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Metaanalysis of the Efficacy of Sublingual Immunotherapy in the Treatment of Allergic Asthma in Pediatric Patients, 3 to 18 Years of Age

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Abstract and Introduction

Abstract

Background: Recent studies have documented the efficacy and safety of sublingual immunotherapy (SLIT) in patients with rhinitis, but the value of this treatment in those with asthma is still debated. We evaluated the efficacy of SLIT in the treatment of allergic asthma in children by a metaanalysis of randomized, double-blind, and placebo-controlled (DBPC) clinical trials.
Methods: Electronic databases were searched up to May 31, 2006, for randomized DBPC trials assessing SLIT in pediatric cases of asthma. Effects on primary outcomes (*ie*, symptom scores and concomitant use of rescue medication) were calculated with standardized mean differences (SMDs) using the random-effects model. We performed the metaanalysis using a statistical software package (RevMan, 4.2.8; The Cochrane Collaboration; Oxford, UK), and we followed the recommendations of the Cochrane Collaboration and the Quality of Reporting of Metaanalyses guidelines.
Results: Seventy-three articles were identified and reviewed. Nine studies, all published after 1990, fulfilled the selection criteria. A total of 441 patients had a final assessment and were included in the analysis. Two hundred thirty-two patients received SLIT, and 209 patients received placebo. The results of the present analysis demonstrated a relevant heterogeneity due to widely differing scoring systems. Overall, there was a significant reduction in both symptoms (SMD - 1.14; 95% confidence interval [CI], - 2.10 to - 0.18; p - 0.02) and medication use (SMD, - 1.63; 95% CI, - 2.83 to - 0.44; p - 0.007) following SLIT.
Conclusion: SLIT with standardized extracts reduces both symptom scores and rescue medication use in children with allergic asthma compared with placebo.

Introduction

Specific immunotherapy, usually administered by the subcutaneous route, is presently considered as the only allergen-oriented biological response modifier, and it is regarded as an essential part of the therapeutic approach for respiratory allergy.[1] The relevance of immunotherapy in the treatment of allergic respiratory diseases is further underlined by the fact that it can exert a preventive effect on the progression of respiratory allergy in children,[2] thus acting as a secondary prevention. The use of sublingual immunotherapy (SLIT) was proposed about 20 years ago with the main rationale of minimizing the risk of severe adverse events, possibly related to the injection route of administration.[3] After some years and many controlled trials performed in adults and children,[4] SLIT was finally accepted as a viable alternative to the traditional subcutaneous administration route.[1,5] The satisfactory safety profile of SLIT was repeatedly confirmed in both clinical trials and postmarketing surveys, even in children <5 years of age.[6] Of note, some double-dummy studies[7,8] failed to detect a significant difference between SLIT and the subcutaneous route of administration as far as clinical efficacy was concerned. Finally, stringent experimental evidence[9,10] of the immunologic effects of the treatment, consistent with the clinical effects, has also been provided.

The abundant literature on injection immunotherapy allowed the performance of detailed metaanalyses of its efficacy in asthma patients.[11] Based on the available randomized and controlled trials, meta-analyses have been also performed with SLIT, and two studies have confirmed its efficacy in adults[12] and in pediatric subjects.[13] Nevertheless, the mentioned metaanalyses were essentially limited to allergic rhinitis, due to the paucity of experimental data available for asthma so that the value of SLIT in asthma patients is still matter of debate. This is especially true in children who are expected to be the ideal candidates for SLIT. During the last years, several new pediatric studies have been published, and further data have become available; thus, we evaluated the efficacy of SLIT in cases of allergic asthma among pediatric patients (3 to 18 years old) by conducting a metaanalysis of the published randomized, double-blind, placebo-controlled (DBPC) clinical trials.

Materials and Methods

Search Strategy

This review was conducted following the Cochrane Collaboration and the Quality of Reporting of Metaanalyses (QUOROM) guidelines standards.[14,15] The MEDLINE, EMBASE, LILACS, and CINAHL databases were searched from 1966 to May 31, 2006, for randomized DBPC trials investigating the efficacy of SLIT in children with allergic asthma using MeSH headings and text words. We searched also for any additional study mentioned in the references of the identified publications, including previous relevant metaanalyses and narrative reviews. Abstracts of relevant meetings were also searched.

