ORIGINAL RESEARCH

Sublingual allergen immunotherapy for respiratory allergy: a systematic review

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Abstract

The objective of the systematic review is to provide complete and updated information on efficacy and safety of sublingual immunotherapy (SLIT) formulations for the treatment of allergic respiratory diseases (ARDs). The literature search was conducted on PubMed database, involving double-blind, randomized clinical trials published between January 1992 and 2018, written in English, and performed in humans. The number of articles finally selected for review was 112. Data from the majority of properly controlled clinical trials demonstrate that SLIT is effective not only with short-term use (first year) but also with long-term use (up to the third year of active therapy), for treating ARDs in children and adults. Both continuous and discontinuous schemes of administration showed significant reductions in symptom and medication scores. Moreover, a SLIT-induced disease-modifying effect has been documented mainly with grass pollen extracts, since improvement is maintained during at least 2 years of follow-up after a 3-year treatment period. Additionally, allergen immunotherapy should also be considered a preventive strategy, especially for decreasing bronchial asthma incidence in children and adolescents with allergic rhinitis treated with SLIT. This therapy is also safe, producing only a few mainly local and mild-to-moderate adverse events, and usually self-limited in time. The registration and authorization of allergen SLIT preparations (grasses and house-dust mite tablets) as drugs by regulatory agencies, such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), has represented a landmark in allergy immunotherapy research. Further long-term studies, specially designed with allergens other than grass pollen or house-dust mites, not only in allergic rhinoconjunctivitis but also on asthmatic subjects, as well as studies comparing different administration schedules and/or routes, are required in order to continue the progress in the modern development of this particularly promising therapy.

Keywords: allergen, allergic respiratory diseases, asthma, rhinoconjunctivitis, sublingual immunotherapy, systematic review.

Citation

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Introduction

The prevalence of allergic respiratory diseases (ARDs) has increased worldwide, becoming an important public health problem.1,2 ARDs are triggered by exposure to allergens and comprise allergic rhinitis (AR), with or without conjunctivitis, and bronchial asthma.3,4 AR affects approximately 1 in 5 individuals of the general population, whereas asthma affects between 1 and 18%.5,6 Asthma is triggered by allergic reactions to house-dust mites [HDMs] or pollens, for instance) in half of cases, affecting up to 40% of subjects with allergic rhinoconjunctivitis (ARC).7 Children with ARC have a three-fold increased risk of developing asthma.8 The ARDs have been associated with impaired quality of life and a high economic burden.9 Allergen-specific immunotherapy is the only disease-modifying therapy preventing the evolution of AR to asthma, and its efficacy has long been known since observations by Leonard Noon in 1911.10,11 Allergen immunotherapy for AR is currently considered when showing strongly suggestive symptoms of AR which interfere with daily activities or sleep (despite pharmacotherapy and/or avoidance strategies), and having evidence of IgE sensitization to ≥1 clinically relevant allergen.12 For preventing asthma and AR symptoms and to spare medication use on a long-term basis, the European Academy of Allergy and Clinical Immunology (EAACI) recommends a minimum of 3 years of treatment with allergen immunotherapy in children or adolescents with moderate-to-severe grass or birch pollen-triggered AR.13 SLIT efficacy has been evidenced from results of controlled clinical trials and meta-analyses.14 Data for determining which administration...
route (subcutaneous immunotherapy [SCIT] or sublingual immunotherapy [SLIT]) is most effective are currently insufficient. Indeed, EAACI recommends both SCIT and SLIT for seasonal and perennial ARC. A landmark in the development of SLIT occurred in 2014 with the registration and authorization of grass pollen extract tablets as drugs by the United States Food and Drug Administration (FDA). Since then, and thanks to a huge research effort reflected by a number of controlled clinical trials involving large cohorts of subjects, the FDA together with the European Medicine Agency (EMA) and Japan regulatory authorities have also approved HDM formulations as drugs for the SLIT treatment of ARDs. The objective of the present manuscript was to provide complete and updated information on the efficacy and safety of SLIT formulations for the treatment of ARDs.

**Methods**

This systematic review was performed by using PubMed database. Keywords were chosen following the PICO methodology: population (pediatric or adult patients experiencing AR, rhinoconjunctivitis [RC], and/or asthma, by pollen, mites, pets, and/or molds); intervention (SLIT); comparator (placebo); and outcome (efficacy and safety). We used the following keywords in the search: (‘rhinitis’ or ‘allergic’ or ‘asthma’) and (‘Sublingual immunotherapy’) and (‘placebo’) and (‘pollen’ or ‘fungi’ or ‘mold’ or ‘dust’ or ‘mite’ or ‘pet’). We searched for studies published between January 1992 and 2018, written in English, and conducted in humans. The search was performed on June 21, 2018. Study selection was independently performed by two investigators (JH and CB).

