 2009[24] | | | SLIT vs placebo: greater increase in specific IgG4. No change in IgE. |
| Wahn et al, 2012[27] | | | SLIT vs placebo, pre-post treatment: specific IgE: no difference; SLIT increase in IgG1 and IgG4 |
| **HDM** | | | |
| Eifan et al, 2010[41] | SCIT and SLIT each vs pharmaceutical group: improved nasal provocation test ($P = .005$ and .01, respectively). No difference in lung function nor methacholine $PD_{20}$ | SCIT and SLIT each vs pharmaceutical group: reduced skin prick test reactivity at 12 mo. SLIT: $P = .006$ for Der p and $P = .01$ for Der f. | SCIT and SLIT vs pharmaceutical group: reduction serum specific IgE. SLIT vs pharmaceutical group: IL-10 increase. No difference in other $T_H1$-$T_H2$ cytokines in PBMC cultured with recombinant Der p 1 and Bet v 1. |
| Han et al, 2011[37] | | | Pre-post treatment pediatric group: Total IgE, no change. Eosinophils decreased (NS) and serum dosinophilic cathionic protein reduced ($P < .05$). Pediatric vs adult group: no differences in any of these 3 immunologic markers. |

(*continued on next page*)

**Table 2** (*continued*)

| Source | Lung function | Inflammatory markers | Immunologic markers |
|---|---|---|---|
| Keles et al, 2011[40] | $FEV_1$ increased in SCIT→SLIT vs pharmaceutical group; nonspecific bronchial provocation test: result turned negative in 4/7 SCIT→SLIT patients (NS). Specific nasal provocation test: improved in all active groups vs pharmaceutical group | SPT: SCIT reduced at 12 mo | IgE total and specific: no change at 12 mo. IgG4 and IgG4/IgE ratio: increase in SCIT and SCIT→SLIT vs pharmaceutical group. No change in SLIT. Der p 1–stimulated PBMC supernatant: TGF-$\beta$ and IL-10: increase from 4 mo on in all 3 groups. IFN-$\gamma$: increase at 4 mo, back to baseline at 12 mo in all 3 groups. IL-17: NS reduction in all 3 active groups. |
| Marogna et al, 2011[43] | CET and passive smoke pre-post treatment: $FEV_1$, $MEF_{25}$ worse. SLIT and passive smoke: $MEF_{25}$ improved; SLIT and nonsmoke pre-post treatment: $FEV_1$ and $MEF_{25}$ improved | CET and passive smoke: methacholine $PD_{20}$ worse, eosinophils increased. SLIT and passive smoke: methacholine $PD_{20}$ improved. SLIT and no smoke: methacholine $PD_{20}$ improved and eosinophils reduced | |
| Yukselen et al, 2012[42] | $FEV_1$ improved in SCIT and SLIT vs baseline. HDM nasal challenge improved in SCIT and SLIT vs baseline. Bronchial challenge improved vs baseline in SCIT. | Titrated skin prick tests: reduced in SCIT and SLIT vs baseline. Nasal eosinophils increment after challenges: SCIT and SLIT significantly reduced vs placebo. SCIT vs baseline: reduction BAL eosinophils after bronchial HDM challenge | SCIT vs SLIT: greater increase in IgG4. SLIT and SCIT vs baseline: IgE HDM reduction, IL-10 increase. SCIT vs baseline: IgG4 increase. IFN-$\gamma$: no differences |
| **Food** | | | |
| Keet et al, 2012[45] | | All groups: reduced end point titration skin prick testing | All groups: increased IgG4 levels and decreased constitutive CD63 and CD203c expression. OIT groups only: decreased CM-specific IgE and reduced spontaneous basophil histamine release |
| Kim et al, 2011[44] | | SPT wheal reduced at 12 mo in active vs placebo group | Active vs placebo: Lower percentage of $CD63^+$ basophils after low-dose peanut stimulation ($P = .009$). Peanut specific IgE: increase at 4 mo and reduction at 12 mo. Peanut specific IgG4: increased at 12 mo. Active vs placebo: IL-5 decreased ($P = .015$), IL-13 decreased (NS), IL-10 and IFN-$\gamma$ no difference, % Treg cells increased (NS). |

Abbreviations: BAL, bronchoalveolar lavage; CET, cetirizine; CM, cow's milk; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75%; FeNO, fractional exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 second: GP, grass pollen; HDM, house dust mite; IFN-$\gamma$, interferon $\gamma$; IL, interleukin; $MEF_{25}$, midexpiratory flow at 25% pulmonary capacity; mRNA, messenger RNA; NS, not stated or not applicable; OIT, oral immunotherapy; PBMC, peripheral blood mononuclear cell; $PC_{20}$, provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20%; $PD_{20}$, provocation dose that caused a decrease in forced expiratory volume in 1 second of 20%; PEF, peak expiratory flow; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMS, symptom medication score; SPT, skin prick test; TGF-$\beta$, transforming growth factor $\beta$; Treg, T-regulatory.

[a]Decreased CpG methylation within the Foxp3 locus is related to more stable suppressive activity of Foxp 3 Treg cells.

with SLIT tablets given precoseasonally for 6 to 8 months. Similar efficacy was shown by the 4 moderate-quality trials with grass pollen SLIT. Interestingly, the findings of Stelmach et al[23](G4) suggest that SLIT drops during 2 years might have a better result when given precoseasonally instead of continuously. Meanwhile, a slightly lower dose of the same grass pollen SLIT administered only coseasonally for 4 months each year did not show clear efficacy during the first 2 seasons to reach levels of clinical improvement similar to the continuously administered product only until the third year of treatment.[28] (G3) Because this latter trial did not include a control group, conclusions should be drawn with caution. The same holds true for a trial in which clinical score improvement was documented when comparing pretreatment and posttreatment values for sublingual with supralingual immunotherapy because a control group was included in this study design only during the first year of the trial.[30] (G2-3) Blaiss et al[20] separately analyzed pediatric (5-11 years) and adolescent subgroups (12-17 years), showing differences in symptom plus medication score in favor of grass AIT in both (32% and 16%, respectively).