Two authors conducted independent search strategies. The first MEDLINE search strategy retrieved citations containing the subject heading "sublingual immunotherapy" (limited to the publication types clinical trial and metaanalysis) or the text words "sublingual or swallow desensitization" or oromucosal immunotherapy." The second MEDLINE search strategy retrieved citations containing the subject heading "sublingual immunotherapy" combined with exploded subject headings describing allergic disease ("asthma," "bronchial," or "wheezing") or text words describing "sublingual immunotherapy efficacy in asthma" appearing in close proximity to each other ("sublingual," "immunotherapy," "asthma," and "efficacy") or those focused to the target population ("children" or "adolescent"). We limited citations from the second search to randomized, controlled trials using a maximally sensitive strategy.16 We modified these searches for other databases. We screened reference lists from all retrieved articles and from recent review articles to identify additional studies. There were no language restrictions.

Study Selection and Characteristics

We included parallel-group randomized, DBPC trials. Patients had to be ≥18 years of age as accepted by the American Academy of Pediatrics,[17,18] with a history of allergic asthma with or without allergic rhinitis and/or conjunctivitis, in whom the causal allergen had been identified, and IgE sensitization had been proven by skin-prick tests and/or specific IgE assays. Immunotherapy had to be delivered by the sublingual route, whether or not the allergen was subsequently swallowed. All appropriate allergens were considered at all doses and for all durations of treatment. Trials of SLIT for allergic rhinitis were considered only if the results for subjects with asthma were separately analyzed.

Trial eligibility was determined on full text format by two authors and checked by the principal investigator. The observed percentage agreement between the investigators for the assessment of inclusion was calculated by using the κ test.[15,19] The κ statistic (Table 1)[19-22,24,26-32,46,54,64,65,71-74] represents the rate of agreement remaining between two independent observers after chance agreement is removed. The κ statistic values range from 1 (excellent) to 0 (no agreement).

Assessment of Validity

The methodological information used that was relevant to the assessment of internal validity was as follows: method of allocation; generation and concealment of randomization; blinding of caregivers/outcome assessors; and the number of and reasons for withdrawals. The quality of trials was quantified in duplicate using the Jadad scale[20,21] that scores from 0 (lower quality) to 5 (excellent quality) [Table 1]. An interrater agreement was again calculated by using the κ statistic.[15,19,22]

Data Extraction

The outcomes measured were asthma symptom and medication scores. Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. Observer variation for continuous data was quantified and plotted using the Bland-Altman test.[23,24] We planned to perform an intention-to-treat analysis and tried to include dropouts in the analysis if the last observation carried forward for both continuous scores was available; if not, we just included them in the analysis of patients with a final assessment. When the results were only presented in graphs, these were digitized and then converted to numbers (DigitizeIt, version 1.5.7; DigitizeIt; Köln, Germany).[25] Additionally, we contacted most of the investigators to obtain more information for data extraction.

Statistical Analysis

Outcomes were quantitative and continuous (*ie*, symptom scores and medication scores). In the original studies, a wide variety of scoring systems and scales were used for symptoms (usually, a daily assessment of symptoms recorded on a diary, and subsequently summarized and averaged) and medication usage (typically, a daily score of the use of β_2-agonists and inhaled corticosteroids). The investigators of each trial provided post-treatment mean and SD values for both the active-treatment and placebo groups. Since the outcome variables continuous data were expressed in different scales, we used the standardized mean difference (SMD). Heterogeneity was calculated with the Cochrane Q statistic test and the I^2 test.[26,27] The I^2 test describes the rate of variation across studies due to heterogeneity rather than chance, and ranges from 0 (no heterogeneity) to 100 (maximum heterogeneity) [Table 1]. All results are reported with 95% confidence intervals (CIs), and all p values are two-tailed.

Given the significant heterogeneity found among the results of the included studies, the random-effects model (REM) according to DerSimonian and Laird[28] was used. This model assumes that the true treatment effects in the individual studies may be different from each other and that these are normally distributed.[28-30] We explored the effect-size distribution with Q-Q plots and histograms. The Q-Q plots compare the quantiles of an observed distribution against the quantiles of the standard normal distribution. In a metaanalysis, such a plot can be used to check the normality assumption, to investigate whether all studies come from a single population, and to search for publication bias.[31] Statistical methods are summarized in Table 1 . The analysis was performed using two statistical software programs (RevMan, version 4.2.8; The Cochrane Collaboration; Oxford, UK;[32] and SPSS, version 14.0 for Windows; SPSS Inc; Chicago, IL).[33]

