

## Review article

# Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

**Background:** Sublingual immunotherapy (SLIT) is effective and safe in the treatment of allergic rhinitis. However, there is no meta-analysis in asthma treatment.

**Methods:** The clinical efficacy of SLIT for asthma was evaluated through a systematic review with meta-analysis. MEDLINE (1966–2005), EMBASE (1974–2005), LILACS (1982–2005), and the Cochrane Library were searched for related literature in any language. Randomized-controlled clinical trials (RCT) on SLIT in asthma treatment for adults and children were selected. From 119 citations, 25 studies with 1706 patients were included in this meta-analysis. For each report, quality scores were assigned and data were extracted in relation to the outcomes analyzed: asthmatic symptoms, use of asthma medications, lung function, and bronchial provocation.

**Results:** According to the Jadad quality method, 64% of the studies were assigned scores of 4 or 5. Immunotherapy was seen to significantly reduce asthma severity when parameter compositions were all analyzed by categorical outcomes. There was a nonsignificant reduction in asthma symptoms when analyzed using standardized mean differences. No severe reactions were observed.

**Conclusions:** This meta-analysis found that SLIT is beneficial for asthma treatment albeit the magnitude of the effect is not very large. Moreover, it is a safe alternative to the subcutaneous route. More RCT with standardization of symptom scores and medications are needed in order to contribute further to this subject.

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The efficacy of subcutaneous-specific immunotherapy (SCIT) is demonstrated in asthma (1, 2) but concerns about it were raised (3, 4). In SLIT, two meta-analyses exist, but one evaluated rhinitis treatment (5, 6) and the other (7) evaluated allergies in general, but only in children.

The objective of the present review was therefore to assess the efficacy and safety of SLIT in asthma using a meta-analysis following the Cochrane Collaboration method.

## Methods

### Types of studies

Only randomized-controlled trials (RCTs) were included. In addition to double-blind studies, open studies were also reviewed.

### Types of intervention

The intervention investigated was immunotherapy delivered by the sublingual route, with or without subsequent swallowing. All types of allergen, all doses, and all lengths of treatment were considered.

### Types of outcome measurements

The following parameters were evaluated.

- Asthmatic symptoms, by means of a symptom score entered on a diary card, with subsequent totaling and averaging. The following asthmatic symptoms were generally quantified daily: dyspnea, cough, wheeze, and chest tightness.
- Asthmatic medication requirement, by means of a score entered on a diary card to evaluate the reduction in the need for medication, with subsequent totaling and averaging. This generally involved quantification of the use of corticoids and bronchodilators in particular.

- Respiratory function tests, including: peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV<sub>1</sub>), and forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25–75%</sub>).
- Nonspecific bronchial provocation (to histamine or methacholine).
- Adverse effects.

#### Literature search

MEDLINE (1966–2005), EMBASE (1974–2005), LILACS (1982–2005), and the Cochrane Controlled Trials Register were searched using the terms: 1, asthma or wheez\*; 2, immunother\* or hyposen\* or desen\* and sublingual; 3, #1 and #2.

The search was undertaken by using the search strategy of highly sensitive filters for RCTs (8). It was extended to relevant studies cited in the reference lists of some reviews that were identified as relevant.

The search was undertaken independently by two reviewers (ZC, ABP), who were both clinical investigators. Final decisions regarding inclusion of studies in the review were made by consensus, and the agreement between the two reviewers was analyzed by using the Kappa test (9). Studies published in languages other than English were considered if the translated abstract or the title indicated that the study might be an RCT on allergen immunotherapy for asthma.

#### Data extraction

All the studies selected were analyzed and further information was requested from the authors when necessary. Following this, the methodological quality was assessed.

Each report chosen was read in detail and relevant data were extracted: study type, methodology, population size, description of the subjects, type of intervention, duration of treatment, type and quantity of allergen used, and outcome measurements. The data were extracted from the reports by one of the authors (ZC) and checked by another author (ABP). Discrepancies were resolved by consensus.

#### Methodological quality

Methodological quality measurements were made using two methods: the Cochrane Handbook (8) and the Jadad quality score (10).

The quality measurements were made by one of the authors (ZC) and checked by another author (ABP).

#### Data analysis

The outcome data extracted from the earlier studies that were included in this study were entered into the REV MAN 4.2 software (11) for statistical analysis.

The majority of the studies presented continuous outcomes, and these were analyzed as standardized mean differences (SMDs), with calculation of 95% confidence intervals (CI). The SMD was used because many studies have measured the same outcomes on different scales.

Categorical outcomes were analyzed as risk difference (RD) and relative risk (RR) both with calculation of the 95% CI. The number needed to treat (NNT) or the number needed to harm (NNH) were also estimated. For categorical outcomes, the analysis was performed according to the intention-to-treat method and for con-

tinuous outcomes, the results were analyzed only in relation to the participants who completed the trial. Because of significant heterogeneity when SMDs were used, the random effects model was utilized to obtain summary statistics for the overall efficacy of sublingual immunotherapy (SLIT). The chi-squared test and I<sup>2</sup> test (8) were performed to assess the heterogeneity between the studies, taking *P*-values of <0.1 to indicate a significant difference between studies. Sensitivity analysis was performed.