Most data from asthma outcomes with pollen SLIT came from studies where seasonal AR was the leading disease and thus are studies not adequately designed or powered to detect changes in asthma symptoms or medication. The only grass pollen SLIT study in pediatric asthma reports encouraging data: asthma clinical parameters improved after 2 years of precoseasonal treatment comparing the active with the placebo group, reaching statistical significance even though the study was underpowered[34] (G2).

Mold allergy was addressed in one RCT of *Alternaria* SLIT in respiratory allergy[47] (G2). After 3 years symptom scores and inhaled corticosteroid use reduced, although total medication scores did not show any difference between the active and control groups.

### *Symptom and Medication Scores: Perennial Allergens*

In the time span of our review there was one moderate-quality study investigating HDM SLIT in pediatric AR and 4 studies of (very) low quality (G1-G2). From these trials no clear conclusions can be drawn because in a placebo group was included in only 2 trials and only some trials showed improvement in nasal symptom and/or medication scores[35,37,38] (G1-3), whereas others did not[36] (G2). As such, the best quality evidence of HDM SLIT efficacy for AR symptoms comes from 4 pediatric asthma trials. The results are also not uniform in these trials because AR symptoms improved compared with a randomized control group in 2 studies,[41,43] (G2 and G4) but not in the other 2 studies[40,42] (G2.5-3).

However, none of these is a simple SLIT trial; each has its peculiarities worth commenting. Keles et al[40] divided 60 children randomly to receive HDM SCIT, SLIT, SCIT build-up followed by SLIT maintenance (SCIT→SLIT), or pharmacotherapy alone. In comparison to the pharmaceutical group in the SCIT→SLIT group rhinitis, asthma symptoms, asthma attacks, and medication all improved at 12 months, reaching statistical significance even though the groups were small. In the SCIT group no rhinitis symptom improvement was seen, and in the SLIT group only asthma medication scores

improved. Two pediatric SLIT-in-asthma trials compared SLIT with SCIT and an open control[41] (G3-G4) or placebo[42] (G2.5-G3.5). The former found that total rhinitis symptoms, asthma symptoms, and medication improved in both active groups compared with the pharmaceutical group, but in the latter no statistically significant benefit of SLIT over placebo was found. SLIT and SCIT were found to be equivalent for all parameters, with the exception of asthma symptom scores in the trial of Yukselen et al. However, neither of these 2 trials was adequately powered to show differences between both active groups, so no conclusion can be drawn in this respect. In the last pediatric SLIT in asthma trial, Marogna et al[43] randomized 68 children with AR and intermittent asthma and positive methacholine provocation test results to receive SLIT or cetirizine. Half of each group consisted of children with exposure to high levels of environmental tobacco smoke in their homes. After 3 years, in passive smokers the methacholine challenge greatly improved in the SLIT group vs the cetirizine group (G3). The other clinical outcomes improve in the passive smoking SLIT group, whereas in the cetirizine group all parameters deteriorate. In the non–passive smoking groups, SLIT improved clinical scores and medication use, whereas there was no change with cetirizine. Unfortunately, no clear between-group comparisons are reported in the published document.

The overall balance of the efficacy of SLIT with HDM as part of the integral treatment in pediatric asthma as studied in these trials is positive, but because the trials are small scientific quality is not optimal.

### *Symptom and Medication Scores: Dual SLIT With Combined Grass Pollen–HDM Extract*

One trial deserves special mentioning because this is the first trial on dual SLIT in children. Swamy et al[26] (G3) conducted a DBPC-RCT of dual SLIT administrating a grass pollen–HDM glycerinated solution during 12 months. The investigators were able to show a statistically significant improvement in the rhinoconjunctivitis symptom score, medication score, and combined score at 12 and 24 months (12 months after treatment discontinuation). Immunologic markers were also tested (Table 2).

### *Clinical Outcomes of SLIT With Food Allergens*

We found 2 trials on SLIT for food allergy in children, both (partly) conducted at Duke University Medical Center, Durham, North Carolina. Kim et al[44] reported beneficial effects after 12 months of daily SLIT with a glycerinated peanut extract (Greer Laboratories): DBPC food challenges showed an increase in the median cumulative dose of peanut in the active group vs the placebo group (1,710 vs 85 mg, $P < .01$). The second study design was more refined: 30 children with milk allergy were randomized to receive SLIT or SLIT build-up followed by oral immunotherapy (OIT) at low or higher dose. At the end of this 140month trial a DBPC food challenge proved OIT to be superior to SLIT alone. Even so, 3 of 8 patients in the high-dose OIT group who performed best regained hyperreactivity after only 6 weeks of milk avoidance, putting in doubt if true tolerance can be obtained with milk OIT.

### *PFT and Nasal and Bronchial Provocation Testing*

No provocation testing was performed in any of the tablet studies. The effect of grass pollen SLIT drops on nasal provocation testing was documented by 2 investigators,[26,34] with the higher-quality trial (G3) recording a reduction in specific nasal hyperreactivity. The effect of grass pollen SLIT on lung function parameters was investigated in 2 studies[23,34]: exhaled nitric oxide was reduced after grass pollen SLIT; however, in PFTs no clear signal could be detected and methacholine bronchial challenges showed no improvement.

HDM SLIT improved specific nasal hyperreactivity in all 3 high-quality trials that investigated this parameter. However, nonspecific methacholine provocation dose that caused a decrease in forced expiratory volume in 1 second of 20%augmented only in 1 of the 4 studies[43] that included this measurement and PFTs improved compared with pretreatment values but showed only a trend for superiority compared with placebo.

### *Skin Prick Testing*

SPT reactivity was investigated in pediatric SLIT trials with grass pollen[30] and HDM,[40,41] in the dual grass pollen–HDM trial,[46] and in both food SLIT trials. It improved in all but one HDM study.[40]

### *Efficacy Summary*

Table 3 summarizes the evidence concerning clinical efficacy in children with respiratory allergies of SLIT with grass pollen, *Alternaria,* and HDM. This summary table is based on all reviewed studies and their scientific quality (GRADE score).