Data Synthesis

Search Results

The primary search identified 286 articles, 73 of which were potentially relevant trials on SLIT in infantile allergic asthma (Fig 1). Twenty-one studies[34-42] were randomized, but only 9 articles[34-42] met the mentioned inclusion criteria for metaanalysis. The κ statistic for interrater agreement on study eligibility was 0.85 (95% CI, 0.75 to 1.0). Consensus was reached on the remaining trials. Some randomized trials were excluded from the review for the following reasons: three trials were not blinded; two trials did not compare SLIT with placebo; two trials were duplicated; and five trials had no suitable data (designed for safety evaluation, postchallenge test studies, or information not obtainable).
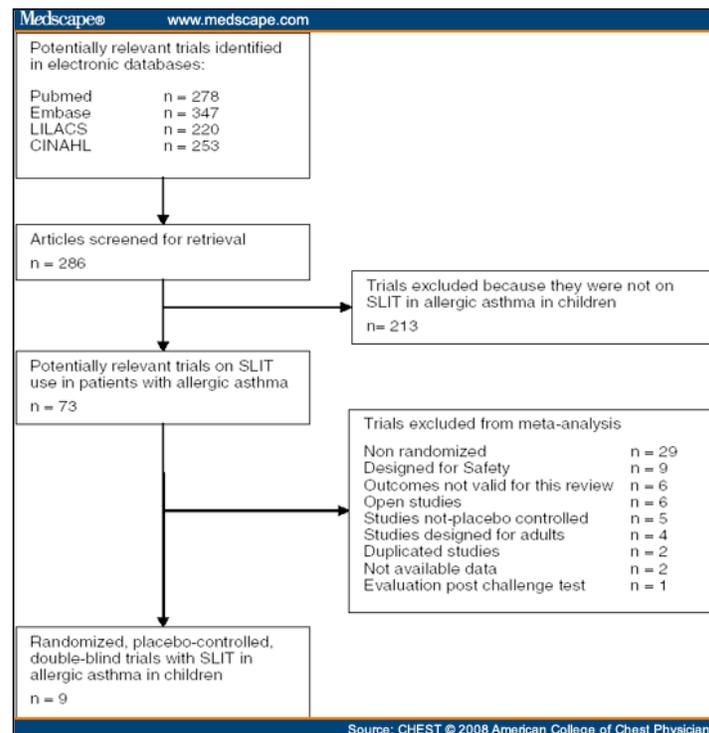
Figure 1.

Handling of trials identified through a search of studies.

The mean and SD for scores were available in text or graphics in three articles.[34,37,42] When the data were not accessible in the articles, authors were contacted, and they provided the data.[35,36,38-41]

Trial Characteristics

Table 2 [34-42] summarizes the characteristics of the studies and subjects included in the metaanalysis. All nine studies[34-42] reported 441 subjects who had concluded treatment and had received a final clinical assessment; consequently, their data were analyzed. Four trials[35-37,41] included patients with either asthma or rhinitis; but only those patients with asthma were included in this analysis. The age range of participants was 3 to 18 years. Each trial included a median of 43 participants (range, 14 to 97 patients). All patients had received a diagnosis of allergic asthma (rhinitis, 77%; conjunctivitis, 59%). There were not enough studies for a reliable evaluation of FEV_1 as a primary outcome.

Table 3 [34-42] displays the characteristics of treatments. The SLIT extracts used in the trials were all standardized either biologically or immunologically in the following units: specific treatment units (or STU); index of reactivity (or IR); allergic units (or AU); biological units (or BU); and micrograms. The allergens were mites (n = 6), grass mix (n = 1), *Olea europaea* (n = 1), and pollen mix (n = 1). Glycerol was the vehicle most frequently used. Eight studies[34-36,38-42] provided the allergen information in drops; one study[37] provided allergen information in tablets. The median for SLIT and placebo administration was 12 months, with a range of 3 to 32 months. Data on asthma symptom scores were obtained from nine trials,[34-42] and data on medication use were obtained from seven trials.[36-42]

Methodological Quality of Included Studies

All the trials were randomized and DBPC. Each trial reported dropouts, withdrawals, and patients completing the trial; the dropout rate varied between 0% and 17%. Based on the Jadad criteria, four studies[35,37,38,41] received a 5/5 quality score and five studies[34,36,39,40,42] a 4/5 quality score. The κ score for interrater agreement on methodological quality was 0.90 (95% CI, 0.80 to 1.0).