## Results

### Search findings

In the first screening, only the abstracts and titles were reviewed. If the information was found to be insufficient, the analysis was extended to the full text. We identified 119 references among the abstracts and titles, of which 54 were immediately considered unsuitable for inclusion (review articles, nonrandomized or noncontrolled trials, studies involving participants with rhinitis and/or conjunctivitis without asthma, and studies without clinically relevant outcomes). The Kappa test between the reviewers showed interobserver agreement of 84%, which was considered to be an excellent result.

A total of 65 studies were therefore reviewed in detail, of which 40 were excluded: 10 with insufficient information (12–21), 15 not randomized (22–36), eight involving participants with rhinitis and/or conjunctivitis rather than asthma (37–44), four using other immunotherapy routes (45–48), three without clinically relevant outcomes (49–51). Insufficient information was one of the main causes of exclusion, and these studies were excluded because no standard deviations were presented and their outcomes were shown as columns and other graphs that made it impossible to use their data in meta-analysis. Although attempts were made to contact the authors to get the necessary information, in some cases no responses were obtained. The flow diagram for the study selection method is illustrated in Fig. 1.

### Characteristics of the studies included

Using the above selection method, 25 studies with 1706 patients were included in this meta-analysis (52–76). The studies included and their methods, participants, interventions, and outcomes are listed in Table 1.

In these studies, the asthma manifestation was generally mild to moderate. Ten trials enrolled only children (54, 58, 61–63, 65, 66, 72, 73, 76). A wide range of allergens was administered: mites in eight studies (54, 55, 58, 61, 62, 64, 67, 72), pollen in 14 (52, 53, 56, 57, 60, 63, 65, 66, 68, 70, 71, 73, 75, 76), a mixture of allergens in two (59, 74), and latex in one (69).

The extracts were generally administered in the form of drops, with the subject fasting. The drops were kept under the tongue for 1–3 min and then swallowed. However, in one study (57), the patients spat out after

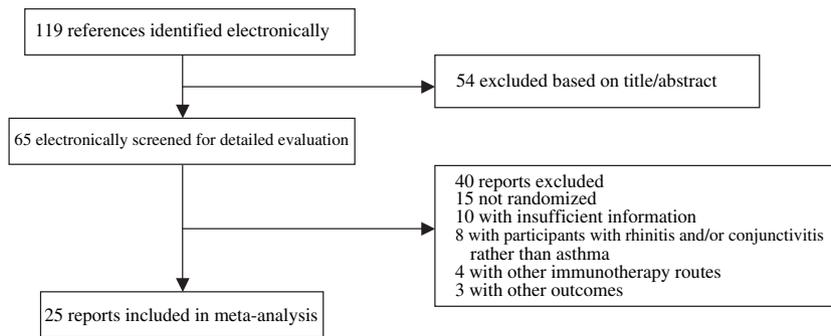


Figure 1. Flow diagram for the study selection method for inclusion in the meta-analysis.

Table 1. Randomized-controlled trials on allergen-specific sublingual immunotherapy for asthma included in this systematic review

Study	Methods	Participants	Allergen	Treatment duration, cumulative dose (µg)	Outcomes	Quality [Jadad (10) and Higgins (8)]
Ariano et al. (52)	RCDBCT	20 adults and children with A and RC	Pollen	1 year	AI S, AI M, NPT, SE	3B
Ariano et al. (53)	RCDBCT	30 adults and children with A and RC	Pollen	3 months	AI S, AI M	3B
Bahçeciler et al. (54)	RCDBCT	15 children with A and R	Mite	6 months (560)	AS, AM, RFT, BPT, SE	5A
Bousquet et al. (55)	RCDBCT	85 adults and children with A	Mite	2 years (4200)	AS, AM, S&M, RFT, BPT, SE	4B
Drachenberg et al. (56)	RCDBCT	68 adults and children with A and RC	Pollen	6 months	S&M, SkT	3B
Feliziani et al. (57)	RCDBCT	34 adults and children with A and RC	Pollen	3 months	AS, AI S, AM, AI M, SE	5A
Hirsch et al. (58)	RCDBCT	30 children with A and R	Mite	1 year (570)	AS, BPT, SeT, SkT, NPT, SE	5A
Marogna et al. (59)	RCOCT	511 adults and children with A and R	Mite, pollen, mould, and dander	3 years (1170)	S&M, RFT, BPT, SE, Ad	3B
Marogna et al. (60)	RCOCT	79 adults with A and R	Pollen	3 years (306)	AI S, NE, AM, RFT, BPT, SE	2B
Niu et al. (61)	RCDBCT	110 children with A	Mite	6 months (3 mg)	AS, AM, SE	4B
Novembre et al. (62)	RCDBCT	20 children with A	Mite	1 year	AS, AM, SE	5A
Novembre et al. (63)	RCOCT	113 children with RC	Pollen	1 year (130)	AI S, AI M, AS, S&M, SE	3B
Pajno et al. (64)	RCDBCT	24 adults and children with A	Mite	2 years (250)	AS, AM, SE	5A
Pajno et al. (65)	RCDBCT	38 children with A and RC	Pollen	13 months (20.3)	AS, AI S, AI M, SE	5A
Pajno et al. (66)	RCDBCT	30 children with A	Pollen	2 years (40)	RFT, BPT	5A
Passalacqua et al. (67)	RCDBCT	20 adults with A and RC	Mite	2 years	AI S, CPT, SE	5A
Passalacqua et al. (68)	RCDBCT	30 adults with A and RC	Pollen	5 months (16)	AI S, AI M, S&M, SE	5A
Patriarca et al. (69)	RCOCT	24 adults and children allergic to latex	Latex	3 months (5500)	SP, SE	3B
Pradaliere et al. (70)	RCDBCT	126 adults and children with A and R	Pollen	5 months (935)	AS, AI M, SkT, SeT, SE	4B
Purello D'Ambrosio et al. (71)	RCDBCT	30 adults and children with A and RC	Pollen	9 months (12.77)	AS, AI S, AI M, S&M, SkT, SeT, SE	5A
Rodriguez Santos (72)	RCOCT	50 children with A	Mite	2 years	RFT, RRVES, AM	2B
Rolinck-Werninghaus et al. (73)	RCDBCT	97 children with A and RC	Pollen	32 months (188) all allergens	AS, AI M, SeT, SkT, NPT, RFT, SE, ENOC, Se	5A
Sambugaru et al. (74)	RCOCT	53 adults and children with A and RC	Mite, pollen	2 years (115.2)	S&M, RFT, SE	3B
Voltoini et al. (75)	RCDBCT	30 adults and children with A and RC	Pollen	5 months (445)	AI S, AI M, NPT, SeT and SkT, S&M, SE	4B
Yuksel et al. (76)	RCDBCT	39 children with A and R	Pollen	18 months	AS, AM, RFT, UL	5A