Duplicate articles were initially removed. Meta-analyses (n=7), systematic reviews (n=15), reviews (n=30), expert opinions (n=1), position papers (n=1), short communications (n=1), letters to editor (n=1), and protocols (n=1), together with articles written in a non-English language (n=1), were then excluded. This first selection was performed reading only the title and abstract of each study. Nonclinical studies, studies with limitations in their methodology, no SLIT, or those with no interest for both investigators were subsequently discarded. Methodological quality of studies was evaluated by using the Jadad scale. Differences between investigators were solved by consensus. Only double-blind, randomized studies were finally selected for review. Manuscripts not available online were requested from the authors. From each study, we extracted information regarding age, number of patients, diagnosis, allergen used, type of administration, study duration, and results from efficacy (symptom and medication scores, improvement in symptoms) and safety (severe or serious adverse events [SAEs], and development of anaphylactic reactions [Ax] related to SLIT treatment). The present study was approved by the Ethics Committee of La Princesa University Hospital, and its design was established in accordance with Equator network guidelines: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

**Results**

A total of 235 articles dealing with allergen SLIT therapy were initially identified. After the selection process, the number of articles finally selected for review was 112 (Figure 1). Briefly, most studies involved only adult or both pediatric and...
adult patients with RC with or without concomitant bronchial asthma (Table 1), although 15 were specifically performed in children and 2 in the elderly (Table 2). Most studies evaluated both efficacy, by symptom and medication scores, and safety; however, 12 of them were addressed to evaluate only SLIT safety profile (Table 3). Grass pollen was the most studied allergen for SLIT (including 5-grass pollen, MK-7243 grass pollen, 3-grass pollen, timothy grass pollen, and 6-grass pollen), followed by ragweed, birch, Japanese cedar, HDMs, Parthenium judaica, Juniperus ashei, Cupressus arizonica, and Alternaria spp. SLIT administration schedule was diverse, varying from pre-/coseasonal to coseasonal, pre-seasonal, continuous, or outside season.

Efficacy results

The list of references involving either adult or both pediatric and adult patients is shown in Table 1. With the exception of four studies, all of them demonstrated a significant reduction in symptoms and medication scores after SLIT administration.

SLIT with grass pollen: SLIT for the treatment of grass pollen–induced AR has demonstrated its efficacy at different administration schedules (continuous and discontinuous). Data from more than 3000 patients revealed that SLIT in a pre-/coseasonal scheme reduces symptom and medication scores up to 30 and 29%, respectively, during the first 12 months of treatment, or to 36 and 45% after 3 years. The registration and authorization of grass pollen extract tablets was mainly based on results of these studies. Efficacy of SLIT has been evidenced since the first month of treatment.

SLIT with HDMs: SLIT has proven its efficacy for HDM-induced AR during 6, 12, and 18 months of continuous treatment. Data from more than 5000 patients demonstrated a significant reduction in symptoms score between 16 and 42% after 12 months of treatment, which led to the registration and authorization of HDM extracts as drugs.

Long-term and disease-modifying effect of SLIT: Both SLIT with grass pollen and HDMs have also demonstrated long-term effects for the treatment of AR. Studies involving 3 years of treatment with grass pollen extracts have shown significant improvements in symptoms scores at season 1, 2, and 3 (with values ranging between 25 and 35%), and between 25 and 36% with grass pollen (for 1 year after a 3-year treatment period), and between 18 and 20% with HDMs (for 1 year after a 1-year treatment).

SLIT and asthma: SLIT efficacy with HDMs has been shown in mild-to-moderate and moderate persistent asthma by a clinically and statistically significant reduction in inhaled corticosteroid (ICS) dose required to asthma control and a greater rate of well- and total-control of asthma, which allowed the inclusion of HDM tablets in the Global Initiative for Asthma (GINA) guideline for the treatment of allergic asthma induced by HDMs. Some studies have also demonstrated that SLIT treatment with HDMs improves asthma symptoms, and reduces the risk of moderate/severe exacerbations. Moreover, SLIT with HDMs prevented the risk of developing asthma in children during a 5-year period (3 years of treatment and 2-year follow-up). This preventive effect was apparently strongest in youngest children.

SLIT in children and the elderly

The reference list involving specific populations (either children or elderly) is shown in Table 2. Studies specifically designed for pediatric population involved approximately 2000 children. Most of these studies demonstrated a significant reduction in symptom (22–28%) and medication scores (27–34%) after 1, 2, or 3 years of treatment with grass pollen extracts. SLIT with HDM also showed significant reduction in symptom and medication scores; however, some of them showed no differences with placebo. There was a scarce number of studies regarding elderly subjects, and they involved only a few patients (about 200). Besides this, symptom scores significantly reduced after 3 years of treatment with HDMs (44%) or 5-grass pollen SLIT (64%), together with medication scores by 51%. A study of 3 years of treatment with HDMs and a 3-year follow-up with no treatment also revealed a reduction in symptoms after this 6-year period.