Among the 9 studies included in this review, only two studies[35,41] calculated the statistical power. One study[41] calculated this *a priori* with the purpose of sample size estimation only. Another study[35] carried out a *post hoc* calculation, but neither for asthma score nor rescue medication use. Then, we calculated the *post hoc* statistical power for each study. Four studies[34,37,40,42] had a *post hoc* power between 0.99 and 1.00; one study[36] had a power of 0.79; and four studies[35,38,39,41] had a power of 0.05 to 0.37.

Outcomes

Asthma Symptom Scores: Of the 441 patients included, 232 received SLIT and 209 placebo. SLIT induced a significant reduction in asthma symptoms compared with placebo (SMD, - 1.14; 95% CI, - 2.10 to - 0.18; p = 0.02). A significant interstudy heterogeneity was found (χ^2 test, 144; p > 0.0001; I^2, 94.4%) [Fig 2].
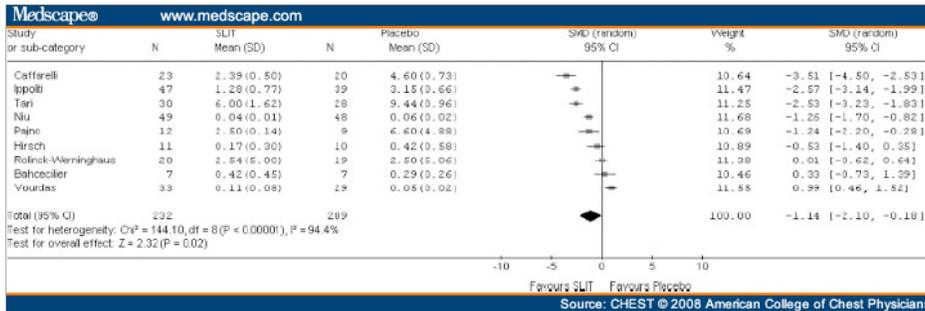

Figure 2.

Outcome: asthma score.

Medication Scores: Three hundred sixty-six patients from seven studies[36-42] were considered for this analysis (192 treated with SLIT; 174 treated with placebo). The results for medication scores following SLIT showed a significant reduction in concomitant rescue drug use (SMD, - 1.63; 95% CI, - 2.83 to - 0.44; p = 0.007) [Fig 3]. A significant heterogeneity between studies also was found (χ^2 test, 130.8; p > 0.0001; I^2, 95.4%).
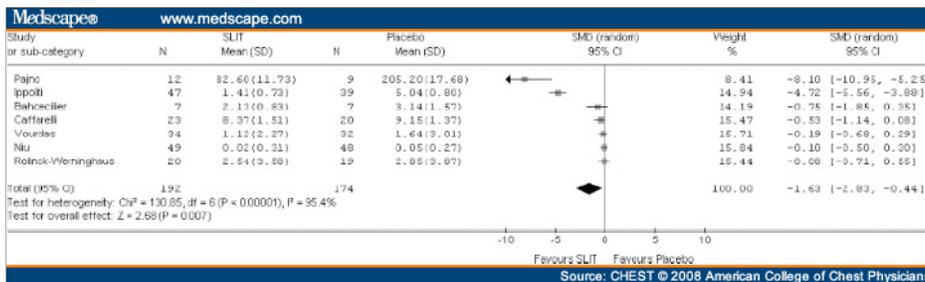

Figure 3.

Outcome: medication score.

We did not find a significant interrater variation for extracted continuous data, when it was plotted and analyzed using the Bland-Altman test (SMD, - 0.005; 95% CI, - 0.02 to -0.01).[23,24] By using Q-Q plots, we found that the studies had different study-specific effects. Those for symptom scores followed a normal distribution. But, the effect sizes for rescue medication scores do not approximate normality.[31]

Sensitivity Analyses

In a subgroup analysis of the trials conducted with mites, SLIT showed a significant effect on reduction of symptom scores (SMD, - 1.36; 95% CI, - 2.16 to - 0.55; p = 0.001) compared to those using pollen SLIT (SMD, - 0.80; 95% CI, - 3.01 to 1.40; p = 0.48). SLIT also reduced significantly the rescue medication use in the mite studies (SMD, - 3.18; 95% CI, - 6.05 to - 0.31; p = 0.03), but not in the pollen studies (SMD, -0.26; 95% CI, - 0.58 to 0.07; p = 0.12). *Post hoc* sensitivity analyses using the fixed-effects model did not substantially change the overall significance for asthma score (SMD, - 1.03; 95% CI, - 1.25 to - 0.81; p > 0.0001) or rescue medication score (SMD, - 0.63; 95% CI, - 0.86 to - 0.40; p > 0.0001).