A, asthma; Ad, adherence; AI M, medications for allergies in general; AI S, allergic symptoms in general; AM, asthma medications; AS, asthmatic symptoms; BPT, bronchial provocation test; CPT, conjunctival provocation test; ENOC, exhaled nitric oxide concentration; µg, microgram; NE, nasal eosinophils; NPT, nasal provocation test; R, rhinitis; RC, rhinitis and/or conjunctivitis; RCDBCT, randomized-controlled double-blind clinical trial; RCOCT, randomized-controlled open clinical trial; RFT, respiratory function test; RRVES, relative risk of visiting emergency service; SE, side effect; Se, severity of eczema; SeT, serologic test; SkT, skin test; SP, symptom provocation; S&M, symptoms plus medications; UL, urinary leukotriene.

keeping the drops under the tongue. In one trial (70), administration started via drops and was then replaced by tablets for the maintenance phase and in another study, administration was by means of tablets during all the phases (67).

In two studies (53, 67), the allergen was used in the monomer form. This is a form in which the allergen is modified under laboratory conditions to reduce its allergenic potential while preserving its immunogenic capacity and thus decreasing the risk of adverse effects.

Latex allergy was studied in one trial (69). Among the clinical manifestations included was a more serious condition of asthma together with rhinitis/conjunctivitis, urticaria/angioedema, and anaphylactic shock. In this study, rapid sublingual desensitization was utilized (4 days), followed by maintenance for 3 months. Evaluation of the treatment was carried out by means of cutaneous, mucous, sublingual, and conjunctival provocation. For the present meta-analysis, the result from mucous provocation was utilized as the outcome.

In one study (63), the patients only presented rhinitis and conjunctivitis, without asthma. This study was nevertheless utilized in the present meta-analysis because one of the outcomes was the development of asthma during treatment.

The duration of treatment varied considerably between studies, ranging from 3 months to 3 years. In three studies (57, 58, 64), even though the authors did not present the standard deviations in relation to the symptom scores, their calculations were based on Cochrane Handbook (8).

Methodological quality

The concealment of allocation was assessed as clearly adequate (category A) in 12 studies (54, 57, 58, 62, 64–68, 71, 73, 76), while it was not described in detail (category B) in 13 studies (52, 53, 55, 56, 59, 60, 61, 63, 69, 70, 72, 74, 75). The score for methodological quality using the Jadad system was 5 in 12 studies, 4 in four studies, 3 in seven studies, and 2 in two studies (Table 1). Nineteen studies were double-blind and six were open-controlled clinical trials (Table 1).

Categorical outcomes

The categorical outcomes analyzed were asthma improvement in general and adverse effects.

Asthma improvement in general

In seven studies (58, 59, 61–63, 70, 72) with 876 patients, the change in asthmatic symptoms was simply reported as worse/same or improved, through combined analysis of the following outcomes: asthmatic symptoms, need for symptom relief medication, respiratory function test and lung hyperreactivity (Fig. 2). Significant improvement was observed in these studies (RD: -0.27 with 95% CI: -0.33 to -0.21; RR: 0.48 with 95% CI: 0.40–0.57). The NNT using immunotherapy was 3.70 patients in order to avoid leaving one patient with the same symptoms or worse. There was no heterogeneity between these studies ( $\chi^2 = 9.41, P = 0.15, I^2 = 36.3\%$ ).