### *Safety Data*

Although in almost all trials safety outcomes were mentioned, 3 trials investigated exclusively safety issues (2 large observational studies and 1 with a DBPC design)[50] (G4) (eTable 3). All 3 studies used an ultrarush, 90-min build-up phase of high-dose SLIT. The latter explored the safety of tree pollen SLIT in asthmatic children. During up-dosing no differences in serious adverse events (G4) or in PFT results (G2) were found between the active and placebo groups. Roger at al[49] (G2) investigated HDM SLIT drops in patients with rhinitis and/or asthma. Eight mild-moderate systemic adverse events were reported, with a higher frequency among asthmatic patients, but none discontinued SLIT. The treatment was equally well tolerated by children younger than 15 years in comparison with adult patients. Meanwhile, Seidenberg et al[48] showed coseasonal rush build-up is relatively well tolerated by rhinitis patients.

Safety issues reported in the rest of the trials were frequent and mild, mostly consisting of local reactions in the oral cavity: oral pruritus, throat irritation, and stomatitis (32%-85% in the active group vs 2%-20% in the placebo group). There were also mild systemic symptoms as eye, nose, or ear pruritus. No life-threatening systemic adverse events were reported in any of the trials, with a total 2469 children receiving active treatment. However, in the milk SLIT and OIT trial, 1 SLIT and 4 OIT children received adrenaline. Treatment-related discontinuation ranged from 0% to 7.4%.[20] In the real-life retrospective study by Trebuchon et al,[39] this number was 8%. In the 2 trials with SLIT and SCIT, treatment-related discontinuations were only reported in the SCIT groups. In some trials, patients with abdominal symptoms were referred with higher frequency in the active group. Epinephrine was used only in the trial conducted by Blaiss et al.[20] During this US DBPC trial with grass pollen SLIT tablets, epinephrine was administered to 3 children (2 in the active group and 1 in the placebo group), with only one administration due to a reaction to the tablet: this patient experienced lip angioedema, slight dysphagia, and intermittent cough with no other symptoms immediately after the first dose; epinephrine administration resolved this moderate local reaction (as judged by the investigator) and the patient discontinued participation in the trial.

### *Immunologic Findings*

Several studies have documented an increase in specific IgG4 and IgE-blocking factor; some also documented an increase in serum interleukin (IL) 10 levels. Specific IgE levels were generally reduced, but in some trials they showed an initial surge. In peripheral blood mononuclear cells Nieminen et al documented

**Table 3**
Summary of the evidence

| Statistically significant difference for active vs placebo (control) | Studies without effect | Evidence[a,b] |
|---|---|---|
| **Grass and/or Birch** | | |
| AR symptoms | None | |
| Blaiss et al, 2012 (G4) | | |
| Wahn et al, 2009 (G4) | | |
| Bufe et al, 2009 (G4) | | |
| Halken et al, 2010 (G3) | | |
| Total Tablets: | | Yes: ●●●● |
| Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation) | | |
| Wahn et al, 2012 (G3) | | |
| Stelmach et al, 2012 (G4) (precoseasonal and continuous SLIT) | | |
| Pajno et al, 2011 (G3) (first year) | | |
| Panzner et al, 2011 (G2.5) (pre-post treatment) | | |
| Stelmach et al, 2009 (G2) | | |
| Total Drops: | | Yes: ●●●●<br>Yes: 12 mo after discontinuation: ●●●○ |
| Medications | Stelmach et al, 2012 (G3) (continuous SLIT) | |
| Blaiss et al, 2012 (G4) | | |
| Wahn et al, 2009 (G4) | | |
| Bufe et al, 2009 (G4) | | |
| Total Tablets: | | Yes: ●●●● |
| Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation) | | |
| Halken et al, 2010 (G3) | | |
| Wahn et al, 2012 (G3) | | |
| Stelmach et al, 2012 (G4) (precoseasonal SLIT) | | |
| Pajno et al, 2011 (G3) (first year) | | |
| Panzner et al, 2011 (G2.5) (pre-post treatment) | | |
| Stelmach et al, 2009 (G2) | | |
| Total Drops: | | Yes: ●●●○<br>Yes: 12 mo after discontinuation: ●●●○ |
| Symptoms and medications | None | |
| Blaiss et al, 2012 (G4) | | |
| Total Tablets: | | Yes: ●●●● |
| Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation) | | |
| Wahn et al, 2012 (G3) | | |
| Panzner et al, 2011 (G2.5) (pre-post treatment) | | |
| Stelmach et al, 2012 (G4) (precoseasonal and continuous) | | |
| Pajno et al, 2011 (G3) (first year) | | |
| Total Drops: | | Yes: ●●●●<br>Yes: 12 mo after discontinuation: ●●●○ |
| Nasal provocation | | |
| Swamy et al, 2012 (G3) (dual grass and HDM) | Stelmach et al, 2009 (G2) | Yes: 6 mo after SLIT: ●○○○ |
| Conjunctival provocation | None | No data |
| Asthma symptoms | Blaiss et al, 2012 (for asthma G3), and Stelmach et al, 2012 (G3) | |
| Bufe et al, 2009 (G4) | | |
| Total Tablets: | | Yes: ●○○○ |
| Pajno et al, 2011 (G3) (first year) | | |
| Stelmach et al, 2009 (G2) | | |
| Total Drops: | | Yes: ●○○○ |
| Asthma medication | None | |
| Stelmach et al, 2009 (G2) | | Yes: ●●○○ |
| Lung function tests and bronchial provocation | PFT: Stelmach et al, 2012 (G3), and methacholine: Stelmach et al, 2012 (G3) | |
| PFT: Stelmach et al, 2009 (G2) | | |
| Methacholine: Stelmach et al, 2009 (G2) (trend $P = .058$) | | |
| FeNO: Stelmach et al, 2012 (G3) | | |
| Total Drops: | | PFT: No: ●○○○<br>Methacholine: No: ●●○○<br>FeNO reduction: Yes: ●●●○ |

(*continued on next page*)

