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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.[12] 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).[15,16] 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.[17,18] 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.

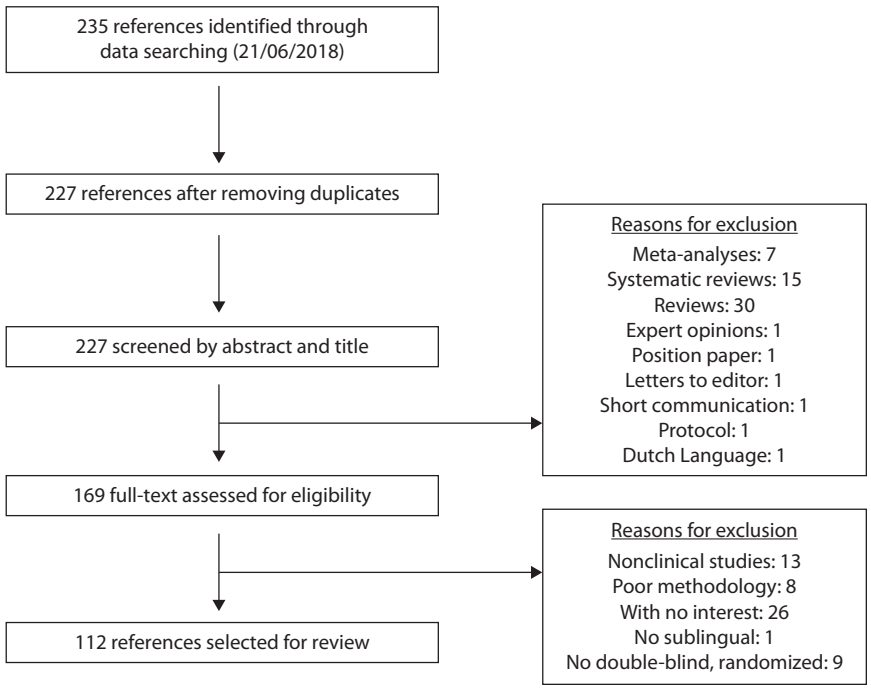
Methods

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).[19] 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.[20] 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).[21–132] Briefly, most studies involved only adult or both pediatric and

Figure 1. PRISMA flow diagram.



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, *Parietaria 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,[63,87,105,116] 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.[41,60,65,66,103] 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.[81]

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,[29,35,36,37,39,52,53] which led to the registration and authorization of HDMs 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%).[60,63] Furthermore, SLIT with grass pollen and HDMs showed a disease-modifying effect after a period of treatment. The reduction in symptoms scores ranged between 25 and 36% with grass pollen (for 2 years after a 3-year treatment period),[41,60,65] and between 18 and 20% with HDMs (for 1 year after a 1-year treatment).[52]

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,[51,53] 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.[35,37] 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).[13,22] 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.[22,77,80] SLIT with HDM also showed significant reduction in symptom and medication scores;[75,118] however, some of them showed no differences with placebo.[95,128] There was a scarce number of studies regarding elderly subjects, and they involved only a few patients (about 200).[25,46,57] Besides this, symptom scores significantly reduced after 3 years of treatment with HDMs (44%)[57] or 5-grass pollen SLIT (64%),[46] 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.[25]

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%.[133] 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.

Scarce 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 periorbital edema).[58] With only one exception,[23] 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	Efficacy[a]	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*)

Mösges et al.[86]	18–50	105	RC	Grass and rye pollen	Out of season	9 months	Reduced TSC	No SAEs No Ax
Moreno-Ancillo et al.[87]	14–55	105	R ± Asthma	Grass and olive pollen	Pre-/coseasonal	6 months (pre) until end of season	Reduction in SS and MS No differences in SS and MS between groups	No SAEs No Ax
de Blay et al.[88]	12–41	127	RC	Standardized 3-grass pollen	Pre-/coseasonal	10 months (pre) until end of season	Trend of improvement in clinical score	No SAEs No Ax
Didier et al.[89]	18–45	628	RC	Standardized 5-grass pollen	Pre-/coseasonal	4 months (pre) until end of season	Reduction in TSS with 300 IR and 500 IR	No SAEs No Ax
Smith et al.[107]	18–60	186	R	5-grass pollen	Continuous	1 baseline year + 1–2 years of treatment	Improvement in SS in years 1 and 2 6.8 and 2.4 times to show reduced nose running and sneezing	7 SAEs No Ax
Clavel et al.[127]	8–55	136	R	Standardized 5-grass-pollen	Coseasonal	6 months	Lower MS during first 6 weeks of the season	No SAEs No Ax
Pfaar et al.[84]	18–59	185	R/RC	6-grass pollen	Continuous	2 years	Improvement in TCS during a 42-day period in season	No SAEs No Ax
Palma-Carlos et al.[98]	19–43	33	R	Grass pollen	Pre-/coseasonal	2 years	Reduction in SS between first and second year, and after 2 years of treatment	No SAEs No Ax
Nelson et al.[66]	18–63	439	RC	Timothy grass pollen	Pre-/coseasonal	16 weeks (pre) until end of season	18 and 20% improvement in DSS and TCS 26% improvement in DMS	No SAEs No Ax
Durham et al.[103]	18–65	855	RC	Timothy grass pollen	Pre-/coseasonal	8 weeks (pre) and season (10 weeks)	16/28% reduction in SS/MS during season with 75,000 SQ-T 21/29% efficacy increased with pre-seasonal (≥8 weeks)	No SAEs No Ax
Lima et al.[116]	18–	56	RC	Timothy grass pollen	Continuous	12–18 months	No differences between groups in SS and MS	No SAEs No Ax
Creticos et al.[48]	18–55	429	R/RC	Ragweed pollen	Pre-/coseasonal	8–16 weeks (pre) until end of season	43% decrease in TCS in entire season 42/41% decrease in DSS in entire/peak season	No SAEs No Ax
Creticos et al.[54]	18–50	784	R/RC	Ragweed pollen	Pre-/coseasonal	12–16 weeks (pre) until end of season	9–24% reduction in TCS in peak season (1.5, 6, 12 Amb a 1-U) 12–27% reduction in DCS in entire season (same doses)	12 SAEs No Ax