Adverse Events

Most of the trials reported the occurrence of adverse effects in some patients (SLIT group, n = 81; placebo group, n = 23). In the SLIT group, oral symptoms (n = 33), nasal-ocular symptoms (n = 22), and GI symptoms (n = 9) were the most common. In the placebo group, 11 patients reported oral symptoms. Neither lethal nor severe systemic reactions were registered in the included studies. Severe asthma was reported in three patients by Tari et al[34] and in one patient by Hirsh et al,[35] who attributed the side effects to SLIT overdoses (Table 4).[34-42]

Discussion

Evidence-based medicine has been gaining popularity in the past decade as it integrates the best research evidence with clinical expertise and patient values for diagnosis, prognosis, and therapeutics.[43-46] According to evidence-based medicine, conclusions from metaanalyses of randomized trials represent the most solid evidence source for assessing the efficacy of a treatment.[44-46] Metaanalysis is a statistical procedure that incorporates the results of different independent studies pooled together, thus allowing a more objective appraisal of the evidence than traditional narrative reviews can. Metaanalyses provide a quantitative estimate of treatment effects, and may explain and quantify the heterogeneity among individual studies.[46,47] To warrant their quality, strategies, standards, and rules have been developed, such as the QUOROM.[14]

SLIT is currently used in routine clinical practice in many European countries, and numerous standardized vaccines are available.[48] The US Food and Drug Administration is going on with the registration procedure, and several phase II studies have been initiated in the United States. A task force of the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology has acknowledged the efficacy of SLIT in 2006 in an extensive review.[49] The clinical efficacy of SLIT has been well-ascertained by metaanalyses in rhinitis,[12,50] but concerns are still present about asthma, especially in pediatric patients. Two previous metaanalyses[12,51] attempted to evaluate the efficacy of SLIT in children with respiratory allergies, but both studies failed to demonstrate a clinical benefit, most likely because of the small numbers of studies available at that time. In 2006, we conducted a metaanalysis[13] of 10 randomized clinical trials of pediatric rhinitis, including more than double the number of patients with respect to previous evaluations, and could demonstrate that SLIT induced a significant reduction in both symptom scores and the requirement for medication. Another meta-analysis concerning asthma was then carried out by Calamita et al,[52] who found a reduction in asthma severity when a qualitative assessment was performed, but the quantitative evaluation was not significant. However, in that meta-analysis[52] the inclusion criteria were not restrictive, few outcomes were considered, and both adults and children were analyzed together.

New studies of SLIT in pediatric asthma have been published, and, by using a wide search strategy in electronic databases, we were able to locate a pertinent number of publications.[16,53] We examined in each clinical trial the relevant outcome measures and focused the direct comparison to placebo. We observed a significant statistical reduction in asthma symptoms, which was constant in five of the evaluated studies,[34,37,38,40,42] particularly in those where mite extracts were used. Pollen-treated patients did not experience a significant effect in two of three studies.[33,38] Regarding rescue medication, all of the studies reported a reduction in their use in patients treated with SLIT. We found a significant statistical reduction in the global effect size, attributable mainly to two studies.[38,40] This variability in clinical responses could be explained by diverse treatment durations and allergen doses. On the other hand, it is reasonable that larger studies have a larger effect on the pooled evaluation.

Our review included only 9 studies of the 273 identified in our search, and 441 patients could be evaluated for the effect of the intervention. In this regard, we selected only those trials conducted with a rigorous methodology in order to provide solid conclusions. Thus, the selection of trials had to be, necessarily, very restrictive, and we acknowledge that using a limited number of studies raises the possibility of a second-order sampling error.[54] Indeed, metaanalyses often include small numbers of studies, and heterogeneity is therefore a necessary consequence. Higgins et al[54] evaluated 39 Cochrane reviews and found that 67% of them included ≤ 5 studies, and 20% included ≤ 10 studies. A lower threshold for the number of studies to be included in a metaanalysis has not yet been established.[54,55]

Even though our analysis was not designed to assess safety, the examined trials consistently described the large majority of adverse effects as mild and self-resolving, according to previous literature.[6,56-58] In our analysis, local and GI side effects were the most common. When systemic reactions were evaluated, 28 events categorized as grade II (rhinoconjunctivitis, 22 events; asthma, 6 events) and 3 events were grade III (urticaria) according to the European Academy of Allergy and Clinical Immunology classification.[1] Although extensive descriptions of adverse events were indeed not included in the studies, no patient required hospitalization, and life-threatening or fatal reactions were not reported. Of note, one trial[59] from 2006 has specifically confirmed the safety of SLIT in patients with current asthma.