**Table 3** (*continued*)

| Statistically significant difference for active vs placebo (control) | Studies without effect | Evidence[a,b] |
|---|---|---|
| SPT reactivity<br>Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo)<br>Panzner et al, 2011 (G2.5) (pre-post treatment)<br>Total Drops: | None | Yes: ●●●○ |
| New sensitizations | None | No data |
| ***Alternaria*** | | |
| Improvement in AR symptoms<br>Pozzan et al, 2010 (G2) | None<br>None | Yes: ●●○○ |
| Improvement in medication score<br>Pozzan et al, 2010 (G2) (pre-post treatment) | Pozzan et al, 2010 (G2) | No: active-control: ●●○○<br>Yes: pre-post treatment: ●●○○ |
| Symptoms and medications | No data | No evidence |
| Asthma medication (ICSs)<br>Pozzan et al, 2010 (G2) | None | Yes: ●●○○ |
| **HDM** | | |
| AR symptoms<br>Eifan et al, 2012 (G4)<br>Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation)<br>Yonekura et al, 2010 (G3)<br>Total | Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5), de Bot et al, 2012 (G2) | Yes: ●●●○<br>Yes: 12 mo after: ●●●○ |
| Medications<br>Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation)<br>Symptoms and medications<br>Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo and 12 mo after treatment discontinuation) | Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5), de Bot et al, 2012 (G2)<br>Yonekura et al, 2010 (G3) | No: ●●○○<br>Yes: 12 mo after: ●●●○<br>Contradictory |
| Nasal provocation<br>Keles et al, 2011 (G4)<br>Eifan et al, 2012 (G4)<br>Yukselen et al, 2012 (G3.5)<br>Total | None | Yes: ●●●● |
| Asthma symptoms<br>Eifan et al, 2012 (G4) | Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5) | Yes: ●○○○ |
| Asthma medication<br>Keles et al, 2011 (G4) (SLIT group)<br>Eifan et al, 2012 (G4)<br>Total | Yukselen et al, 2012 (G2.5) | Yes: ●●●● |
| Pulmonary function tests<br>No positive studies | Eifan et al, 2012 (G4) (methacholine), Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5) | No: ●●●○ |
| Specific/specific bronchial challenge<br>Marogna et al, 2011 (G3) (passive smokers) | Eifan et al, 2012 (G4) (methacholines), Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5) | Methacholine: No: ●●●○ |
| SPT reactivity<br>Eifan et al, 2012 (G4) (12 mo)<br>Swamy et al, 2012 (G3) (dual grass and HDM at 12 mo)<br>Total | Keles et al, 2011 (G3) (SLIT group) | Yes: ●●●● |
| New sensitizations | Not studied | No evidence |
| Prevention asthma | Not studied | No evidence |

Abbreviations: AR, allergic rhinitis; FeNO, fractional exhaled nitric oxide; HDM, house dust mite; PFT, pulmonary function test; SLIT, sublingual immunotherapy; SPT, skin prick test.

[a] ●●●●, high; ●●●○, moderate; ●●○○, low; ●○○○, very low.

[b] Yes/no: there is scientific evidence to support there was statistically significant improvement (yes) or not (no) of the item stated in the left column of each line, in patients undergoing SLIT compared with patients from the placebo (control) group. In some studies only intragroup statistically significant improvement (pre- vs posttreatment) was documented: this was not considered acceptable evidence and is not documented in this table.

a increase in Foxp3 messenger RNA (mRNA) expression, which correlated with an increase in IL-10 and tumor growth factor $\beta$ mRNA, and allergen-induced peripheral blood mononuclear cell IL-17 mRNA expression correlated with symptom medication scores. However, Stelmach et al found no difference between the active and placebo groups in the induction of CD4CD25Foxp3-positive cells. Both milk[45] and peanut[44] trials showed a reduction in the percentage of $CD63^+$ basophils after SLIT.

The dual SLIT trial by Swamy et al intensively studied immunologic changes. Basophil activation after specific stimulation was reduced after treatment (grass pollen and HDM) but remained unchanged after stimulation with a third allergen. Decreased CpG methylation within the Foxp3 locus is believed to be related to a more stable suppressive activity of Foxp3 T-regulatory (Treg) cells. Thus, these investigators detected epigenetic modification of induced Treg cells after 12 months of dual SLIT: DNA methylation in CD45RO1 memory Treg cells was decreased and Foxp3 transcript levels of memory Treg cells was augmented, with opposite findings in allergic patients not receiving SLIT compared with healthy controls. Finally, comparing those SLIT patients who 6 months after the trial had become tolerant vs nontolerant SLIT patients, the memory Treg cells of the tolerant patients had an increased expression of Foxp3 ($P < .05$) and programmed cell death protein 1 already at baseline. The investigators suggest that these Treg cell markers might be predictive of clinical tolerance.[26] In trials where both SLIT and SCIT were given, immunologic changes were usually more marked after SCIT.[40,42]

## Discussion

We analyze articles published on SLIT in the pediatric age group published between 2009 and 2012. Without restricting for study design we found a total of 29 articles that met the inclusion criteria, corresponding to 28 trials; a total of 2469 patients were treated in the SLIT group (2127 were analyzed on efficacy and 2225 on safety). After analyzing articles on their scientific quality with the GRADE system, we composed a summary table in which all evidence for the efficacy of SLIT in children is expressed per allergic disease and per allergen. Only a statistically significant difference between the active and placebo (control) groups was considered valuable evidence because such intragroup improvements are not included in this table.

Compared with a similar analysis of data on pediatric SLIT up until 2008,[59] the efficacy of grass pollen SLIT drops in reducing AR symptoms and medication is reconfirmed and new evidence for efficacy of grass pollen tablets is added. High-quality new evidence shows efficacy of dual grass-HDM SLIT. Also, a prolonged effect, reducing the combined rhinitis symptom medication score still 1 year after treatment discontinuation, was shown. Only one asthma trial was conducted with pollen SLIT in children in the time span of our review.[34] Thus, for seasonal asthma there is moderate evidence of a reduction in exhaled nitric oxide, but the quality of evidence for medication reduction stays low and the effect of grass pollen SLIT on asthma symptoms, PFT results, and nonspecific bronchial hyperreactivity is uncertain.