Adverse effects

For 20 studies (52, 54, 55, 57–65, 67–71, 73–75) with 1501 patients, no severe reactions were observed but, rather, only mild adverse effects (Fig. 3). These were predominantly local reactions, generally in the mouth, such as pruritus, erythema, and edema. These usually occurred within 30 min following the vaccine use and generally resolved spontaneously. The risks found were RR: 1.83 with 95% CI: 1.40–2.40; and RD: 0.07 with 95% CI: 0.04–0.10, and the NNH using SLIT was 14.28 patients, in order to cause an adverse effect in one patient.

Continuous outcomes

*Asthma symptoms.* In nine studies (54, 55, 58, 64, 65, 70, 71, 73, 76) with 303 patients, the asthmatic symptoms were analyzed separately from other allergic symptoms, such as rhinitis and conjunctivitis (Fig. 4). The combined SMD for the symptom score following SLIT was -0.38 with 95% CI: -0.79 to 0.03. This CI included zero, thus indicating a nonsignificant reduction in asthmatic symp-

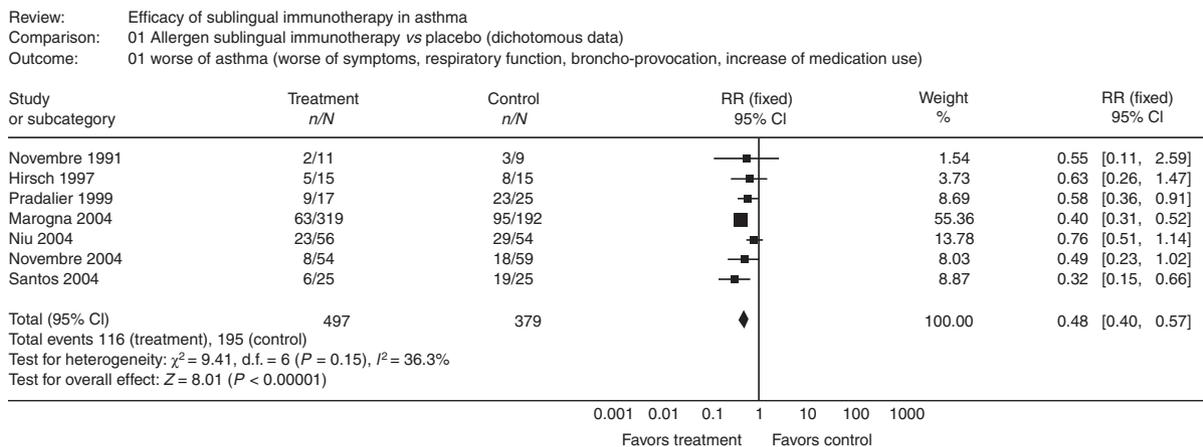


Figure 2. Meta-analysis of overall asthma parameter improvement (asthmatic symptoms, respiratory function test, symptom relief medication, lung reactivity) from placebo-controlled trials: relative risk (RR) with 95% confidence interval (CI) for each study and all studies combined (including test for heterogeneity).

Review: Efficacy of sublingual immunotherapy in asthma  
 Comparison: 01 Allergen sublingual immunotherapy vs placebo (dichotomous data)  
 Outcome: 02 Side effect

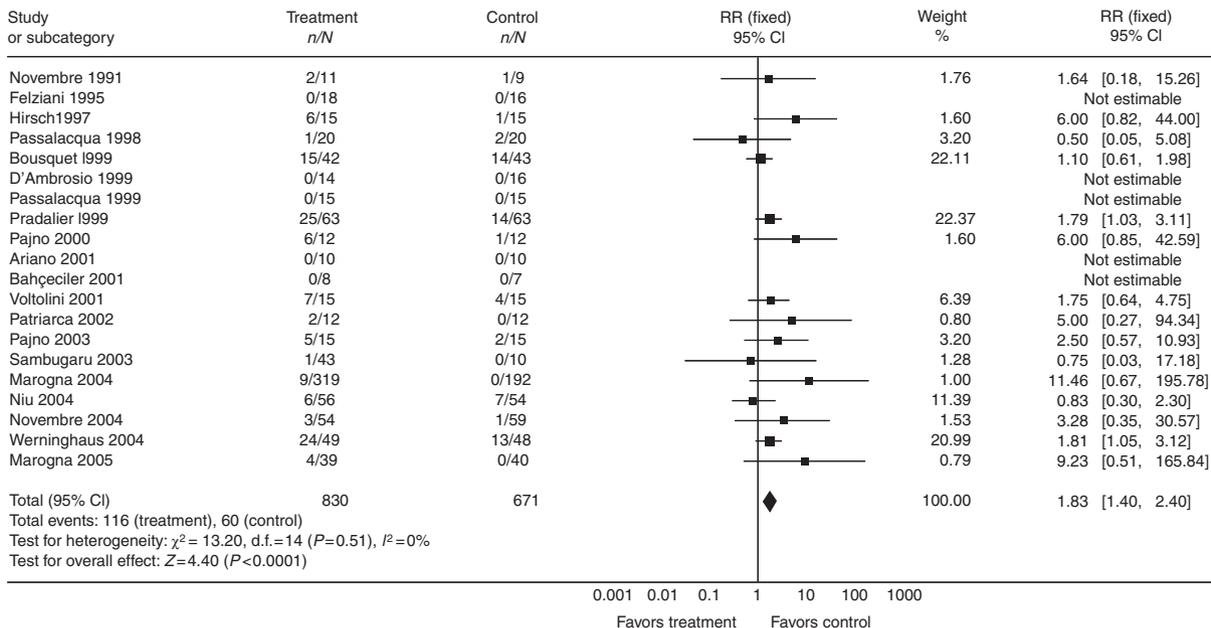


Figure 3. Meta-analysis of side effects from placebo-controlled trials: relative risk (RR) with 95% confidence interval (CI) for each study and all studies combined (include test for heterogeneity).