Concerning the optimal dose for SLIT, this is still a matter of debate since each manufacturer standardizes the extracts based on internal references and the clinical trials used largely variable doses. For this reason, in this metaanalysis it is not possible to derive evidence-based recommendations about allergen doses. Of note, only in 2006 was this subject addressed in two large dose-finding studies,[60,61] which partially elucidated this specific aspect. In one study,[60] a safety evaluation was conducted in seven dosage groups (from 25,000 to 1,000,000 standardized quality tablets). Although no severe or life-threatening event was described, the dose dependency of the side effects was apparent. In another study,[61] participants were randomized to receive 2,500, 25,000, or 75,000 standardized quality grass allergen tablets or placebo for sublingual administration over 18 weeks. Also, this study revealed a clear dose-dependent efficacy and was able to identify the optimal dosage to be used, equivalent to 15 μg of *Phleum pratense* major allergen (*ie*, Phl p 5) a day.

We identified some possible bias sources in the present metaanalysis. First was the heterogeneity of the scores used to evaluate the outcomes. Nonetheless, heterogeneity is not uncommon; about a quarter of metaanalyses have I^2 values of > 50%.[54] To reduce this bias, we utilized some control measures, as the SMD is a robust measure for managing outcome diversity. Moreover, to reduce the bias of interstudy heterogeneity, we used the REM[28,29,46,54,62] (Table 1). Second, four studies[35,38,39,41] with a low statistical power were included, due to the reduced sample size in each trial. These studies were included because one of the rationales for a metaanalysis is that, by combining the samples of the individual studies, the overall sample size can be increased, thereby improving the statistical power of the analysis as well as the precision of the estimates of the treatment effects. The results from small studies are more subject to the play of chance and should therefore be given less weight. REM controls this bias by using a weighted average of the results, in which the larger trials have more influence than the smaller ones. Publication bias is a risk when small studies are excluded[43,46,63-65] (Table

1). Third, individual patient data were not available from each of the studies to test normality. Using graphic methods, we found that effect sizes for symptom scores followed a normal distribution. However, effect sizes for rescue medication scores did not approximate the normality. We have investigated whether a particular model is available to analyze data that are not normally distributed. As has been addressed by the Cochrane Collaboration and other authors,[29,30] methods for conducting a metaanalysis of skewed data are now unavailable, though they are the subject of current research. Fourth, it was not possible to carry out an intention-to-treat analysis because the last observation carried forward for continuous scores was not always available; we analyzed only patients with a final assessment. In this way, an inaccurate global effect due to sample size overestimation was avoided.

Finally, three clinical trials[66-68] about SLIT efficacy in asthmatic children were excluded from our analysis. The study by Rodriguez-Santos[66] included 50 patients; he observed a significant reduction in both disease severity and corticosteroid requirements in treated patients, but the study was not blinded. Bufe et al,[67] found a significant reduction in symptom scores (20%) in patients with severe disease who received SLIT, but target data were not available. Moreover, Velarde-Domínguez et al[68] reported a symptom score reduction (33%) in patients treated with immunotherapy compared with those treated with placebo (p < 0.001); however, SDs were not available.

In this regard, publication bias is an important drawback of systematic reviews and is difficult to avoid. Although we searched for articles in the most important electronic databases available, in all the abstract books of meetings, and in the most disparate languages, it is possible that not all studies were found. Concerning the quality of the studies included, overall it was good (median Jadad score, 4/5); however, we found some methodological deficiencies in some trials, such as inconsistency in the outcome assessment and the general lack of a sample size calculation. It is clear that the small numbers of patients in some studies increases the probability of underestimating the treatment efficacy (type II error). The use of methodological guidelines, such as the Consolidated Standards of Reporting Trials[69] and the US Food and Drug Administration recommendations,[70] could likely improve the evidence level of subsequent trials.