There is some new stimulating evidence for SLIT with *Alternaria* in children with respiratory allergy[47] (G2), but further trials are needed to improve the strength of the evidence and give recommendations.

For HDM SLIT in children there were 9 new trials. However, most of these trials were with small groups of patients, and half of them did not directly investigate the efficacy of SLIT against placebo (control). Even so, evidence of moderate-high quality could be added to its efficacy in the control of nasal symptom, the reduction in nasal specific hyperreactivity, and the reduction in asthma medication. No effect was documented in reducing rhinitis medication, asthma symptoms, PFTs, or nonspecific bronchial hyperreactivity. High-quality evidence shows SPT reactivity reduces with both grass pollen and HDM SLIT. We found no new data on the preventive effect of SLIT in children.

For peanut and milk allergy no SLIT trials existed 4 years ago. New evidence is added in this field, although OIT showed better results than SLIT in the milk allergy trial.[45]

By the end of 2011 a similar evidence analysis was published for SCIT in children.[51] With respect to pollen SCIT, evidence of a benefit in rhinitis symptoms and medication was scarce; only one high-quality trial showed combined symptom and medication score improvement.[60] For seasonal asthma there was very low-quality evidence of symptom reduction. However, the specific provocation tests (nasal, ocular, and bronchial) reported clear improvement (G4) with pollen SCIT, as opposed to the nonspecific testing performed with methacholine in the pollen SLIT trials, where no favorable effect could be documented. This probably points to the fact that when provocation testing is performed in a trial, it should be specific. Several positive trials with *Alternaria* SCIT (G1-G4)[61] result in better quality evidence for this treatment in rhinitis than for *Alternaria* SLIT, whereas both have low-quality evidence for efficacy in asthma. Compared with SLIT, the evidence for HDM SCIT efficacy in asthma is superior: high-quality evidence exists for a reduction in asthma symptoms, medication and combined scores, and improved specific bronchial challenge testing. Interestingly, almost all trials in pediatric HDM allergy were in asthma, so evidence of HDM immunotherapy efficacy in AR was better in the SLIT trial review presented in this article.

Three randomized trials compared SLIT with SCIT, all for HDM allergic asthma (and AR).[40–42] One had a double-blind, double-dummy design. However, all of them were underpowered, with only 10 to 16 patients in each group. Even so the tendency was clear: both treatments showed improvement of asthma (and rhinitis) symptoms and medication scores compared with the control groups, but changes only reached statistical significance with SCIT. An indirect meta-analysis—based comparison of SCIT and SLIT for seasonal AR, although not restricted to the pediatric population and with several other limitations, came to the same conclusion.[62] Keles et al[40] revealed that a combination of both routes could give specific benefits.

In our analysis we tried to differentiate between the effect of SLIT given in drops or as tablets. Tablet SLIT has only been studied thoroughly in seasonal AR: here the evidence is slightly better than for drops, as was also commented on in a recent review of US trials.[16]

In conclusion although publication bias can never be discarded completely, collectively the presented data show grass pollen SLIT is effective in seasonal allergic rhinitis in children from 5 years of age onward and might be effective in 4-year-old children. Grass or HDM SLIT can be used for allergic rhinitis in children with asthma, and HDM SLIT is probably effective in children with asthma and allergic rhinitis but should never be used as monotherapy in children with active asthmatic symptoms. Immune mechanisms are better understood. Currently, there is not enough evidence to recommend *Alternaria* SLIT in children. Initial results with milk and peanut SLIT show up-dosing should be slow (even so it is not without risks), but finally some patients develop tolerance. No new data on the preventive effect of SLIT in children have been published after initial positive trials of low-moderate quality.[59] Thus, at this moment the best evidence to recommend SLIT in children with allergic rhinitis for the prevention of asthma development is maintained at the low-moderate level. More large randomized trials are needed, especially with HDM SLIT and mold SLIT in children.

## Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2013.02.017

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**eTable 1**
Quality of evidence of pediatric SLIT studies published in 2009-2012, according to the GRADE Approach