Review: Efficacy of sublingual immunotherapy in asthma  
 Comparison: 02 Allergen sublingual immunotherapy vs placebo (continuous data)  
 Outcome: 01 Asthma symptoms only

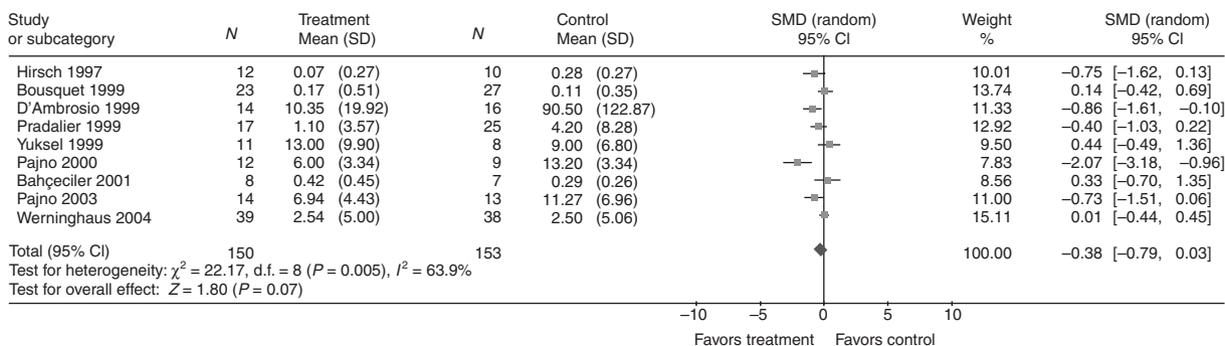


Figure 4. Meta-analysis of asthmatic symptom scores from placebo-controlled trials of allergen immunotherapy for asthma: standardized mean difference (SMD) with 95% confidence interval (CI) for each study and for all studies combined (including test for heterogeneity).

toms. There was a significant heterogeneity between the studies ( $\chi^2 = 22.17$ ,  $P = 0.005$ ,  $I^2 = 63.9\%$ ).

Subgroups analyzed according to age (children), allergen type or duration of immunotherapy failed to identify differences in the benefits from treatment.

**Allergic symptoms in general.** Ten studies (52, 53, 57, 60, 63, 67–69, 71, 75) with 360 patients gave analyses of asthmatic symptoms together with other allergic symptoms (rhinitis, conjunctivitis, and latex allergy). The

combined SMD following SLIT was  $-1.18$  with 95% CI:  $-1.93$  to  $-0.43$ , thus indicating a significant reduction in allergic symptoms (Fig. 5). There was a significant heterogeneity between the studies ( $\chi^2 = 84.71$ ,  $P < 0.00001$ ,  $I^2 = 89.4\%$ ).

**Symptoms plus medication.** Composite symptom plus medication scores were available in seven studies (56, 59, 63, 68, 71, 74, 75) with 724 patients (Fig. 6). However, these two outcomes were for allergies in general (asthma

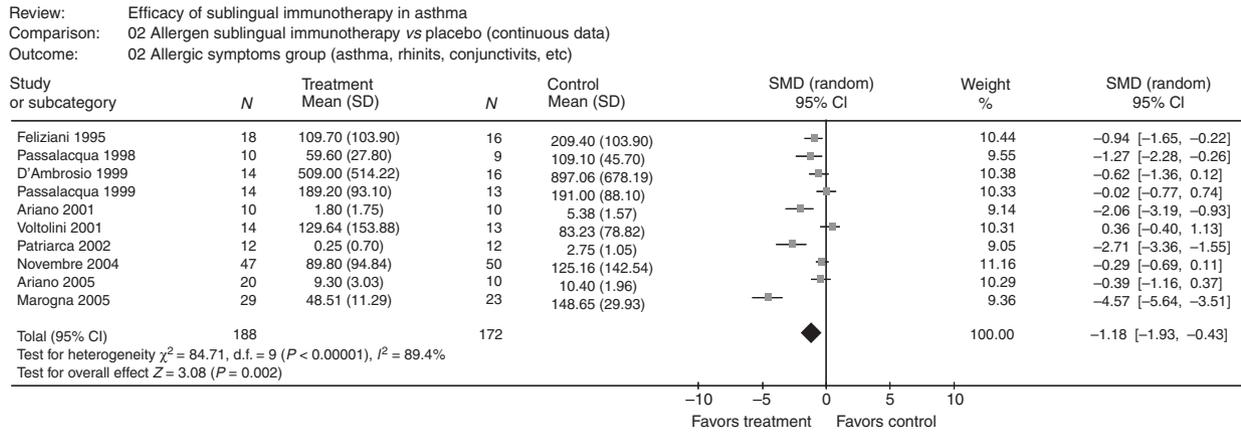


Figure 5. Meta-analysis of allergic symptom scores from placebo-controlled trials of allergen immunotherapy for asthma: standardized mean difference (SMD) with 95% confidence interval (CI) for each study and for all studies combined (including test for heterogeneity).