On the other hand, the present metaanalysis has several strengths, such as the restrictive inclusion criteria for the studies, the statistical significant effect size found according to Cohen's criteria (Table 1),[71] the robust statistical methods for controlling both interstudy and intrastudy variability, and the quantitative approach that was carried out.[45,46] Additionally, all of the QUOROM requirements were eventually fulfilled in this review.[14]

Implications for Practice

The present study, using a well-accepted meta-analysis methodology, provides significant evidence that SLIT is clinically effective in the treatment of asthma in children. Due to the favorable safety profile and its potential in modifying the evolution of disease, SLIT is of relevant value in the treatment of asthma in association with standard drug therapy, as recommended in the official documents.

Implications for Research

SLIT trials in children should be properly conducted as soon as possible, according to the recent World Allergy Organization recommendations[75] for specific immunotherapy clinical trials, to determine the most effective dose and regimen of administration. Also, clinical trials in children < 3 years of age should be designed and conducted to fully appreciate the possible preventive effect. Pollen allergen studies are highly suggested by this metaanalysis, since, as previously reported, only a few patients were part of the present analysis. As with past experiences, when few studies are considered, the results can be doubtful; however, it is conceivable to reach significance by including a larger sample size.

Table 1. Description of the Statistical Methods Used in This Review*

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	Study Design				**Participants**				
Study/Year/Journal	Study Design	Quality Score†	Individual Effect Size	Dropout Rate, %	Asthma Type or Severity	Diagnosis	Subjects Included in the Analysis,‡ No.	SLIT, No.	Placebo, No.	Age, yr
Caffarelli et al[37]/2000/Allergy	RCTDB	5/5	0.87	8	Seasonal asthma	R, A, C	43	23	20	4–14
Ippoliti et al[40]/2003/Pediatric Allergy and Immunology	RCTDB	4/5	− 0.87	0	Mild-to-moderate asthma	R, A, C	86	47	39	5–12
Tari et al[34]/1990/Allergologia et Immunopathologia	RCTDB	4/5	− 0.79	12	Persistent asthma	R, A	58	30	28	5–12
Niu et al[42]/2006/Respiratory Medicine	RCTDB	4/5	− 0.53	12	Persistent mild and moderate	R, A	97	49	48	6–12
Pajno et al[35]/2000/Allergy	RCTDB	5/5	− 0.51	13	Mild-to-moderate asthma	A	21	12	9	8–15
Hirsch et al[39]/1997/Pediatric Allergy and Immunology	RCTDB	5/5	− 0.26	5	Mild-to-moderate asthma	R, A	21	11	10	6–16
Rolinck-Werninghaus et al[41]/2004/Allergy	RCTDB	5/5	0.004	17	Seasonal asthma	R, A	39	20	19	3–14
Bahçeciler et al[39]/2001/Pediatric Pulmonology	RCTDB	4/5	0.17	0	Persistent asthma	R, A	14	7	7	7–17
Vourdas et al[38]/1998/Allergy	RCTDB	4/5	0.45	3	Mild asthma	R, A, C	62	33	29	7–17

*RCTDB = Randomized clinical trial, double-blind; R = rhinitis; A = asthma; C = conjunctivitis.
†Jadad score.
‡Postdropout data available for analysis; only patients with asthma were included.

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Table 2. Characteristics of Studies and Participants*

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Study/Year/Journal	Study Design				Participants					
	Study Design	Quality Score†	Individual Effect Size	Dropout Rate, %	Asthma Type or Severity	Diagnosis	Subjects Included in the Analysis,‡ No.	SLIT, No.	Placebo, No.	Age, yr
Caffarelli et al[37]/2000/Allergy	RCTDB	5/5	0.87	8	Seasonal asthma	R, A, C	43	23	20	4–14
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Tari et al[34]/1990/Allergologia et Immunopathologia	RCTDB	4/5	− 0.79	12	Persistent asthma	R, A	58	30	28	5–12
Niu et al[42]/2006/Respiratory Medicine	RCTDB	4/5	− 0.53	12	Persistent mild and moderate	R, A	97	49	48	6–12
Pajno et al[38]/2000/Allergy	RCTDB	5/5	− 0.51	13	Mild-to-moderate asthma	A	21	12	9	8–15
Hirsch et al[35]/1997/Pediatric Allergy and Immunology	RCTDB	5/5	− 0.26	5	Mild-to-moderate asthma	R, A	21	11	10	6–16
Rolinck-Werninghaus et al[41]/2004/Allergy	RCTDB	5/5	0.004	17	Seasonal asthma	R, A	39	20	19	3–14
Bahçeciler et al[39]/2001/Pediatric Pulmonology	RCTDB	4/5	0.17	0	Persistent asthma	R, A	14	7	7	7–17
Vourdas et al[36]/1998/Allergy	RCTDB	4/5	0.45	3	Mild asthma	R, A, C	62	33	29	7–17

*RCTDB = Randomized clinical trial, double-blind; R = rhinitis; A = asthma; C = conjunctivitis.
†Jadad score.
‡Postdropout data available for analysis; only patients with asthma were included.

