

Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials

Martin Penagos, MD, MSc*†; Enrico Compalati, MD*; Francesco Tarantini, MD*; Rodrigo Baena-Cagnani, MD*; Jose Huerta, MD‡; Giovanni Passalacqua, MD*; and Giorgio Walter Canonica, MD*

Objective: To evaluate the efficacy of sublingual immunotherapy (SLIT) in the treatment of allergic rhinitis in children.

Data Sources: A comprehensive search of the EMBASE, MEDLINE, LILACS, and CINAHL databases from January 1966 to February 10, 2006, was performed.

Study Selection: Randomized, double-blind, placebo-controlled trials of SLIT in the treatment of allergic rhinitis in patients 18 years or younger were selected. Outcomes measured were symptom scores and rescue medication use. Analysis was performed with standardized mean differences (SMDs) and a random-effects model.

Results: Seventy articles were identified and reviewed. Ten studies, published between 1990 and 2004, fulfilled the selection criteria. Five hundred seventy-seven patients were initially included in the studies. Of these patients, 484 (245 SLIT and 239 placebo) had a final clinical evaluation and could be evaluated. A relevant heterogeneity due to widely differing scoring systems was found. Overall, there was a significant reduction in both symptoms (SMD, 0.56, 95% confidence interval, 1.01–0.10; $P = .02$) and medication use (SMD, 0.76; 95% confidence interval, 1.46–0.06; $P = .03$) after immunotherapy. The subanalyses performed for treatment duration and type of allergen showed that SLIT for more than 18 months and with pollen extracts was effective compared with SLIT courses shorter than 18 months and with mites.

Conclusion: The results of this meta-analysis showed that, compared with placebo, SLIT with standardized extracts is effective in pediatric patients with allergic rhinitis.

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INTRODUCTION

Allergen-specific immunotherapy, together with drug therapy and allergen avoidance, is a cornerstone in the management of respiratory allergy in both adults and children.^{1–4} Specific immunotherapy has been widely used for 90 years as a symptom-

atic treatment for allergic diseases and is now recognized as an immunomodulatory agent that alters the immune response to allergens. Sublingual immunotherapy (SLIT) has been regarded as a viable alternative to subcutaneous immunotherapy (SCIT) since its introduction in 1986, especially because of its optimal safety profile. During the last 20 years, increasing evidence on the clinical efficacy of SLIT in rhinitis and asthma has been provided, together with objective evaluations of its safety and compliance.^{5–10} Based on controlled and postmarketing surveillance studies, an international panel of experts, on behalf of the World Health Organization, in the recent Allergic Rhinitis and Its Impact on Asthma document accepted SLIT for routine clinical use in adults and children, with the same indications of SCIT. Currently, SLIT is widely used in many European countries.^{10–13} Furthermore, recently Plaut and Valentine,¹⁴ in a critical and comprehensive review of allergic rhinitis treatments, quoted the Allergic Rhinitis and Its Impact on Asthma document as one of the official sources of evidence.

* Allergy & Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy.

† Infants Service, Pediatrics Hospital, CMN “Siglo XXI”, IMSS, Mexico City, Mexico.

‡ Allergy Service, National Pediatrics Institute, Mexico City, Mexico.

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Recently, Wilson et al¹⁵ published a meta-analysis of 22 double-blind, placebo-controlled SLIT trials, involving 979 patients with allergic rhinitis. Overall, there was a significant reduction in symptoms and medication use, but the subanalysis performed in children could not find a significant effect on the considered outcomes due to the small population size studied. Another meta-analysis by Olaguibel and Álvarez-Puebla,¹⁶ including 232 pediatric patients, found a nonstatistically significant reduction in nasal scores. Nevertheless, during the last 3 years, new pediatric trials have been published, and new data for meta-analysis have become available.^{17–22} The objective of this study was to evaluate the efficacy of SLIT in treating rhinitis in pediatric patients (3 to 18 years old, as defined by the American Academy of Pediatrics^{23–25}).

METHODS

Search Strategy

We performed a comprehensive search of the MEDLINE, EMBASE, LILACS, and CINAHL databases to identify all clinical trials, published between January 1, 1966, and February 10, 2006, with SLIT in children with allergic rhinitis. The search was performed using the following keywords: *sublingual immunotherapy, children, adolescent, allergic rhinitis, hay fever, swallow, drops, oral, oromucosal, desensitization, randomized clinical trials, and meta-analysis*. The search was further augmented by scanning references of identical articles and reviews. Abstracts of relevant meetings were also searched.