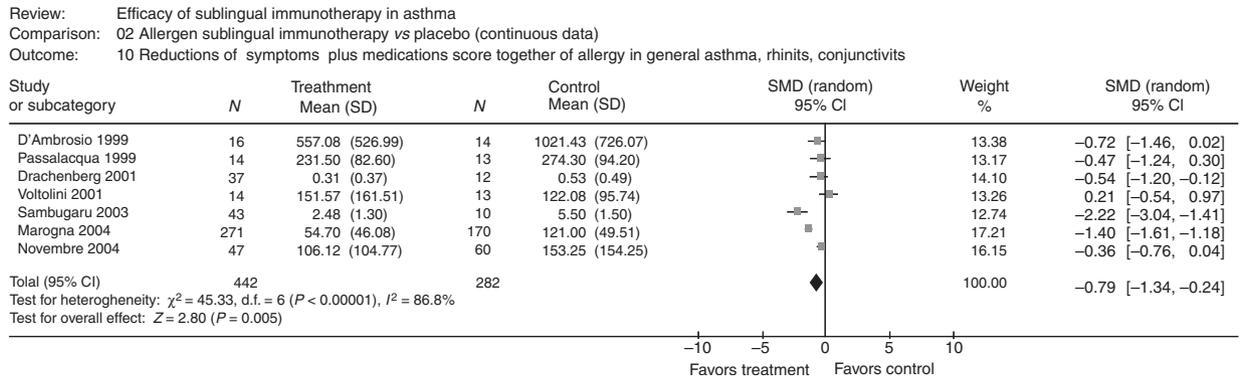


Figure 6. Meta-analysis of symptoms plus medication score for allergic symptoms (asthma together with rhinitis and conjunctivitis) from placebo-controlled trials: standardized mean difference (SMD) with 95% confidence interval (CI) for each study and all studies combined (include test for heterogeneity).

together with rhinitis and conjunctivitis), and the combined SMD following SLIT was  $-0.79$  with 95% CI:  $-1.34$  to  $-0.24$ , thus demonstrated significance. In the only study that analyzed symptoms plus medication score for asthma alone (55), SLIT was no better than placebo. There was a significant heterogeneity between the studies ( $\chi^2 = 45.33$ ,  $P < 0.00001$ ,  $I^2 = 86.8\%$ ).

**Medication use.** In 10 studies (52, 53, 57, 63, 65, 68, 70, 71, 73, 75) with 488 patients (Fig. 7), there was a significant reduction in the use of medication for asthma together with rhinitis and conjunctivitis (SMD  $-0.82$  with 95% CI:  $-1.25$  to  $-0.39$ ). However, in six studies (54, 55, 60, 61, 64, 76) with 254 patients (Fig. 8), there was no significant reduction in the need for medication for asthma alone (SMD  $-0.91$  with 95% CI:  $-1.94$  to  $0.12$ ). There was also a significant heterogeneity in these two outcomes (respectively  $\chi^2 = 40.53$ ,  $P < 0.00001$ ,  $I^2 = 77.8\%$  and  $\chi^2 = 60.74$ ,  $P < 0.00001$ ,  $I^2 = 91.8\%$ ).

Respiratory function and bronchial provocation tests

Among the respiratory function tests evaluated (FEV<sub>1</sub>, FEV1%, PEF, and FEF25–75%), FEV1% showed a significant improvement (SMD 1.48; 95% CI: 0.13–2.82), among 144 patients in four studies (54, 55, 60, 66) and FEF25–75% (SMD 1.06; 95% CI: 0.40–1.72) among 42 patients in two studies (54, 66); the values in these studies, which are greater than zero, indicated that treatment by SLIT was favored. Other evaluations, including the bronchial provocation test, did not show any significant improvement favoring treatment by SLIT.

Sensitivity analysis

The sensitivity analysis was performed to assess the symptomatic response of asthma when evaluated by means of the SMD (Fig. 4). It was observed that, except for two studies (55, 70) that were classified with a score of 4 (according to the Jadad scale), the other seven studies

Review: Efficacy of sublingual immunotherapy in asthma  
 Comparison: 02 Allergen sublingual immunotherapy vs placebo (continuous data)  
 Outcome: 09 Reduction of medication use to allergies general (asthma and rhinoconjunctivits)