Safety profile

In the majority of studies, AEs were local and mild or moderate in severity. Most of these AEs commonly occurred during the first weeks of treatment. The frequency of treatment-related AEs (TRAEs) ranged between 46 and 69%. The majority of cases (>80%) were oral reactions, including throat irritation (reported in 17–43% of subjects), oral pruritus (11–43%), ear pruritus (7–29%), mouth edema (4–11%), oral paresthesia (5–10%), tongue pruritus (5–9%), lip swelling (3–11%), swollen tongue (3–10%), glossodynia (1–9%), and dysgeusia (0.2–5%). Other TRAEs reported in more than 5% of subjects were: nausea (1–8%), and upper abdominal pain (1–6%). Asthma, cough, and dyspnea were also the most frequently reported asthma-related AEs among subjects with concomitant asthma. Approximately 5% of subjects discontinued the trials because of the TRAEs.

Scarcie studies have reported serious TRAEs regarding SLIT. For instance, in a study with 80 adults with RC receiving ragweed pollen SLIT or placebo, there were reported 10 serious TRAEs (chest discomfort, chest pain, dysphagia, oral pruritus, allergic conjunctivitis, mouth edema, swollen tongue, conjunctivitis, allergic conjunctivitis, and peri-orbital edema). With only one exception, none of these studies, involving in total more
Table 1. Double-blind, randomized studies (versus placebo, comparator) selected in this systematic review involving either adult or both pediatric and adult patients.

| Ref*       | Age†  | Cohort size | Diagnosis | Allergen | Administration type | Study duration | Efficacya | Safety |
|------------|-------|-------------|-----------|----------|---------------------|----------------|-----------|--------|
| Mäkelä et al.21 | 12–65 | 637         | RC        | Birch pollen | Pre-/coseasonal     | 16 weeks (pre) + 6 months during birch and tree seasons | 30–33% reduction in DSS for 7DU | 68 SAEs No Ax |
| Pfaar et al.33 | 19–59 | 269         | R/RC      | Birch pollen | Outside season      | 5 months | Stepwise improvement in SS, significant in 20,000 AUN/mL and 40,000 AUN/mL doses | - |
| Voltolini et al.73 | 44±9  | 24          | R         | Birch pollen | Pre-/coseasonal     | 4 months over 2 consecutive seasons | Rhinorrhea and nasal obstruction decreased | No SAEs No Ax |
| Khinchi et al.111 | 20–58 | 71          | R         | Standardized birch pollen | Coseasonal | 1 baseline year + 2 years treatment | 0.36/0.29 improvement in SS/MS in first season | No SAEs No Ax |
| Didier et al.41,65 | 18–50 | 633         | RC        | 300 IR 5-grass pollen | Pre-/coseasonal     | 2 or 4 months (pre) until end of season 1–3 years of treatment + 2 years of follow-up | 34.5–36.0% reduction in AASS at season 3 25.3–31.1% reduction in AASS after 1 year of follow-up 28.1% reduction in AASS after 2 years of follow-up | 3 SAEs at year 1 No Ax |
| Maloney et al.47 | 5–65  | 1501        | R/RC      | MK-7243 grass | Pre-/coseasonal     | 12 weeks (pre) until end of season | 23/29% improvement in TCS in entire/peak season 20% improvement in DSS in entire-season 35% improvement in DMS in entire-season | No SAEs No Ax |
| Durham et al.60 | 18–65 | 634         | RC        | SQ-grass pollen | Pre-/coseasonal     | 4–8 months (pre) until end of season 3 years of treatment + 2 years of follow-up | 25–36% reduction in DSS after 5 seasons 20–45% reduction in DMS for 1–4 seasons 27–41% reduction in TCS after 5 seasons | No SAEs No Ax |
| Horak et al.81  | 19–50 | 89          | RC        | 300 IR 5-grass pollen | Pre-/coseasonal     | 4 months | 33% improvement in TSS Effect since first and second month of treatment | No SAEs No Ax |

(Continued)
### Table 1. (Continued)