Types of Patients

Patients 18 years or younger with a history of allergic rhinitis with or without allergic asthma and/or conjunctivitis in whom the causal allergen was identified and IgE sensitization was ascertained by prick test and/or specific IgE assays were studied. Trials that dealt with asthma alone were not included.

Types of Intervention

We considered SLIT whether or not the allergen was subsequently swallowed. All appropriate allergens were considered at all doses and all durations of treatment.

Study Selection

Two investigators (M.P., E.C.) independently evaluated studies for inclusion. Clinical trials were considered in the review if they were randomized, placebo controlled, and double-blinded. Trial eligibility was determined on full-text format by 2 authors (R.B.C., F.T.), which was checked by the principal investigator (G.W.C.). The observed percentage agreement between the investigators for the evaluation of inclusion was calculated by using the κ test.^{26,27}

Evaluation of Validity

Trials were rated for methodologic quality in duplicate using the Jadad scale and scored out of a maximum of 5.^{28,29} An interrater agreement was also calculated by using the κ statistic.^{26,30}

Data Extraction

The outcomes measured were both the nasal symptom and medication scores. Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. We planned to perform an intention-to-treat analysis, and we tried to include dropouts in the analysis if last observation carried forward for both continuous scores was available; if not, we included dropouts in the analysis of patients with a final evaluation. Scores from studies that evaluated seasonal pollens were adjusted for local peak allergen counts. When numeric data were not available, graphics were digitalized using DigitizerIt 1.5.7.³¹ Additionally, we contacted the investigators of included studies to obtain more information for data extraction.

Data Synthesis

Outcome data analyzed was quantitative and continuous (symptom scores, medication scores), but the authors of the original studies used a wide variety of scoring systems and scales for symptoms (most frequently a daily quantification of nasal symptoms entered on a patient's diary and subsequently summarized and averaged) and medication use (typically a daily score reflecting use of nasal sprays and antihistamines entered in a patient's diary). For those studies that assessed a treatment effect from baseline, the investigators provided the SD of the distribution separately for baseline and posttreatment values for both the active treatment and placebo groups. The baseline and posttreatment SD were then combined for the analysis, assuming independence.

Since outcome variables were given in continuous data that were expressed in different scales, we calculated the standardized mean difference (SMD). This measure provides the effect size of the intervention in SD units, and its value does not depend on the measurement scale. Heterogeneity was calculated with the χ^2 and the I^2 test. The I^2 statistic explores the degree of heterogeneity and can be interpreted as the proportion of the observed discrepancy in the estimation of the effect, within a group of trials, which cannot be accounted for by random variation. All results are reported with 95% confidence intervals (CIs) and all P values are 2-tailed.^{32,33}

Given the significant heterogeneity found among the results of the included studies, the random-effects model was used because it accounts for the possibility of significant interstudy heterogeneity and provides wider CIs than fixed-effect models.³⁴ Analysis was performed with the RevMan 4.2.7 program.³⁵

RESULTS

Search Results

The initial scanning identified 136 articles, 70 of which were potentially relevant trials on SLIT use in patients with allergic rhinitis (Fig 1). Twenty-seven studies were randomized and 10 met inclusion criteria for the meta-analysis.^{17–20,36–41} The κ statistic for interrater agreement on study eligibility was 0.90 (95% CI, 0.80–1.0). Consensus was reached on the remaining