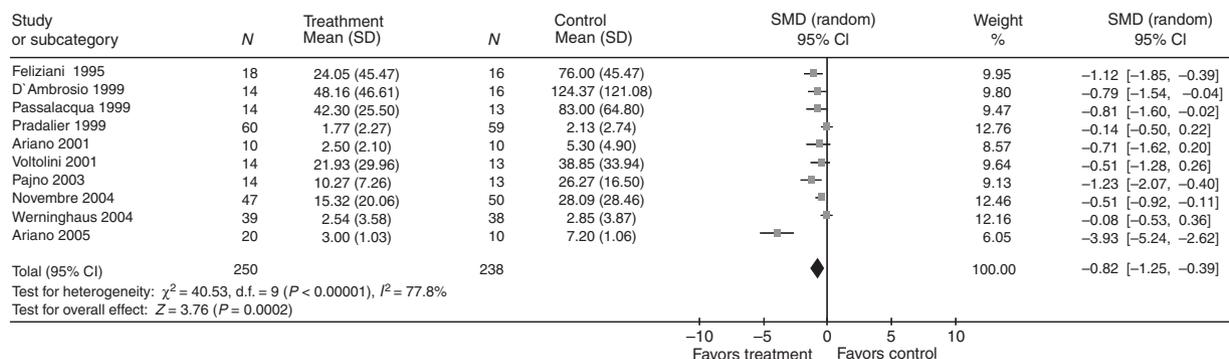


Figure 7. Meta-analysis of medication use score for allergic symptoms (asthma together with rhinitis and conjunctivitis) from placebo-controlled trials: standardized mean difference (SMD) with 95% confidence interval (CI) for each study and all studies combined (include test for heterogeneity).

Review: Efficacy of sublingual immunotherapy in asthma  
 Comparison: 02 Allergen sublingual immunotherapy vs placebo (continuous data)  
 Outcome: 08 Reduction of medication use to asthma

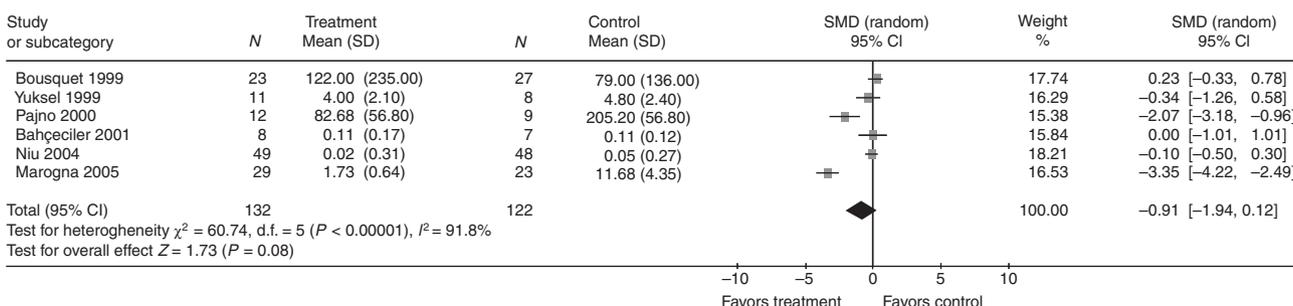


Figure 8. Meta-analysis of medication use score only for asthma symptoms from placebo-controlled trials: standardized mean difference (SMD) with 95% confidence interval (CI) for each study and all studies combined (include test for heterogeneity).

included in the specific meta-analysis for this outcome (improvement in the asthma symptoms) were all classified with a score of 5, thus showing that all the studies were of good quality. Also, with regard to the concealment allocation, only two studies (the same ones with score of 4, above) were classified in category B (allocation process not described in detail), while all the others were classified in A. We saw that the result for this outcome was favorable for SLIT, but without statistical significance. When we removed the two studies that were classified as 4B in the meta-analysis and only analyzed the studies classified as 5A, we obtained SMD: -0.48 with CI: -1.03 to 0.07 ( $\chi^2 = 19.59$ ,  $P = 0.003$  and  $I^2 = 69.4\%$ ), which thus did not modify the statistical significance of the result and also had no great repercussion on the heterogeneity of the analysis. We, therefore, were able to believe that the heterogeneity observed in this was unlikely to be methodological (related to the quality of the studies analyzed) but, rather, it was probably related to the differences in the scores utilized in the different studies.

Comment

In this systematic review of SLIT for asthma treatment, we identified 25 RCTs with sufficient information for inclusion in this meta-analysis. Out of the 119 references identified electronically, 65 reports were initially reviewed in detail. Among these 65 studies, one of the main causes of exclusion was insufficient data available from the published manuscript. This was generally because of the lack of standard deviations and also in many cases the results were presented by the authors in tabular columns and graphs that could not be transformed into numbers for utilization in the meta-analysis. Despite attempts to contact the authors, a small proportion did not reply to our questions.

Regarding the methodological quality of the studies included, they were all classified in category A or B with regard to the concealment allocation process, and 64% were classified via the Jadad quality score as 4 or 5.

Regarding the clinical efficacy of SLIT for asthma treatment, analysis of the improvement in clinical and laboratory asthma parameters by categorical outcomes

(seven studies with 876 patients) showed that the trials were significantly favorable to SLIT, without heterogeneity. For this, all the outcomes were analyzed together (reduction in asthmatic symptoms, lower need for medication, improvement in respiratory function test, and decreased bronchial hyperreactivity).

When asthmatic symptoms (nine studies with 303 patients) and reduction in the use of specific asthma medication (six studies with 254 patients) were analyzed using SMDs (continuous outcomes), there was a tendency toward improved asthma outcomes favored by SLIT, but without statistical significance. However, when all the allergic symptoms together (asthma plus rhinitis and conjunctivitis) and the reduction in the use of medication for allergy combinations (asthma plus rhinitis and conjunctivitis) were analyzed, as well as the symptom plus medication scores for all allergies, a significant improvement favored by SLIT was seen.