| Study | Country | Age | Pollen | Season | Duration | Treatment | Efficacy | Side Effects | Comments |
|-------|---------|-----|--------|--------|----------|-----------|----------|--------------|----------|
| Mösges et al. | Germany | 18–50 | Grass and rye pollen | Out of season | 9 months | Reduced TSC, Reduced in SS and MS | No SAEs | No Ax | Reduction in TSS, no differences in SS and MS between groups |
| Moreno-Ancillo et al. | Spain | 14–55 | Grass and olive pollen | Pre-/coseasonal | 6 months (pre) until end of season | Improvement in SS in years 1 and 2 | No SAEs | No Ax | No difference in SS and MS between groups |
| de Blay et al. | Belgium | 18–60 | Grass pollen | Pre-/coseasonal | 10 months (pre) until end of season | Reduction in TSS with 300 IR and 500 IR | No SAEs | No Ax | Trend of improvement in clinical score |
| Smith et al. | USA | 18–45 | Grass pollen | Pre-/coseasonal | 4 months (pre) until end of season | 1 baseline year + 1–2 years of treatment | No SAEs | No Ax | More reduced nose running and sneezing |
| Clavel et al. | France | 8–55 | Grass pollen | Coseasonal | 6 months | Reduction in TSS during 42-day period in season | No SAEs | No Ax | Improvement in SS between first and second year, and after 2 years of treatment |
| Pfaar et al. | Germany | 18–59 | 6-grass pollen | Continuous | 2 years | Reduction in TSS during 42-day period in season | No SAEs | No Ax | No SAEs No Ax No Ax |
| Palma-Carlos et al. | Spain | 19–43 | Grass pollen | Continuous | 2 years | Reduction in TSS during 42-day period in season | No SAEs | No Ax | No SAEs No Ax No Ax |
| Nelson et al. | USA | 18–63 | Timothy grass pollen | Pre-/coseasonal | 16 weeks (pre) until end of season | 18 and 20% improvement in DSS and TCS | No SAEs | No Ax | No differences between groups in SS and MS |
| Durham et al. | USA | 18–65 | Timothy grass pollen | Pre-/coseasonal | 8 weeks (pre) and season (10 weeks) | 16/28% reduction in SS/MS during season with/without SQ-T | No SAEs | No Ax | No SAEs No Ax No Ax |
| Lima et al. | Brazil | 18–50 | Timothy grass pollen | Continuous | 12–18 months | 9 SAEs | No SAEs | No SAEs | 43% decrease in TSS in entire season and MS |
| Creticos et al. | USA | 18–48 | Ragweed pollen | Continuous | 8–16 weeks (pre) until end of season | 9–24% reduction in TCS in peak season | 24 SAEs | No Ax | 42/41% decrease in TSS and MS in entire season |
| Creticos et al. | USA | 18–50 | Ragweed pollen | Continuous | 12–18 weeks (pre) until end of season | 12–27% reduction in DCSS in entire season (same dose) | 12 SAEs | No Ax | 12–27% reduction in TCS in peak season |
| Study                     | Dose (Days) | Patients | Route | Dose | Seasonal/Preseasonal | Duration | Outcome                                                                 | SAEs | Ax? |
|--------------------------|-------------|----------|-------|------|----------------------|----------|------------------------------------------------------------------------|------|-----|
| Skoner et al.            | 18–50       | 115      | RC    |      | Pre-/coseasonal      | 8–10 weeks (pre) until end of season | 15% reduction in rhinoconjunctivitis SS in entire season DSS and DMS reduced in 48 mg Amb a 1/d (same period) | 18    | No Ax |
| Bowen et al.             | 6–58        | 83       | RC    |      | Pre-/coseasonal      | 1–2 weeks (pre) and season (3 months) | No differences between groups in SS and MS | No    | No Ax |
| André et al.             | 7–55        | 110      | R     |      | Pre-/coseasonal      | 28 days + 30 days (pre) and co-seasonal 6.5 months with maintenance treatment | Lower SS and MS during the season Highest doses showed highly response for TSS than lower ones | No    | No Ax |
| Okamoto et al.           | 12–64       | 531      | RC    |      | Continuous           | 4 months (pre) until end of second consecutive season | 18 and 30% lower TNSMS in first and second seasons | No    | No Ax |
| Okubo et al.             | 40±15       | 61       | RC    |      | Pre-/coseasonal      | 6 weeks (pre) until end of season | Lower TSS for some days | No    | No Ax |
| Horiguchi et al.         | 20–37       | 77       | RC    |      | Pre-/coseasonal      | 4 months (pre) until end of season | Lower SS | No    | No Ax |
| Vervloet et al.          | 19–60       | 76       | RC    |      | Coseasonal           | 2 seasons | 40–60% reduction in TMS No differences between groups in TSS | No    | No Ax |
| Tonnel et al.            | 7–45        | 120      | R     |      | Continuous           | 24 months | SS decreased after 1 year and persisted | No    | No Ax |
| Bousquet et al.          | 7–42        | 85       | Asthma|      | Continuous           | 25 months | Reduction in SS | No    | No Ax |
| Guo et al.               | 18±9        | 48       | R     |      | Continuous           | 12 months | Improvement in individual nasal SS and TNSS after 11–12 months of treatment | No    | No Ax |
| Okubo et al.             | 12–64       | 946      | R     |      | Continuous           | 12 months | 19 and 22% reduction in TCRS with 20,000 and 10,000 JAU 18 and 22% improvement in SS with same respective doses | No    | No Ax |
| Zieglmayer et al.        | 18–58       | 106      | R/RC  | Asthma| Continuous           | 12 months | Improvement of symptoms in patients with 12 SQ-HDM Reduction in 65% in TASS | No    | No Ax |
| Nolte et al.             | 12–85       | 1482     | R/RC  |      | Continuous           | Up to 52 weeks | 17% improvement in TCRS 16% reduction in DSS | No    | One Ax |