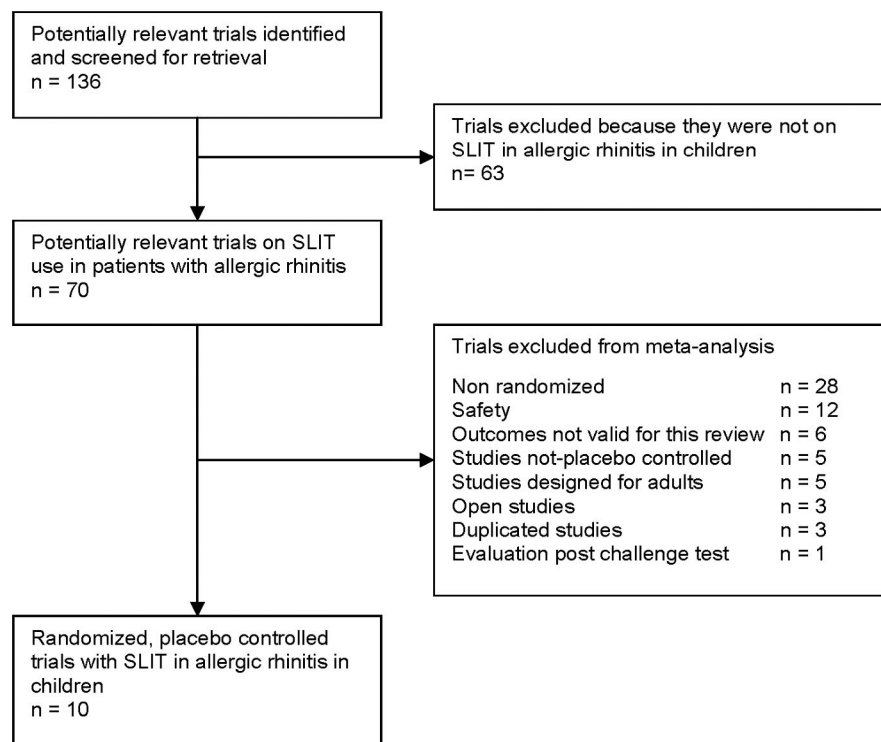


Figure 1. Classification of material reviewed for this meta-analysis. SLIT indicates sublingual immunotherapy.

trials. Trials were excluded from the review for the following reasons: 3 trials were not blinded, 5 trials did not compare SLIT with placebo, 3 trials were duplicated, and 6 studies had unsuitable data (not designed for children or designed for safety evaluation).

Trial Characteristics

Table 1 summarizes the characteristics of the studies and the

participants included in the meta-analysis. The trials globally enrolled 577 participants. Of them, 484 concluded the studies and could therefore be analyzed. The age range of participants was 3 to 18 years. Each trial included a median of 33 participants (range, 14–130). All patients had a diagnosis of allergic rhinitis: 59% asthma and 73% conjunctivitis.

Table 2 gives the characteristics of treatments. The SLIT used in the studies was standardized in the following units:

Table 1. Characteristics of Studies and Participants

Source, y	Study design				Participants					
	Study design	Evidence level	Quality score*	Informed consent	Diagnosis	No.†	SLIT	Placebo	Age range, y	Dropout rate, %
Tari et al, ³⁶ 1990	RCTDB	Ib	4/5	Yes	R, A	58	30	28	5–12	12
Hirsch et al, ³⁸ 1997	RCTDB	Ib	5/5	Yes	R, A	21	11	10	6–16	5
Vourdas et al, ³⁷ 1998	RCTDB	Ib	4/5	Yes	R,A,C	66	34	32	7–17	3
La Rosa et al, ³⁹ 1999	RCTDB	Ib	4/5	Yes	R,A,C	33	16	17	6–14	19
Caffarelli et al, ⁴⁰ 2000	RCTDB	Ib	5/5	Yes	R,A,C	34	17	17	4–14	8
Bahceciler et al, ⁴¹ 2001	RCTDB	Ib	4/5	Yes	R, A	14	7	7	7–18	0
Ippoliti et al, ¹⁷ 2003	RCTDB	Ib	4/5	Yes	R,A,C	33	18	15	5–12	0
Wüthrich et al, ¹⁸ 2003	RCTDB	Ib	4/5	Yes	R, A	22	10	12	4–11	21
Rolinck-Werninghaus et al, ¹⁹ 2004	RCTDB	Ib	5/5	Yes	R, A	77	39	38	3–14	17
Bufe et al, ²⁰ 2004	RCTDB	Ib	5/5	Yes	R, A	126	63	63	9 ± 2.8	18

Abbreviations: A, asthma; C, conjunctivitis; R, rhinitis; RCTDB, randomized clinical trial, double-blind; SLIT, sublingual immunotherapy.

* Jadad scale.

† After dropout. Available data for analysis.