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Table 3. Treatment Description*

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Study/Year/Journal	Study Treatment						Asthma Treatment+
	Allergen	Control Drug	Units	Vehicle	Duration, mo	Cumulative Dose	
Tari et al[34]/1990/Allergologia et Immunopathologia	Mites	Placebo	STU	AE + phenol	18	365 STU	Antihistamines prn, SAβ₂As
Hirsch et al[35]/1997/Pediatric Allergy and Immunology	Mites	Placebo	μg	Glycerol	12	570 μg	SAβ₂As, ICSs, theophylline prn
Vourdas et al[36]/1998/Allergy	O europaea	Placebo	IR	Glycerol	24	60,000 IR Ole e 1 (8.1 mg)	SAβ₂As, ICSs, oral steroids
Caffarelli et al[37]/2000/Allergy	Holcus, P pratense	Placebo	AU	Tablets	3	37,250 AU	SAβ₂As, ICSs
Pajno et al[38]/2000/Allergy	Dermatophagoides pteronyssinus	Placebo	BU	Glycerol	24	250 μg Der p 1; 125 μg Der p 2	SAβ₂As, ICSs, oral steroids
Bahçeciler et al[39]/2001/Pediatric Pulmonology	Mites	Placebo	IR	Glycerol	6	7,000 IR	Budesonide, 800 μg/d; SAβ₂As as needed
Ippoliti et al[40]/2003/Pediatric Allergy and Immunology	D pteronyssinus	Placebo	BU	Glycerol	6	12 mg	ICS, 400–800 μg/d; albuterol, 250–750 μg/d
Rolinck-Werninghaus et al[41]/2004/Allergy	Grass mix	Placebo	STU	Glycerol	32	188 μg	SAβ₂As, ICSs
Niu et al[42]/2006/Respiratory Medicine	Mites	Placebo	IR	Glycerol	6	1.7 mg Dpt, 3.0 mg Df	SAβ₂As, ICSs, antihistamines

*STU = specific treatment units; IR = index of reactivity; AU = allergic units; BU = biological units; SAB₂A = inhaled short-acting β₂-agonist; ICS = inhaled steroids; AE = amino ethyl; Dpt = Dermatophagoides pteronyssinus; Df = Dermatophagoides farinae; Der p 1/2 = major allergens of D pteronyssinus; Ole e 1 = major allergen of O europaea.

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Table 4. Adverse Effects in the Patients Included in the Safety Evaluation*

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	Patients Reporting Adverse Events, No.					
Study/Year/Journal	Patients Oral Itching (Local)	GI (Local)	Nasal and Ocular (Grade II)	Asthma (Grade II)	Urticaria (Grade II)	Others (NS)
Tari et al[34]/1990/*Allergologia et Immunopathologia*	24/0		4/0	14/0	3/0	3/0
Hirsch et al[35]/1997/*Pediatric Allergy and Immunology*	7/1	6/1			1/0	
Vourdas et al[36]/1998/*Allergy*	10/2	8/2		1/0		1/0
Caffarelli et al[37]/2000/*Allergy*	1/1		0/1			1/0
Pajno et al[38]/2000/*Allergy*	7/1	1/0			1/0	5/1
Bahçeciler et al[39]/2001/*Pediatric Pulmonology*	0					
Ippoliti et al[40]/2003/*Pediatric Allergy and Immunology*	0					
Rolinck-Werninghaus et al[41]/2004/*Allergy*	23/11	15/8		7/3	1/0	
Niu et al[42]/2006/*Respiratory Medicine*	6/7	2/NS	4/NS			

*Values are given as active/placebo. EAACI classifications are in parentheses in column headings. NS = not specified; EAACI = European Academy of Allergy and Clinical Immunology.

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Abbreviation Notes

CI = confidence interval; DBPC = double-blind, placebo-controlled; QUOROM = Quality of Reporting of Metaanalyses; REM = random-effects model; SLIT = sublingual immunotherapy; SMD = standardized mean difference

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