Among the respiratory function tests, FEV1% and FEF25–75% showed significant improvement. One important question addressed by the present review is in relation to adverse effects. Considering that no severe reactions were observed in 20 trials with 1501 patients, this suggests that SLIT is a safe treatment, and this is in agreement with the literature (26, 49, 57, 77).

With regard to other reviews covering immunotherapy for asthma treatment, there is one Cochrane review in which Abramson et al. (1, 2) studied the subcutaneous route. This showed that SCIT reduced asthmatic symptoms and the use of medication for asthma. We saw that when these outcomes were analyzed from the viewpoint of SLIT, although they showed a tendency toward a favorable response to treatment, there was no statistical significance. This is perhaps attributable to the smaller number of clinical trials on SLIT in relation to the number of trials on SCIT. In analyzing these continuous outcomes, Abramson et al. (1, 2) was able to utilize 28 studies of the reduction in asthma symptoms and 15 on the need for the use of asthma medication in his examination. On the other hand, in our meta-analysis, we only had nine and six studies available, respectively, for analyzing the same outcomes. Therefore, if we had had a greater number of studies on SLIT available, we might have also found significant values.

In analyzing the asthma symptom outcomes within the categories in which the symptoms were simply reported as having worsened, remained unchanged or improved, Abramson et al. (1, 2) observed a significant RR of 0.51 for deterioration of the symptoms, and also an NNT of 4, i.e. it would be necessary to treat four patients with asthma to avoid one worsening. We obtained a significant RR of 0.48 for worsening of asthma (which encompassed asthma symptoms) and also an NNT of 3.7. Thus, these values are also favorable toward SLIT and they are very close to those of Abramson et al. (1, 2) when SCIT was analyzed.

With regard to the respiratory function tests, contrary to Abramson et al. (1, 2), who did not find significant values favoring SCIT, in the present review, we found a

response that was significantly favorable toward SLIT, when FEV1% and FEF25–75% were analyzed.

With regard to the sublingual route, there are a few reviews covering SLIT for asthma treatment alone, let alone meta-analyses. There is one Cochrane review on SLIT, albeit for rhinitis (5, 6), which shows that SLIT is a safe treatment that significantly reduces the symptoms and use of medication relating to allergic rhinitis. Another review with meta-analysis, which was published recently, dealt with the efficacy of SLIT for respiratory allergy in children alone (7). There are other reviews on SLIT (78–83), but they covered asthma together with rhinitis and/or conjunctivitis, and none with meta-analysis. These reviews have generally showed that SLIT represents a possible safe alternative to SCIT for the treatment of allergic asthma, with some positive results and other disappointing results in relation to effectiveness.

Some caution is required in interpreting the present meta-analysis, because of the significant heterogeneity between the studies, in relation to continuous outcomes. This may, in part, be explained by the wide variety of scoring systems used in different studies and therefore, standardization of symptoms and medication scores are needed.

Another suggestion is that authors should follow the CONSORT guidelines (84), in order to achieve a better uniformity in relation to the methodological quality of future studies.

It would also be useful to standardize the allergen doses used. Independent of the unit used (reactivity index, biologic unit, etc.), the quantity of each allergen used should also be presented in terms of micrograms ( $\mu\text{g}$ ), along with the maintenance and cumulative doses used.

The mechanism of the action of SLIT is still unclear, especially in comparison with specific injection immunotherapy, which today is the best-understood method (78, 85, 86). However, some studies have demonstrated possible decreases in IgE levels, increases in IgG4 levels, variations in IgG1 levels, increases in CD8+ T cells, and reductions in the CD4/CD8 T-cell ratio (51); also, SLIT therapy might modulate the Th1/Th2 balance, thereby inhibiting Th2 lymphocytes (13). Nonetheless, this subject requires further study.

## Conclusions

Even though the evidence found in this meta-analysis is not very strong, the results from analyzing all the parameters together (asthmatic symptoms, respiratory function tests, relief medication, and lung hyperreactivity) suggest that SLIT reduces asthma expression. It reduces the need for medication for allergy combinations (asthma together with rhinitis and conjunctivitis), reduces allergic symptoms (when analyzed together with asthma symptoms), reduces the composite symptom plus medication score for allergies together and improves the FEV1% and

FEF25–75% respiratory function test result. One important implication for clinical practice is its safety. As SLIT did not show any significant adverse effects, it can therefore be prescribed as an alternative to SCIT.

With regard to the implications for research, as the effectiveness of SLIT is still subject to discussion, further high-quality RCTs are needed. Standardization of the principal end points utilized would also be an important achievement, i.e. the symptom and medication scores, and also quantification of the allergens studied (in µg), with presentation of the maintenance and cumulative doses.

Future research will also be needed in order to investigate the optimal maintenance doses and the length of treatment, identify whether there are subsets of patients capable of responding better to the treatment, and analyze the cost-effectiveness ratio and adherence to treatment.

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Therefore, although this meta-analysis does not demonstrate a definitive result regarding the efficacy of SLIT for asthma treatment, it has increased the weighting of the balance of evidence, so that it points toward an official position of validation for the use of SLIT in adults and children. It does, however, still seem to be necessary to conduct further studies in this respect.

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