Table 2. Characteristics of Study Treatments

Source, y	Treatment						Available outcomes
	Allergen	Control drug	Units	Vehicle	Duration, mo	Cumulative dose	
Tari et al, ³⁶ 1990	Mites	Placebo	STU	AE and phenol	18	365 STU	Nasal symptom score
Hirsch et al, ³⁸ 1997	Mites	Placebo	Micrograms	Glycerol	12	570 μ g	Nasal symptom score
Vourdas et al, ³⁷ 1998	Olive	Placebo	IR	Glycerol	24	30,000 IR	Nasal symptom score, rescue medication
La Rosa et al, ³⁹ 1999	<i>Parietaria</i>	Placebo	IR	Glycerol	24	75,000 IR	Nasal symptom score, rescue medication
Caffarelli et al, ⁴⁰ 2000	<i>Holcus, Phelum, Poa</i>	Placebo	AU	Tablets	3	37,250 AU	Nasal symptom score, rescue medication
Bahceciler et al, ⁴¹ 2001	Mites	Placebo	IR	Glycerol	6	7,000 IR	Nasal symptom score, rescue medication
Ippoliti et al, ¹⁷ 2003	<i>Dermatophagoides pteronyssinus</i>	Placebo	BU	Glycerol	6	12 mg	Nasal symptom score, rescue medication
Wüthrich et al, ¹⁸ 2003	Grass mix	Placebo	Micrograms	Glycerol	24	139.88 μ g	Nasal symptom score, rescue medication
Rolnick-Werninghaus et al, ¹⁹ 2004	Grass mix	Placebo	STU	Glycerol	32	188 μ g	Nasal symptom score, rescue medication
Bufe et al, ²⁰ 2004	Grass mix	Placebo	AU	Diluent	36	2,625,000 AU	Nasal symptom score

Abbreviations: AU, allergic units; BU, biologic units; IR, index of reactivity; STU, specific treatment units.

allergic units (AU), biologic units (BU), index of reactivity (IR), specific treatment units (STU), and micrograms. The allergens used in the studies were mites ($n = 4$), grasses mix ($n = 3$), *Parietaria* ($n = 1$), olive ($n = 1$), and pollen mix ($n = 1$). Glycerol was the vehicle most frequently used. Nine studies provided the allergen in drops and 1 study in tablets. The mean duration of study drug or placebo administration was 21 months (range, 3–36 months). The cumulative dose was variable and measured in different units. Data on nasal symptom score were obtained from 10 trials,^{17–20,36–41} and data on medication use were obtained from 7 trials.^{18–20,37,39–41}

Methodologic Quality of Included Studies

All of the trials were randomized, double-blind, and placebo controlled. All authors required informed consent. Each trial

reported dropouts and withdrawals and analyzed patients who completed the trial; the dropout rate ranged from 0% to 21%. According to the Jadad scale, 4 studies received a quality score for blinding of 5 of 5 and 6 studies received a score of 4 of 5. The κ score for interrater agreement on methodologic quality scores was 1.0.

Nasal Symptoms Scores

For this analysis, we included 484 patients; 245 received SLIT and 239 placebo. SLIT induced a significant reduction in nasal symptoms compared with placebo (SMD, 0.56; 95% CI, 1.01–0.10; $P = .02$). A significant inter-study heterogeneity was found ($\chi^2 = 47.73$; $P < .001$; $I^2 = 81.1\%$) (Fig 2).

Review: Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta-analysis of randomized controlled trials.
Comparison: 01 Nasal score rhinitis
Outcome: 01 Nasal score rhinitis

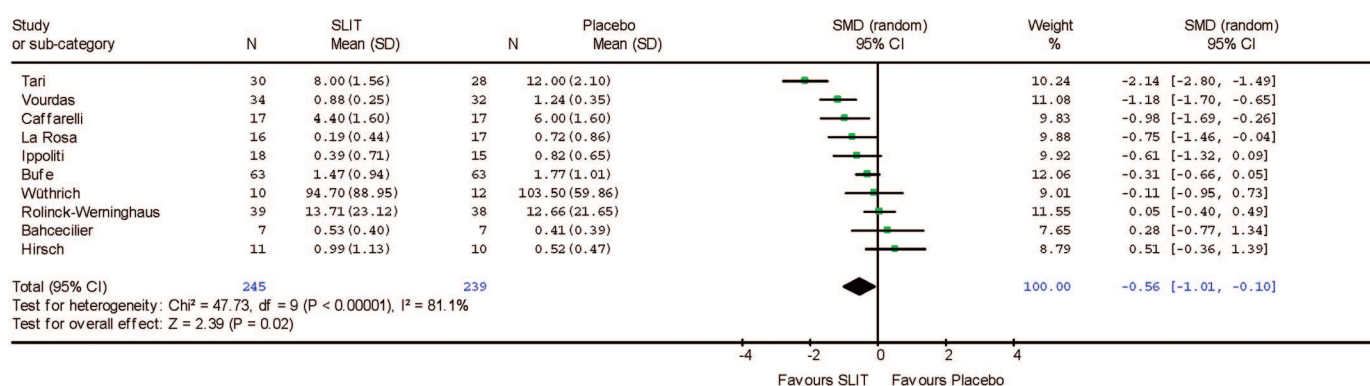


Figure 2. Nasal symptom scores. CI indicates confidence interval; SLIT, sublingual immunotherapy; SMD, standardized mean difference.