| Source | Design (starting score) | Large effect | Confound annulated[a] | Dose-response gradient | Total positive | Limitations in design and execution | Inconsistency of results | Indirectness of evidence | Imprecision of results | Publication bias | Total negative | Quality of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Rhinitis Studies** | | | | | | | | | | | | |
| Blaiss et al, 2011[1]: AR (and mild persistent asthma), 5-17 y, precoseasonal for 1 season, SLIT 175, placebo 169, 15 μg of Phl p 5 daily | DBPC (4) | X | X | X | 0 | Good: ITT analysis) | X | X | X | X | 0 | 4, high |
| Nieminen et al, 2010[2]: mechanistic study, respiratory allergy, 5-15 y, SLIT low dose 10, high 10, placebo 10, low: 24,000 SQ U/wk, high: 200,000 SQ U/wk, 2 y | DBPC (4) | X | X | +1 | +1 | X | X | X | Small groups | X | −1 | 4, high |
| Wahn et al, 2009[3]: SAR (21% mild asthma), 131 SLIT, 135 placebo; 4-17 y, precoseason, 25 μg of group 5 grass tablet per day | DBPC (4) | X | X | X | 0 | X | X | X | X | X | 0 | 4, High |
| Bufe et al, 2009[4]: | DBPC (4), rhinitis | X | X | X | 0 | X | X | X | X | X | 0 | 4, High |
| SAR (42% mild asthma), 114 SLIT, 120 placebo; 5-16 y, precoseason, 15 μg of Phl p 5 tablet per day | DBPC (4), asthma | X | X | X | 0 | X | X | Only symptom + medication | Very small numbers (9 vs 3 days) | X | −2 | 2, Low |
| Swamy et al, 2012[5]: AR (mild/moderate persistent asthma), 6-57 y (55% of SLIT group are children), dual SLIT 20, placebo 10, 15 μg of Phl p 1 and 20 μg Der f 1+2, daily for 12 months. Posttreatment evaluations 12 and 6 and 12 and 12 mo. | DBPC (4) | X | Small groups and even so statistically significant difference | X | +1 | Randomization method not described, −1 | X | X | Small groups | X | −2 | 3, moderate |
| Halken et al, 2010[6,d]: moderate-severe AR (intermit asthma), SLIT 131, placebo 135, 5-17 y, 25 μg of group 5 daily, precoseason 6 mo | DBPC (4) | +1 | X | X | +1 | No description of dropouts | X | X | Large CI | X | −2 | 3, moderate |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wahn et al, 2012[7]: ARC (and GINA grade I-II asthma), 4-12 y, precoseasonal SLIT, placebo, 40 $\mu$g of group 5 daily in drops, 8 mo | DBPC (4) | X | X | X | **0** | No ITT mentioned, −1, 16.5% dropout in active group, <20% | X | X | Change in lung sympt not reported | X | −1 (for RC) | 3 (for RC) |
| Yonekura et al, 2010[8]: AR, 7-15 y, SLIT 21, placebo 10, 0.5 $\mu$g of Der f 1 once per week, 40 wk | DBPC (4) | X | X | X | 0 | Use of nonvalidated adapted symptom score | X | X | X | X | −1 | 3, moderate |
| Stelmach et al, 2012[9]: rhinitis (20 also asthma), 6-18 y, precoseasonal 20, continuous 20, placebo 20, for 2 y, 10 $\mu$g of group 5 grass drops daily | DBPC (4) | X | X | X | 0 | Preestablished adjusted to 1,000 pollen grains/$m^3$ of symptom and medication scores: no reduction | X | X | Small groups, underpowered | X | -1 | 3, moderate |
| Panzner et al, 2011[10] (24-mo open continuation of 12-mo DBPC[11]): AR, mean (SD) age 17.6 (10) y, No. of children unknown, 3-y study continuation after 1-y DBPC, SLIT 26, supralingual 25, 11.2 $\mu$g of group 5 (6-grass pollen extract) 3 times per week for 3 y | Randomized, no-controlled (4) | X | X | Year by year improvement in symptom and medication, +1 | +1 | No control group, small groups: only statistically significant difference pre-post treatment, not between both active groups; no description dropout per group | X | Post hoc fusion of groups to improve statistics but does not seem to affect outcomes; −0.5 | X | Incorrect conclusion: medication score in supralingual not improved | SLIT treatment 2.5; supralingual −3.5 | SLIT: 2.5 supralingual 1.5 |
| De Bot et al, 2012[12]: rhinitis (54% + mild asthma), 6-18 y; 125 SLIT, 126 placebo, 700BU HDM twice per week for 2 y | DBPC (4) | X | X | X | 0 | Patient selection incorrect: (1) no SPT, (2) no clinical history of symptom exacerbation on exposure, (3) recall bias[c] | X | X | SD high (1.8 for sympt) | X | −2 | 2, low |
| Pozzan et al, 2010[13]: AR (mild-moderate asthma), mean of 20 (9) y; *Alternaria alternaria* extract, for 3 y; 34 SLIT, 18 controls; ? $\mu$g of Alt a 1 dose daily | Randomized controlled (4) | +1, large effect sympt reduction | X | X | +1 | Once yearly evaluation of patients' VAS and medication score: −2 | X | No complete symptom evaluation | X | X | -3 | 2, low |
| Agostinis et al, 2009[14]: AR (60% mild asthma), 4-16 y, SLIT 20, control 20, precoseasonal for 2 y; 1000 AU drops 5 times week | Randomized controlled (4) | X | Small groups, even so statistically significant | X | +1 | No medication score | X | VAS well-being only once a year: −2 | X | X | −3 | 2, low |

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**eTable 1** (*continued*)