(Continued)
Table 1. (Continued)

| Study            | Duration | Treatment | Route | Placebo | Dose | Baseline | Outcomes                                                                 |
|------------------|----------|-----------|-------|---------|------|----------|--------------------------------------------------------------------------|
| Okamoto et al.²⁹ | 12–64    | 968       | R ± Asthma | House-dust mite | Continuous | 52 weeks | 18 and 13% improvement in AASS in the weeks 44–52 for 300 IR and 500 IR | No SAEs No Ax |
| Roux et al.³⁶  | 18–55    | 355       | R     | House-dust mite | Continuous | 6 months | 33, 29, and 20% reduction in SS with 300 IR, 300 IR and 100 IR | No SAEs No Ax |
| Virchow et al.³⁷| 17–83    | 834       | R + Asthma | SQ-House-dust mite | Continuous | Up to 18 months | Both 6 SQ and 12 SQ doses reduced the risk of asthma exacerbation (moderate or severe, or with deterioration in asthma symptoms) | No SAEs No Ax |
| Demoly et al.³⁹ | 18–66    | 992       | R/RC ± Asthma | SQ-House-dust mite | Continuous | 12 months | 18–22% reduction in TCS with 6 and 12 SQ. Significant reduction in SS and MS with both doses | No SAEs No Ax |
| Potter et al.⁴⁰ | 18–60    | 60        | R ± Asthma | House-dust mite | Continuous | 24 months | Progressive improvement in TSS No differences between SLIT and placebo | No SAEs No Ax |
| Nolte et al.⁴⁴  | 18–58    | 124       | R/RC ± Asthma | House-dust mite | Continuous | 24 weeks | 27 and 49% reduction in TNSS at week 24 with 6 DU and 12 DU | No SAEs No Ax |
| Mosbech et al.⁴⁵| 14–73    | 604       | R + Asthma | House-dust mite | Continuous | 12 months | 29% improvement in TCRS with 6 SQ dose in the end of treatment | 4 SAEs No Ax |
| de Blay et al.⁴⁹| >14      | 108       | Asthma    | House-dust mite | Continuous | 12 months | Significant reduction in ACQ at the end of study with 6 SQ | No SAEs No Ax |
| Wang et al.⁵⁰   | 14–50    | 484       | Asthma    | House-dust mite | Continuous | 12 months | 80.5 and 54.0% improvement in well-, or totally-controlled asthma in subjects with moderate, persistent asthma and SLIT | No SAEs No Ax |
| Bergmann et al.⁵²| 18–50    | 509       | R        | House-dust mite | Continuous | 12 months + 12 months follow-up | 17.9 and 20.2% reduction in AASS with 300 IR and 500 IR maintained during the follow-up | 4 SAEs No Ax |
| Mosbech et al.⁵³| >14      | 604       | R + Asthma | SQ-House-dust mite | Continuous | 12 months | 42.0 and 50.0% relative mean and median reduction for 6 SQ | 2 SAEs No Ax |

(Continued)
### Table 1. (Continued)

| Study | Allergen | Route | Duration | Start Season | End Season | Efficacy | Safety | Notes |
|-------|----------|-------|----------|--------------|------------|----------|--------|-------|
| Wang et al. [5] | House-dust mite | R | 4–60 | Continuous | 120 | Significant reduction in TSS since week 14 | No SAEs | No Ax |
| Cortellini et al. [6] | Alternaria | Continuous | 14–42 | Coseasonal | 27 | Improvement in mean SS at the end of treatment | No SAEs | No Ax |
| Ariano et al. [7] | Cupressus arizonica | R | 35±13 | Coseasonal | 20 | Reduction in MS compared with run-in season and placebo | No SAEs | No Ax |
| Passalacqua et al. [8] | Parietaria judaica | Pre-seasonal | 19–47 | Coseasonal | 30 | Lower SS and MS during the season | No SAEs | No Ax |
| Purello-D’Ambrosio et al. [9] | Parietaria judaica | Pre-/coseasonal | 32±17 | Pre-seasonal | 30 | Decrease in SS and MS after therapy | No SAEs | No Ax |

Subanalyses (with redundant results), pooled studies, or references with not available full-text were not included in the table. Age is shown as range (minimum–maximum) or mean ± standard deviation. *If not indicated, efficacy results are referred to the active treatment group. Comparisons are made with placebo. Only significant results are shown (p<0.05). AASS, average adjusted symptoms score; ACQ, asthma control questionnaire; Ax, anaphylactic reaction; DMS, daily medication score; DSS, daily symptom score; DU, development units; IR, index of reactivity; JAU, Japanese allergy units; MS, medication score; R, rhinitis; RC, rhinoconjunctivitis; SAE, severe or serious adverse events (related to SLIT); SS, symptom score; TASS, total asthma symptom score; TCRS, total combined rhinitis score; TCS, total combined score; TMS, total medication score; TNMS, total nasal symptom and medication score; TNS, total nasal symptom score.
### Table 2. Double-blind, randomized studies (versus placebo, comparator) selected in this systematic review involving specific populations (either children or elderly).