Table 3. Subanalysis of Efficacy (Nasal Symptoms) According to Treatment Characteristics

Subanalysis	No. of studies	No. of patients	SLIT	Placebo	SMD (95% CI)	P value
Pollen	6	358	179	179	-0.53 (-0.94 to -0.12)	.01
Mites	4	126	66	60	-0.52 (-1.77 to 0.72)	.41
>18 months' duration	6	382	192	190	-0.73 (-1.35 to -0.12)	.02
≤18 months' duration	4	102	53	49	-0.26 (-0.95 to 0.44)	.47

Abbreviations: CI, confidence interval; SLIT, sublingual immunotherapy; SMD, standardized mean difference.

Subgroup and Sensitivity Analysis

We performed a subgroup analysis evaluating the trials that used SLIT for pollens or mite. The reduction was significant (SMD, 0.53; 95% CI, 0.94–0.12; $P = .01$) with pollens compared with mite SLIT (SMD, 0.76; 95% CI, 1.77–0.72; $P = .41$). Similarly, analyses of patients who received SLIT for less than 18 months did not show a significant effect on symptom scores (Table 3). Sensitivity analysis showed that this study was robust when we used a fixed-effects model.

Medication Scores

Two hundred seventy-nine patients from 7 studies were considered for this analysis, 141 treated with SLIT and 138 placebo. The medication scores after SLIT showed a significant reduction in medication use (SMD, 0.76; 95% CI, 1.46–0.06; $P = .03$) (Fig 3). A significant heterogeneity among studies also was found ($\chi^2 = 41.52$; $P = .03$; $I^2 = 85.5\%$).

Adverse Effects

All authors reported the number of adverse effects (SLIT: $n = 132$; placebo: $n = 28$). In the SLIT group, oral ($n = 51$), nasal-ocular ($n = 24$), and gastrointestinal ($n = 23$) adverse effects were the most common. In the placebo group, 15 patients reported oral itching. Neither lethal nor severe systemic reactions were reported in included studies. Four patients were reported to have severe asthma, 3 active patients in the study by Tari et al³⁶ and 1 placebo patient in the study by La Rosa et al.³⁹ Tari et al attributed these to SLIT overdose.^{36,39} Overall, SLIT treatments were well tolerated (Table 4).

DISCUSSION

Specific immunotherapy proved to be an efficient treatment for patients with respiratory and Hymenoptera venom allergy. Its usefulness has been highlighted in a recent World Health Organization report, which advocates its use in selected patients with specific IgE antibodies to clinically relevant allergens. SLIT is currently accepted as a viable alternative to SCIT, and its efficacy in adults with rhinitis is supported by a meta-analysis evaluation,¹⁵ whereas there are still too few trials in asthma to allow an efficient meta-analysis. On the other hand, the safety of SLIT has been well ascertained in adults and children, even in those younger than 5 years.^{42,43}

Since immunotherapy is a biological response modifier that is capable of altering the natural course of the disease and reducing the risk of asthma,^{22,44} its use at the early stages of the disease is recommended, and children would probably represent the ideal population in whom to achieve the maximum benefit. One previously published meta-analysis of SLIT failed to detect a significant clinical effect in children, although the authors acknowledged that the number of pediatric patients at that moment was too small.¹⁵

Since new studies have been recently published, we repeated the meta-analysis and could include more than double the number of patients considered in the previous article. We examined, in each clinical trial, the relevant outcome measures and focused on the direct comparison to placebo. The results of the meta-analysis were significantly in favor of SLIT vs placebo in the considered pediatric population. The sensitivity and subgroup analyses showed that the type of