| Source | Design (starting score) | Large effect | Confound annulated[a] | Dose-response gradient | Total positive | Limitations in design and execution | Inconsistency of results | Indirectness of evidence | Imprecision of results | Publication bias | Total negative | Quality of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Han et al, 2012[15]: AR, 6-18 y (54 patients) and ≥18 y (22 patients), all HDM SLIT, Pangramin, 12 mo | Observational (2) | X | X | X | 0 | No control group; underpowered to show difference between groups | X | Symptom and medication scores only evaluated 2 times: before and after treatment | X | X | −2 | 1, very low |
| Trebuchon et al, 2012[16]: 735 patients 5-18 y (1289 patients total), 97% AR (54% + asthma), HDM SLIT, several doses, most Der p and Der f 300 IR daily | Retrospective observational (2) | X | X | X | 0 | Physician selected 10 patients: selection bias | X | X | X | X | −1 | 1, very low |
| Lee et al, 2011[17]: AR (and asthma), monosensitized (70 patients), polysensitized (64 patients), mean age (range) 14.3 (4-53) y, Der p to Der f 5 drops of 1,000 STU/mL every 3 wk for 1 year | Observational (2) | X | X | X | 0 | X | X | Nonvalidated outcome measure: Q filled in twice on sympt (pre-post treatment) and each 2 mo taking medication | X | X | −1 | 1, very low |
| Ahmadiafshar et al, 2012[18]: ARC, 5-18 y, SLIT 12, placebo 12, 900 IR Lolium drops, 3 times per wk for 6 mo | Randomized controlled (4) | X | X | X | 0 | Very small groups. No comparison of symptom-medication reduction SLIT vs placebo | Much more adverse effects in placebo group | Incomplete nasal sympt score (no congestion measured) | No SD or CI given for symptoms or medications | X | −4 | 0, very low |
| Acquistapace et al, 2009[19]: SAR/PAR, 90 SLIT, 81 control; 7-16 y, low-dose SLIT daily for 2 y various allergens | OCT (2), symptom reduction | Symptom reduction 50% | X | X | +1 | No blinding investigator, no blinding patient | X | No diary data, point evaluation | X | X | -2 | 1, Very low |
| | New asthma | X | X | X | 0 | | X | Asthma = reply yes to wheezing question | X | X | −2 | 0, very low |
| | New sensitizations | 6% vs 36% $P < .001$ | X | X | +1 | | X | SPT of study compared with historical data | X | X | −2 | 1, very low |
| **Asthma** | | | | | | | | | | | | |
| Yukselen et al, 2012[20] (see also above): asthma and rhinitis, mean 10 y, SCIT 10, SLIT 10, placebo 10; SLIT: 1,000 TU of HDM 28 drops every 3 wk for 1 y; SCIT: 3,365 TU each 4 wk, no μg dose stated (Allergopharma) | DBPC, double-dummy (4), SCIT vs SLIT | X | Small groups, even so statistically significant improved SCIT symptoms vs SLIT | X | +1 | No combined symptom-medication score, no μg dose stated; small groups: underpowered to compare SLIT vs SCIT | X | X | X | X | −1.5 | SLIT vs SCIT: 2.5 = low-mod (Sympt 3.5) |
| | SCIT vs placebo, SLIT vs placebo | X | Small groups, even so statistically significant improved | X | +1 | | X | X | X | X | −1.5 | SCIT and SLIT vs placebo: 3.5 = Mod-high. |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pajno et al, 2011[21]: seasonal asthma and AR to grass, 72 children, 8-16 y, 8 μg of group 5 grass 5 times week; for 3 y continuous vs coseasonal | Randomized, no controls (4) | X | X | X | 0 | No control group (IRB: not allowed) | X | X | X | X | −1 | 3, moderate |
| Keles et al, 2011[22]: asthma and AR, 5-12 y, (1) SCIT, (2) SLIT, (3) build-up SCIT then SLIT, (4) pharmacotherapy: 15-15-15-15 patients, respectively; SCIT: 13 μg of Der p and Der f once per mo; SLIT: 0.75 μg Der p and Der f 1 3 times per w for 18 mo | Randomized controlled, asthma (4) and rhinitis outcome (4) | X | X | X | 0 | Dropout just <15% (13.8) | X | X | X | X | 0 | 4 (very low dose SLIT) |
| Marogna et al, 2011[23]: AR and intermittent asthma (positive methacholine challenge at inclusion), 68 children, 5-17 y, HDM allergy 34: passive smokers, 34 not. Each group 17-17: SLIT HDM allergoid 1,000 AU once per week or cetirizine for 3 y | Randomized controlled (4) | Methacholine challenge SLIT-no vs SLIT-yes, passive smoke | X | X | 0 (+1 metacholin es challenge) | Patient selection based on RAST class II+. Poor statistical evaluation | X | X | Statistical calculations only vs baseline, not between groups | X | −2 | 2 (3 for methacholine challenge, SLIT-no versus SLIT-yes passive smoke) |
| Eifan et al, 2010[24]: asthma (+AR), 5-10 y, HDM drops (dose stated is confusing), for 12 mo | Randomized controlled (4) | X | SLIT and SCIT vs pharmaceutical group: small groups but even so statistically significant difference | X | +1 (compared against pharmaceutical group) | SCIT vs SLIT: underpowered to show statistically significant difference | X | X | X | X | −1 | SLIT vs SCIT: 3, SLIT and SCIT vs pharmaceutical group: 4 |
| Stelmach et al, 2009[25]: asthma mild-moderate persist, 6-17 y, SLIT 20, placebo 15, precoseasonal for 2 y, 10 μg of group 5 grass drops daily | DBPC (4) | X | X | X | 0 | 40% dropout in placebo group. Symptoms and medications adjusted for pollen count | X | X | No pollen count reported | X | −3 | 2, low |
| **Safety** | | | | | | | | | | | | |
| Roger et al, 2011[26]: AR, 4-64 y (122: 4-15 y), HDM drops safety of an ultrarush 90-min build-up 30-60-120-240 IR; 8 mild-moderate systemic AEs | Observational (2) | X | X | X | 0 | X | X | X | X | X | 0 | 2, low |

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**eTable 1** (*continued*)

| Source | Design (starting score) | Large effect | Confound annulated[a] | Dose-response gradient | Total positive | Limitations in design and execution | Inconsistency of results | Indirectness of evidence | Imprecision of results | Publication bias | Total negative | Quality of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mosges et al, 2010[27]: mild-moderate asthma, 6-14 y, 27 SLIT, 27 placebo; tree pollen SLIT ultrarush build-up (in 90 min to 30-90-150-300 IR); no serious adverse events, PFR increase more than in placebo | DBPC (4) | X | X | X | 0 | X | PFR is supposed to decrease when SLIT is started: it increased, probably learning effect | One of the primary outcome measures: PFR: reflected learning effect instead of lung function | X | X | −2 | 4 for SAE, 2 for PFR |
| Seidenberg et al, 2009[28]: rhinitis (58% mild-moderate asthma), high-dose daily coseasonal SLIT, build-up in 90 min, 4 mo; 5-17 y, varying allergens | Observational (2) | X | X | X | 0 | 28% did not finish study | X | X | X | X | −1 | 1, very low |
| **Other Indications** | | | | | | | | | | | | |
| Keet et al, 2012[29]: SLIT up-dosing, then 10 SLIT, 10 low-dose OIT, 10 high-dose OIT, 6-17 y, 7 mg of milk protein (SLIT), 1,000 mg (OIT-A), 2,000 (OIT-B) daily for 60 wk | Randomized, no controls (4) but DBPC food challenges | X | Small groups, even so stat sign difference | X | +1 | Small groups | X | X | X | X | −1 | 4, high |
| Kim et al, 2011[30]: 18 children, 1-11 y, 6 mo up-dosing, 6 mo maintenance, 2,000 μg of peanut drops daily, for 12 mo | DBPC (4) and DBPC food challenges | +1 | Small groups, even so stat sign difference | X | +2 | No DBPC food challenge at study start: −0.5, interim analysis: 11 in active, 7 placebo | X | X | X | X | −1 | 4+, high |

Abbreviations: AE, adverse event; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; CI, confidence interval; DBPC, double-blind, placebo-controlled; GINA, Global Initiative for Asthma; IR, index of reactivity; ITT, intent to treat; HDM, house dust mite; OCT, open controlled trial; OIT, oral immunotherapy; PAR, perennial allergic rhinitis; PFR, pulmonary flow reserve; RCT, randomized controlled trial; RR, relative risk; SAR, seasonal allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test.