| Ref* | Age† | Cohort size | Diagnosis | Allergen | Administration type | Study duration | Efficacy | Safety |
|------|------|-------------|-----------|----------|---------------------|----------------|----------|--------|
| **Children** | | | | | | | | |
| Valovirta et al. | 5–12 | 812 | RC | SQ-grass pollen | Continuous | 3 years of treatment + 2 years of follow-up | 22% reduction in DSS after 5 years | 6 SAEs No Ax |
| Wahn et al. | 4–12 | 207 | R/RC | Grass pollen | Pre-/coseasonal | 8 months | Changes of –212.5 in AUC of TCS from baseline to first season Changes of –126.6/–85.9 in AUC of SS/MS (same period) | No SAEs No Ax |
| Stelmach et al. | 6–18 | 60 | R | 5-grass pollen | Pre-/coseasonal versus continuous | 2 years | Reduction in TCS/TSS in pre-/coseasonal and continuous Pre-/coseasonal reduced more nasal symptoms than continuous | No SAEs No Ax |
| Stelmach et al. | 6–17 | 50 | Asthma ± RC | 5-grass pollen | Pre-/coseasonal | 2 weeks (pre) until end of season 2 seasons | 25 and 41% improvement in nasal and asthma SS 10% improvement in use of rescue medication | No SAEs No Ax |
| Bufe et al. | 5–16 | 253 | RC | SQ-grass pollen | Pre-/coseasonal | 8–23 weeks (pre) until end of season | 24 and 34% reduction in rhinoconjunctivitis SS and MS 64% reduction in asthma SS | No SAEs No Ax |
| Wahn et al. | 5–17 | 278 | RC | 300 IR 5-grass pollen | Pre-/coseasonal | 4 months (pre) until end of season | 28.0% improvement in TSS −0.20 mean reduction in rescue MS | 17 SAEs No Ax |
| Röder et al. | 6–18 | 204 | RC | Grass pollen | Continuous | 2 years | No differences between groups in SS | - |
| Röder et al. | 6–18 | 204 | RC | 5-grass pollen | Continuous | 2 years | No differences between groups in TSS | - |
| Rolink-Werninghaus et al. | 3–14 | 97 | RC | 5-grass pollen | Continuous | 32 months | TCS reduced by 77.3% of placebo group MS reduced by 67.3% of placebo group | 1 SAE No Ax |
| Wüthrich et al. | 4–11 | 28 | RC | 5-grass pollen | Continuous | 2 years | 70% improvement in MS in second year compared with first | No SAEs No Ax |
| Valovirta et al. | 5–15 | 88 | RC | Birch, alder, and hazel pollen | Continuous | Up to 18 months | Reduction in SS and MS with 24,000 and 200,000 SQ-U doses No differences between doses | No SAEs No Ax |
| Pajno et al. | 8–15 | 24 | Asthma | House-dust mite | Continuous | 2 years | Reduced SS and MS after 2 years of treatment | No SAEs No Ax |

(Continued)
| Study                  | Duration | Age Range | Allergy Type          | Treatment | Efficacy                                                                 |
|-----------------------|----------|-----------|-----------------------|-----------|--------------------------------------------------------------------------|
| de Bot et al.65       | 6–18     | 251       | R                     | Continuous | No significant effect in mean NSS after treatment                       |
| Yonekura et al.75     | 7–15     | 31        | R                     | Continuous | Reduction in mean NSS in week 32 and 35                                 |
| Pham-Thi et al.95     | 5–15     | 111       | Asthma ± R            | Continuous | No SAEs                                                                  |
| Hirsch et al.108      | 6–15     | 30        | Asthma ± R            | Continuous | No SAEs                                                                  |
| Pajno et al.112       | 8–14     | 38        | Asthma ± RC           | Continuous | Improvement in SS and MS in active and placebo groups                   |
| La Rosa et al.112     | 6–14     | 41        | RC                    | Continuous | Reduction in SS during the second season                                 |
| Vourdas et al.125     | 7–17     | 66        | RC                    | Pre-/coseasonal | Decreased SS during first and second seasons                           |

**Elderly**

| Study                  | Duration | Age Range | Allergy Type          | Treatment | Efficacy                                                                 |
|-----------------------|----------|-----------|-----------------------|-----------|--------------------------------------------------------------------------|
| Bozek et al.25        | 66±5     | 47        | R                     | Continuous | 4.01 mean reduction in AASS after 3 years                                |
| Bozek et al.57        | 60–75    | 111       | R                     | Continuous | 3.17 mean reduction in AASS after 6 years                                |
| Bozek et al.46        | 60–70    | 78        | R                     | Preseasonal | 64% decrease in nasal SS at the end of treatment                         |

*Subanalyses (with redundant results), pooled studies, or references with not available full-text were not included in the table. †Age is shown as range (minimum–maximum) or mean ± standard deviation. ‡If not indicated, efficacy results are referred to the active treatment group. Comparisons are made with placebo. Only significant results are shown (p<0.05).