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Comparison: 02 Medication score rhinitis
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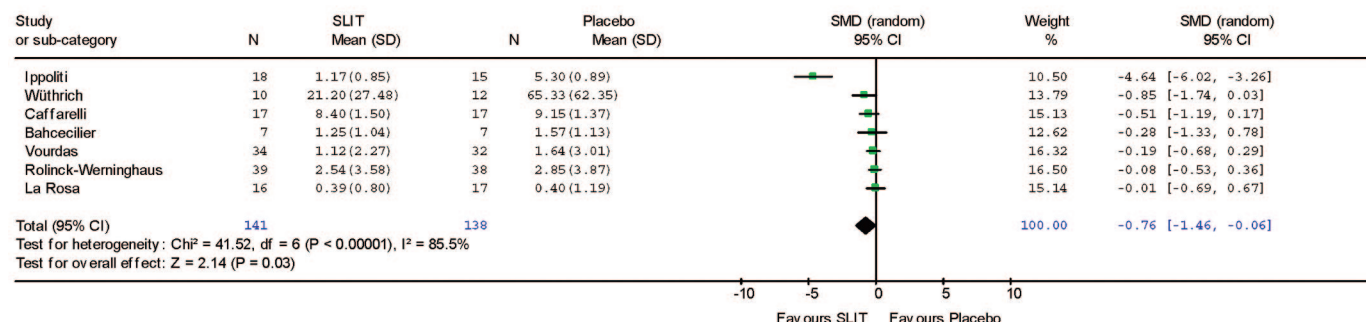


Figure 3. Rescue medication scores. CI indicates confidence interval; SLIT, sublingual immunotherapy; SMD, standardized mean difference.

Table 4. Reported Adverse Effects in the Active and Placebo Patients Included in the Safety Evaluation

Source, y	No. of patients reporting adverse events (active/placebo)						
	Patients	Oral itching	Gastrointestinal	Nasal-ocular	Asthma	Urticaria	Others
Tari et al, ³⁶ 1990	32/0		4/0	14/0	11/0	3/0	
Hirsch et al, ³⁸ 1997	7/1	6/1			1/0		
Vourdas et al, ³⁷ 1998	10/2	8/2		1/0			1/0
La Rosa et al, ³⁹ 1999	31/13	5/4	19/1	2/2	0/2	1/1	4/3
Caffarelli et al, ⁴⁰ 2000	1/1		0/1				1/0
Bahceciler et al, ⁴¹ 2001	0						
Ippoliti et al, ¹⁷ 2003	0						
Wüthrich et al, ¹⁸ 2003	0						
Rolinck-Werninghaus et al, ¹⁹ 2004	23/11	15/8		7/3	1/0		
Bufe et al, ²⁰ 2004	18/0	17/0				1/0	

allergen used, the treatment duration, and the allergen dose influenced the efficacy of SLIT. SLIT courses shorter than 18 months appeared not to be effective, whereas more prolonged treatments were effective. In fact, the effect size for patients treated for more than 18 months was -0.73 (95% CI, -1.34 to -0.12), whereas the effect size was 65% smaller with shorter courses.

Another noteworthy aspect is the observation that the efficacy analysis by Bufo et al could not detect clinically significant differences between long-term SLIT and placebo, and only the subanalysis of patients with severe disease showed a significant improvement.²⁰ As a general opinion, immunotherapy is considered more effective in monosensitized or paucisensitized patients. This meta-analysis confirms this point of view, because all but one of the studies in polysensitized children did not show significant results in terms of efficacy. Only the study by Caffarelli et al⁴⁰ reported a significant clinical efficacy. However, it is relevant to consider that the children included were sensitized to cross-reacting allergens (grass pollen) and the immunotherapy was a mixture of grass pollen allergens.

SLIT was found to be effective with pollens but not with mites. One possible explanation of this fact could be the allergen dose. In fact, in the study that used a cumulative dose of 12 mg of major allergen, the clinical efficacy was clearly greater than in trials that used lower dosages,^{17,36,38,41} although an absolute comparison cannot be made due to the variable dose units used in the studies. Recently, Niu et al⁴⁵ published a randomized, placebo-controlled, double-blind study that assessed the efficacy of SLIT to mites in children with mild to moderate asthma. In this study, SLIT significantly reduced symptom scores and improved the pulmonary function compared with placebo, and patients received a cumulative dose of 41,824 IR, equivalent to 1.7 mg of Der p 1 and 3.0 mg of Der f 1 in 24 weeks. Thus, high allergen doses in a short induction period seem to be effective and safe. However, looking at the available literature, the optimal maintenance dose (ie, to obtain the maximum effect and to achieve long-term efficacy) still has to be determined. The effective dose of allergen for SLIT ranges from approximately 5 to 375 times the doses of SCIT. This interval is wide, and there is no

convincing proof that one particular dosage performs better than others. Furthermore, there is no clear evidence that the efficacy is dose dependent within the mentioned range.