[a]All plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.[b]Large effect RR $< 0.5$, very large effect RR $< 0.2$. RR has been calculated from the data given in the articles.

[c]Inclusion criterium: 3-month retrospective nose symptom score: recall bias.

[d]Same study as Wahn et al, 2009, already analyzed in the original World Allergy Organization SLIT paper.[31]

**eTable 2**
Included and excluded pediatric SLIT studies

| Reference | Included/excluded | Reason |
|---|---|---|
| Wahn U, Klimek L, Ploszczuk A, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol.* 2012;130:886-893. | Included | |
| Han DH, Choi YS, Lee JE, et al. Clinical efficacy of sublingual immunotherapy in pediatric patients with allergic rhinitis sensitized to house dust mites: comparison to adult patients. *Acta Otolaryngol.* 2012;132(suppl 1):S88-S93. | Included | |
| Ahmadiafshar A, Maarefvand M, Taymourzade B, Mazloomzadeh S, Torabi Z. Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study. *Iran J Allergy Asthma Immunol.* 2012;11:175-181. | Included | |
| Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol.* 2012;130:215-224. | Included | |
| Stelmach I, Kaluzińska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy*. 2012;67:312-320. | Included | |
| de Bot CM, Moed H, Berger MY, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol.* 2012;23:150-158. | Included | |
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(*continued on next page*)

**eTable 2** (*continued*)

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

**eTable 3**
Adverse events for SLIT, 2009-2012

| Source | No. receiving SLIT | Treatment discontinuation due to AE (active/placebo) | Life-threatening systemic AE | Treatment-related systemic AE | Most common local AE |
|---|---|---|---|---|---|
| Blaiss et al, 2011[a] | 175 | 13 (7.4%)/5 (3%) | None | No SAE, urticaria 3/175 (1.7%)/ 0% | Oral pruritus (39% vs 3.4%), throat irritation (37.1% vs 3%), stomatitis (15% vs 1.2%) |
| Stelmach et al, 2012[a] | 20 | 0/0/0 | None | No SAE, headache, stomachache | Sublingual pruritus (45% vs 15.3%) |
| Wahn et al, 2009[a] | 139 | 7 (5%)/2 (1.4%) | None | No SAE. 12.2% SAE in active | Oral pruritus (32.4% vs 1.4%), mouth edema (13% vs 0%), throat irritation (8% vs 5%) |
| Bufe et al, 2009[a] | 126 | 4 (3%)/2 (2%) | None | SAE: 2 SLIT, 2 placebo, cough | Oral pruritus (32% vs 2%) , throat irritation (10% vs 2%), swollen lip (7% vs 0%) |
| Swamy et al, 2012[a] | 20 | 0/0 | None | GI concerns 15%, urticarial 10% | Itchy mouth/throat (85% vs 20%), rhinitis/ sneezing (30% vs 20%) |
| Wahn et al, 2012[a] | 158 | 10 (6.3%)/0 | None | No SAE, abdominal concerns equal in active-placebo | Oral administration concerns (71% vs 12.2%) |
| Pajno et al, 2011[a] | 40/40 | 5 (6.3%) = coseasonal 4, continuous 1 | None | GI symptoms | mouth burning |
| Panzner et al, 2011[a] | 26 | ? | None | No SAE, 35% systemic adverse events: rhinitis, painful breathing, conjunctivitis (treatment related?) | Undesirable taste, difficult swallowing, local swelling, or burning |
| Agostinis et al, 2009 | 20 | 0 | None | No SAE | ? |
| Ahmadiafshar et al, 2012 | 12 | 0 | None | No SAE | Higher AE score in placebo group (no statistical analysis) |
| Stelmach et al, 2009[a] | 20 | 0/0/0 | None | No SAE, headache, stomachache | Sublingual pruritus (50% vs 14.3%). less second year (35% vs 20%) |
| Yonekura et al, 2010 | 20 | 0 | None | No SAE | Bitter taste. |
| De Bot et al, 2012 | 126 | 0 | None | No SAE, rhinitis, conjunctivitis, shortness of breath (similar in active-placebo) | Oral pharyngeal irritation/ swelling |
| Han et al, 2012 | 76 | No safety data | | | |
| Lee et al, 2011 | 134 | No safety data | | | |
| Trebuchon et al, 2012 | 735 | 8% | None | Systemic AE 4%. | Local, mild |
| Keles et al, 2011 | 15 | 0[b] | None | No SAE | None reported |
| Eifan et al, 2010 | 16 | 0[c] | None | No SAE | None reported |
| Yukselen et al, 2012 | 11 | 0 | None | No SAE | Local, mild |
| Marogna et al, 2011 | 34 | No safety data reported | | | |
| Kim et al, 2011[a] | 11 | | None | No SAE, SLIT: after 11 doses (0.26%) antihistamine was needed, after 1 dose (0.02%) $\beta_2$-agonist was needed | Oropharyngeal reactions (9.3% vs 1.5%) |
| Keet et al, 2012 | 10 | SLIT-SLIT: 0, SLIT-OIT low: 1, SLIT-OIT high: 1 | Epinephrine given: with SLIT: 1, with OIT: 4 | Systemic AE more frequent in OIT vs SLIT ($P = .01$-$P < .001$) and more need for $\beta$-agonist and antihistamine treatment | Local AE with SLIT and oral immunotherapy similar (29% vs 23%) |

Abbreviations: AE, adverse event; GI, gastrointestinal; OIT, oral immunotherapy; SAE, serious adverse event; SLIT, sublingual immunotherapy.
[a]Studies reporting clearly treatment-related and non–treatment-related events.
[b]Keles et al, 2011: 2 of 13 children in SCIT group discontinued because of AEs.
[c]Eifan et al: 2 SCIT patients discontinued because of SAEs.

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