AASS, average adjusted symptoms score; AUC, area under the curve; Ax, anaphylactic reaction; DMS, daily medication score; DSS, daily symptom score; MS, medication score; NSS, nasal symptom score; R, rhinitis; RC, rhinoconjunctivitis; SAE, severe or serious adverse events (related to SLIT); SS, symptom score; TCS, total combined score; TMS, total medication score; TNSS, total nasal symptom score; TSS, total symptom score.
| Ref | Age† | Cohort size | Diagnosis | Allergen | Administration type | Study duration | Safety |
|-----|-------|-------------|-----------|----------|----------------------|----------------|--------|
| Birk et al. 23 | 19-61 | 70 | Birch pollen | Out of season | 26-29 days | 5 SAEs with 2 and 4 DU | No Ax |
| Devillé et al. 28 | 14-50 | 484 | Asthma | Continuous | 12 months | No SAEs | No Ax |
| Nayak et al. 38 | 18-50 | 80 | Ragweed pollen | Out of season | 28 days | 10 SAEs | No Ax |
| Sieber et al. 62 | 8-65 | 209 | 5-grass pollen | Continuous | 3 consecutive seasons | No SAEs | No Ax |
| Pfaar et al. 67 | 18-65 | 80 | 12 grass pollens | Outside season | 8 weeks | No SAEs | No Ax |
| Calderón et al. 77 | 18-42 | 43 | R + Asthma | Continuous | 28 days | No Ax | No Ax |
| Larson et al. 100 | 18-50 | 30 | R | Continuous | 10 days | No SAEs | No Ax |
| Malling et al. 102 | 18-65 | 47 | Grass pollen | Continuous | 8 weeks (pre) until end of season | No SAEs | No Ax |
| Kleine-Tebbe et al. 104 | 18-65 | 84 | Grass pollen | Outside season | 28 days | No SAEs | No Ax |
| Grosclaude et al. 115 | 5-46 | 64 | 5-grass pollen | Continuous | 5 months ahead season, for 8 months | No SAEs | No Ax |
| Children | 5-12 | 60 | Birch pollen | Continuous | 28 days outside the grass pollen season | No SAEs | No Ax |
| Ibañez et al. 90 | 5-12 | 60 | SQ standardized grass pollen | Continuous | 28 days outside the grass pollen season | No SAEs | No Ax |

*Subanalyses (with redundant results), pooled studies, or references with not available full-text were not included in the table. †Age is shown as range (minimum–maximum).

Ax, anaphylactic reaction; R, rhinitis; RC, rhinoconjunctivitis; SAE, severe or serious adverse events (related to SLIT).
than 4000 subjects, have reported cases of Ax during SLIT. The reference list involving studies only addressed to evaluate SLIT safety profile is shown in Table 3. Among them, Birk and colleagues evaluated SQ tree SLIT tablet (ALK, doses from 1 to 24 DU) tolerability for 26–29 days outside birch pollen season in 70 adults with RC with or without asthma, and reported 3 TRAEs: asthma (at 2 DU dose), eye pruritus (4 DU), and Ax (8 DU).

Discussion

Registration and authorization of allergen SLIT preparations (firstly grass pollen, and secondly HDMs) as drugs by regulatory agencies represented a landmark in the research on allergy immunotherapy. Apart from standardizing preparation content and production procedures (reproducibility), which in turn increased patient safety, its clinical development by the inclusion of a large number of patients in phase III clinical trials allowed registration and authorization of these products. The amount and quality of studies shown in the present manuscript is a consequence of such decision.

Since the first published trial in 1986, SLIT has become the most promising alternative to SCIT. The present systematic review clearly shows that SLIT is both effective (by reducing symptom and medication scores) and safe, at least regarding HDM and certain pollen preparations. SLIT has clearly shown to be effective for the treatment of ARDs, maintaining its effectiveness up to 2 years after a 3-year treatment period, thus demonstrating not only long-term efficacy but also a disease-modifying effect.

However, several aspects should also be taken into account. First, allergen content and dosing (either for SCIT and SLIT) is not standardized, and varies among products. Several grass pollen SLIT formulations were used in studies considered, including 5-grass pollen, MK-7243 grass pollen, 3-grass pollen, timothy grass pollen, and 6-grass pollen. In this line, a study of SLIT products from US and European manufacturers has already shown a difference from 7 to 200-fold in major allergen concentration of timothy grass, HDM, ragweed, and cat extracts. Given the variability in allergen content, comparisons between different studies should be made cautiously.