(Continued)

Table 1. (*Continued*)

Skoner et al.[71]	18–50	115	RC	Ragweed pollen	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 SAEs No Ax
Bowen et al.[105]	6–58	83	RC	Ragweed pollen	Pre-/coseasonal	1–2 weeks (pre) and season (3 months)	No differences between groups in SS and MS	No SAEs No Ax
André et al.[114]	7–55	110	R	Standardized ragweed pollen	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 SAEs No Ax
Okamoto et al.[42]	12–64	531	RC	Japanese cedar pollen	Continuous	4 months (pre) until end of second consecutive season	18 and 30% lower TNSMS in first and second seasons	No SAEs No Ax
Okubo et al.[83]	40±15	61	RC	Japanese cedar pollen	Pre-/coseasonal	6 weeks (pre) until end of season	Lower TSS for some days	No SAEs No Ax
Horiguchi et al.[85]	20–37	77	RC	Japanese cedar pollen	Pre-/coseasonal	4 months (pre) until end of season	Lower SS	No SAEs No Ax
Vervloet et al.[93]	19–60	76	RC	*Juniperus ashei* pollen	Coseasonal	2 seasons	40–60% reduction in TMS No differences between groups in TSS	No SAEs No Ax
Tonnel et al.[110]	7–45	120	R	House-dust mite	Continuous	24 months	SS decreased after 1 year and persisted	No SAEs No Ax
Bousquet et al.[123]	7–42	85	Asthma	House-dust mite	Continuous	25 months	Reduction in SS	No SAEs No Ax
Guo et al.[27]	18±9	48	R	House-dust mite	Continuous	12 months	Improvement in individual nasal SS and TNSS after 11–12 months of treatment	No SAEs No Ax
Okubo et al.[28]	12–64	946	R	House-dust mite	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 SAEs No Ax
Zieglmayer et al.[34]	18–58	106	R/RC ± Asthma	SQ-House-dust mite	Continuous	12 months	Improvement of symptoms in patients with 12 SQ-HDM Reduction in 65% in TASS	No SAEs No Ax
Nolte et al.[35]	12–85	1482	R/RC	SQ-House-dust mite	Continuous	Up to 52 weeks	17% improvement in TCRS 16% reduction in DSS	No SAEs One Ax

(Continued)

Table 1. (*Continued*)

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 500 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*)

Wang et al.[56]	4–60	120	R	House-dust mite	Continuous	6 months	Significant reduction in TSS since week 14	No SAEs No Ax
Cortellini et al.[69]	14–42	27	R	Alternaria	Coseasonal	10 months	Improvement in mean SS at the end of treatment Reduction in MS compared with run-in season and placebo	No SAEs No Ax
Ariano et al.[117]	35±13	20	RC	*Cupressus arizonica*	Coseasonal	12 months	Lower SS and MS during the season	No SAEs No Ax
Passalacqua et al.[120]	19–47	30	RC	Parietaria sp.	Pre-seasonal	5 months	Decrease in SS and MS after therapy	No SAEs No Ax
Purello-D'Ambrosio et al.[121]	32±17	30	RC ± Asthma	*Parietaria judaica*	Pre-/coseasonal	1 season	Reduced SS and MS especially during the 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) or mean ± standard deviation. ºIf 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; TNSMS, total nasal symptom and medication score; TNSS, total nasal symptom score; TSS, total 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[a]	Safety
Children								
Valovirta et al.[22]	5–12	812	RC	SQ-grass pollen	Continuous	3 years of treatment + 2 years of follow-up	22% reduction in DSS after 5 years 27% reduction in DMS after 5 years	6 SAEs No Ax
Wahn et al.[59]	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.[61]	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.[76]	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.[77]	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.[80]	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.[82]	6–18	204	RC	Grass pollen	Continuous	2 years	No differences between groups in SS	-
Röder et al.[92]	6–18	204	RC	5-grass pollen	Continuous	2 years	No differences between groups in TSS	-
Rolinck-Werninghaus et al.[106]	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.[113]	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.[99]	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.[118]	8–15	24	Asthma	House-dust mite	Continuous	2 years	Reduced SS and MS after 2 years of treatment	No SAEs No Ax