Rolinck-Werninghaus et al¹⁹ found a higher difference in nasal symptom score reduction in patients who received SLIT, yet this finding was not significant. The authors stated that patients treated with SLIT in this study had a more severe clinical condition than the patients treated with placebo; therefore, this lack of homogeneity between the 2 groups represents an important factor that could have contributed to such a large difference. Groups were not homogenous probably because the study design was multicentric and the randomization method did not allow allocation of patients in a balanced way. Even correcting the values with the maximum pollen count, according to the data provided by the author, these differences were not statistically significant (SLIT: -9.08 ± 32.53 vs placebo: -3.03 ± 23.74).

SLIT safety has been widely evaluated in previous studies.^{9,12,13} Although our analysis was not designed to evaluate this outcome, almost all adverse effects were considered mild, and patients treated in included studies did not present with fatal or severe systemic reactions.

We identified some bias sources in our study. Several trials did not have homogeneity in studied outcomes; outcomes are important in detecting significant modification in a patient's clinical condition. It is essential that these measures are valid (ie, that it measures exactly what has to be measured) and responsive (ie, that it is sensitive to change). For this reason, we used a robust measure to control the outcome diversity (SMD). To reduce the bias given for interstudy heterogeneity, we used the random-effects model. Since we found significant heterogeneity, we performed a sensitivity analysis of SLIT efficacy. Treatment effect size was maintained even when the individual trial with the most significant SMD (the study by Tari et al) was excluded from the analysis³⁶ (overall SMD, -0.39 ; 95% CI, -0.74 to -0.04 ; $P = .03$; $I^2 = 65\%$).

Some recently published trials have reported that SLIT is an effective treatment; however, they have been excluded from this analysis because of the lack of an appropriate control group. Consequently, SLIT efficacy could not be well established.^{21,22} Publication bias is an important risk to the

validity of systematic reviews and is difficult to manage except through the prospective registration of all randomized controlled trials on human participants. Although we searched for articles in the most important electronic databases available, in all the abstract books, and in the most diffuse languages, it may be possible that not all the studies have been included.

Even if the Jadad scale scores of the studies included were good (median score, 4 of 5), we found some methodologic problems in the included trials, such as the lack of description of the randomization method (table of random numbers, computer generated) or the absence of sample size calculation. The small numbers of patients in some of the included studies increase the probability of underestimating the treatment efficacy (type II error). We are confident that the use of methodologic guidelines like CONSORT and scores in agreement with the Food and Drug Administration recommendations on monitoring clinical symptoms in allergic diseases (<http://www.fda.gov/cder/guidance/index.htm>) could improve the evidence level of subsequent trials.^{20,46,47}

On the other hand, this analysis has diverse strengths. We included 2-fold more patients in contrast to previous reviews. This resulted in a significant effect size according to the Cohen criteria.⁴⁸ All authors were contacted to extend available data in articles, especially concerning the exact SDs. Also, we used solid statistical methods to control both interstudy and intrastudy variability, and several objective scores were used to evaluate both study design and methodologic quality. Since an intention-to-treat analysis was not possible, because last observation carried forward for continuous scores was not always available, we just analyzed patients with a final evaluation. In this way, an inaccurate global effect due to sample size overestimation was avoided.

Implications for Practice

The present study, using a well-accepted meta-analysis method, proved that SLIT is effective as an early treatment of allergic rhinitis in children. Immunotherapy has the potential to modify the natural history of the disease. As a consequence, SLIT should not be considered as an ultimate treatment of respiratory allergy after the failure of drug therapy. SLIT treatment should be used in children for at least 18 months.

Implications for Research

A SLIT trial in children sensitive to mites should be properly performed as soon as possible to investigate the potential clinical effect of SLIT in children using this allergen extract. Also, a clinical trial in children younger than 3 years should be appropriately designed and conducted to conform with scientific data on the assumption of using SLIT in very young children. We recommend the design of future trials following CONSORT recommendations.

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Requests for reprints should be addressed to:
Giorgio Walter Canonica, MD
Allergy and Respiratory Diseases Clinic
DIMI
University of Genoa
Pad. Maragliano
L. go R. Benzi 10
16132 Genoa, Italy
E-mail: canonica@unige.it