The registration of SLIT grass pollen and HDM preparations have contributed to reduce this allergen content variability. Currently, the FDA has recommended the use of the bioequivalent allergy unit for establishing the allergenic activity (potency) of grass pollen extracts of different origins. By contrast, European regulatory authorities need to adopt a standardized unit. It has been documented that high antigen doses are needed to achieve immunotherapy-induced clinical benefits, thus it is expected that studies carried out with low antigen doses may not be successful. In this regard, one of the SLIT main advantages, as compared to the more traditional SCIT route, is that you can increase the extract allergen content to a certain range without compromising safety profile.

Another aspect to consider is the administration schedule. SLIT has been shown to be effective for allergic RC, both under continuous (year-round) or discontinuous (pre-seasonal, coseasonal, or pre-/coseasonal) schemes. SLIT with HDMs is used under a continuous scheme. Pre- and coseasonal regimens are frequently employed for SLIT, especially with grass pollen, and have some advantages over continuous regimens. In fact, long treatment periods have been associated with poor adherence and, in turn, lower effectiveness. Diverse studies have demonstrated that discontinuous schemes are, at least, as effective and safe as continuous ones. However, pre-/coseasonal treatment, as used with grass pollen, might enhance the adherence to long treatments. If SLIT products are initiated before the pollen season, it is important for practitioners to be familiar with specific pollen seasonal patterns in their locations.

The third consideration derives from the lack of comparative studies (efficacy and safety) between SLIT and SCIT. In this context, SLIT may provide some clear advantages over SCIT, such as the comfort of receiving treatment at home, without painful injections, and as mentioned earlier a better safety profile, which together with pre-/coseasonal schemes would probably improve treatment adherence. Due to the lack of studies specifically designed to compare both administration routes we have to be cautious with conclusions.

On the other hand, clinical trials with HDM-induced asthma have demonstrated that SLIT treatment not only significantly reduces asthma symptoms and exacerbations but also can prevent asthma onset. However, the number of studies involving asthmatic subjects or designed to evaluate changes in asthma symptoms is limited. Given the increasing prevalence of asthmatic patients and the impact of SLIT over the ‘allergic march’, it seems necessary to perform additional long-term controlled clinical trials with, at least, the most prevalent allergens.

Interestingly, a recent study focused on SLIT immunological mechanisms, using a grass pollen tablet and with a 3-year treatment and 2-year follow-up protocol, has suggested that SLIT sustained effect is linked to the generation of a long-term regulatory T cell response. However, up to 2 years of therapy is needed to develop this regulatory response in many patients, thus explaining why some short-term studies have failed to demonstrate SLIT efficacy.

Most studies that have failed to demonstrate SLIT efficacy show a low allergen content, a short treatment time, and/or a small study population sample size. In consequence, when evaluating SLIT, we need to focus on studies performed not only with high-dose allergen formulations but also on a long-term basis and with a large sample size, such as those used to register as drugs, both grass pollen and HDM preparations.

Final considerations about the difficulty in assessing the evidence in these studies include the following: the severity of the disease in recruited patients (SLIT showed no significant results when analyzing patients with intermittent mild asthma
or AR, whereas when analyzing by moderate persistent asthma, authors did find significant results; concomitant treatments can mask the effect of immunotherapy; and intrinsic effects of clinical trials or ‘nursing effect’ can explain the improvement achieved by the treatment with placebo.

One limitation of our systematic review is intrinsically associated with the nature of the literature search, that is, using only data from published and available clinical trials. Another limitation may derive from the heterogeneity between studies, regarding factors such as treatment, inclusion criteria, or variables evaluated. Also, our study goal was to perform a complete (from 1992) and updated (to 2018) search from PubMed database on allergen SLIT, to try to provide a clear vision of the current situation of this specific therapy.

**Conclusion**

Data from the majority of properly controlled clinical trials demonstrate that SLIT is an effective treatment for ARDs in children and adults, since continuous and discontinuous schemes of administration show significant reductions in symptom and medication scores, both at short (first year) and long-term (sustained effect during a 3-year treatment period). Furthermore, a disease-modifying effect of SLIT has been documented mainly with grass pollen extracts, maintaining its effect for a 2-year follow-up without immunotherapy after a 3-year SLIT treatment period. At the same time, allergen immunotherapy should also be considered a preventive strategy, especially for preventing asthma in children and adolescents with AR. SLIT treatment appears to be safe in that it produces only a few self-limiting and mainly local and mild-to-moderate AEs.

Further long-term studies, specially designed with allergens other than grass pollen or HDMs, not only in ARC but also on asthmatic subjects, as well as studies comparing different administration schedules and/or routes, are required to continue the progress in the modern development of this particular promising therapy.

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