(Continued)

Table 2. (*Continued*)

de Bot et al.[63]	6–18	251	R	House-dust mite	Continuous	2 years	No significant effect in mean NSS after treatment	No SAEs No Ax
Yonekura et al.[75]	7–15	31	R	House-dust mite	Continuous	40 weeks	Reduction in mean NSS in week 32 and 35 Reduction in mean TSS in week 24	No SAEs No Ax
Pham-Thi et al.[95]	5–15	111	Asthma ± R	House-dust mite	Continuous	18 months	Decrease in rhinitis SS, but no difference with placebo	No SAEs No Ax
Hirsch et al.[128]	6–15	30	Asthma ± R	House-dust mite	Continuous	12 months	Reduction in mean NSS, but no difference with placebo	No SAEs No Ax
Pajno et al. [112]	8–14	38	Asthma ± RC	*Parietaria Judaica* pollen	Coseasonal	13 months	Improvement in SS and MS in active and placebo groups	-
La Rosa et al.[122]	6–14	41	RC	*Parietaria judaica*	Continuous	2 years	Reduction in SS during the second season	No SAEs No Ax
Vourdas et al.[125]	7–17	66	RC	Olive pollen	Pre-/coseasonal	2 seasons	Decreased SS during first and second seasons	No SAEs No Ax
Elderly								
Bozek et al.[25]	66±5	47	R	House-dust mite	Continuous	3 years of treatment + 3 years of follow-up	4.01 mean reduction in AASS after 3 years 3.17 mean reduction in AASS after 6 years Significant differences SLIT – placebo after 3 and 6 years	-
Bozek et al.[57]	60–75	111	R	House-dust mite	Continuous	3 years	44% decrease in TNSS at the end of treatment 51% decrease in TMS at the end of treatment	No SAEs No Ax
Bozek et al.[46]	60–70	78	R	5-grass pollen	Preseasonal	3 years	64% decrease in nasal SS at the end of treatment 51% decrease in TMS at the end of treatment	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. [a]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.

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Table 3. Double-blind, randomized studies (versus placebo, comparator) selected in this systematic review addressing only the evaluation of the safety profile.

Ref*	Age†	Cohort size	Diagnosis	Allergen	Administration type	Study duration	Safety
Children and adults							
Birk et al.[23]	19–61	70	RC	Birch pollen	Out of season	26–29 days	5 SAEs with 2 and 4 DU 1 Ax with 8 DU
Devillier et al.[38]	14–50	484	Asthma	House-dust mite	Continuous	12 months	No SAEs No Ax
Nayak et al.[58]	18–50	80	RC	Ragweed pollen	Out of season	28 days	10 SAEs No Ax
Sieber et al.[62]	8–65	209	R	5-grass pollen	Coseasonal	3 consecutive seasons	No SAEs No Ax
Pfaar et al.[67]	18–65	80	R	12 grass pollens	Outside season	8 weeks	No SAEs No Ax
Calderón et al.[97]	18–42	43	R + Asthma	5-grass pollen	Out of season	28 days	No SAEs No Ax
Larsen et al.[100]	18–50	30	R	5-grass pollen	Out of season	10 days	8 SAEs No Ax
Malling et al.[102]	18–65	47	RC	Grass pollen	Pre-/coseasonal	8 weeks (pre) until end of season	No SAEs No Ax
Kleine-Tebbe et al.[104]	18–65	84	RC	Grass pollen	Outside season	28 days	No SAEs No Ax
Grosclaude et al.[115]	5–46	64	RC	5-grass pollen	Out of season	5 months ahead season, for 8 months	3 SAEs No Ax
Children							
Maloney et al.[32]	12–17	195	R/RC	6- or 12-SQ house-dust mite	Out of season	28 days	No SAEs No Ax
Mösges et al.[68]	6–14	54	R	Birch pollen	Out of season	3 months	No SAEs No Ax
Ibañez et al.[90]	5–12	60	RC	SQ standardized grass pollen	Out of season	28 days outside the grass pollen season	18 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[23] 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.[15–18] 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.[132] 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.[134] 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.[135] 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.[14] 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.[136] In fact, long treatment periods have been associated with poor adherence and, in turn, lower effectiveness.[137] 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.[22,37,44,45] 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.[138,139] 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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