

Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A systematic review and meta-analysis

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Background: The benefit of sublingual immunotherapy (SLIT) with grass allergens for seasonal allergic rhinitis has been extensively studied, but data on efficacy are still equivocal.

Objective: To assess the effectiveness of SLIT with grass allergens in the reduction of symptoms and medication in patients with seasonal allergic rhinitis to grass pollen.

Methods: Computerized bibliographic searches of MEDLINE (1995-2010) were supplemented by hand searches of reference lists. Studies were included if they were double-blind randomized controlled trials (RCTs) comparing SLIT to placebo and if they included patients with history of allergy to grass pollen treated with natural grass pollen extracts. Nineteen RCTs with 2971 patients were analyzed. The outcomes assessed were symptom and medication scores.

Results: Using a random-effects model, SLIT with grass allergens significantly reduces both symptoms (standardized mean difference, -0.32 ; 95% CI, -0.44 to -0.21) and medication use (standardized mean difference, -0.33 ; 95% CI, -0.50 to -0.16) compared with placebo. The treatment is more efficacious in adults than in children. Prolonging duration of preseasonal treatment for more than 12 weeks improves the treatment efficacy.

Conclusion: This meta-analysis found that SLIT with grass allergens is effective in patients with seasonal allergic rhinitis compared with placebo. The benefit is clinically modest, and criteria are needed to identify patients most likely to benefit from SLIT. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Sublingual immunotherapy, rhinitis, grass, meta-analysis

Allergic rhinitis (AR) is an increasingly prevalent condition affecting about one quarter of adults in the developed world.

Abbreviations used

AE: Adverse event
AR: Allergic rhinitis
RCT: Randomized double-blind controlled trial
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SMD: Standardized mean difference

Grass pollen is one of the most common causes of AR, responsible for more than 50% of cases.¹

Subjects with AR resistant to usual pharmacotherapy can be treated by allergen-specific immunotherapy, which has been recognized by the World Health Organization as the only causal treatment for allergic diseases. Traditionally, allergen-specific immunotherapy has been administered as subcutaneous injections. However, after reports of deaths and adverse reactions,² safer routes of immunotherapy administration have been evaluated in recent years. The sublingual approach has gained considerable interest as an alternative, and now several European countries use sublingual immunotherapy (SLIT) for the treatment of AR in preference to subcutaneous immunotherapy (SCIT) because of improved safety and easy administration. However, uncertainty persists, particularly on the clinical efficacy of SLIT, mainly in the United States, where SCIT is widely accepted and used and SLIT is still subject to review.³

Two different meta-analyses of controlled trials of SLIT as treatment for AR published in recent years, one as full text,⁴ the other as a conference abstract,⁵ have shown that SLIT is significantly more efficacious than placebo in reducing symptoms and drug use. These meta-analyses included studies evaluating the efficacy of SLIT for both seasonal and perennial AR. The efficacy of SLIT for seasonal AR by grass pollen was evaluated only in a subgroup analysis⁵ and was reported lower than that reported for other allergens. In the last 2 years, other randomized controlled trials (RCTs) have been published on SLIT with grass allergens for AR.⁶⁻¹⁴ However, the results of these studies remain inconsistent, and the overall assessment of the treatment efficacy is still difficult to evaluate. Some possible explanations for the inconsistency between the results of individual studies are the heterogeneity of the design and conduct of the RCTs and the heterogeneity of the enrolled populations.

To overcome some of these limitations, increase the relevance of statistical analysis, and improve estimates of effect magnitudes, we performed a meta-analysis of all available RCTs published within the last 2 decades to assess the clinical efficacy of sublingual grass allergen-specific immunotherapy for seasonal AR.

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METHODS

Selection of randomized trials

The primary source of the reviewed studies was MEDLINE with the following medical subject headings: *rhin** (which covers rhinitis, rhinopathy, rhinosinusitis, and rhinoconjunctivitis), *SLIT*, *grass*, *sublingual*, and *immuno-therapy*. The computer search was supplemented with manual searches of reference lists for all available review articles, primary studies, and abstracts from conferences.

All of the included studies reported symptom score as the primary outcome measure. In the majority of the RCTs, results were reported as means $\pm$ SDs. For studies not reporting all the values required for the analysis, data were provided by the authors of the original studies or by the pharmaceutical companies.^{8,11-14,15} Studies were included in the meta-analysis if (1) they were RCTs comparing grass pollen SLIT with placebo, (2) they included patients of any age with at least a 2-year history of AR to grass pollen with or without mild allergic asthma and/or conjunctivitis with a positive grass allergen-specific skin prick test and raised serum grass allergen-specific IgE, and (3) and symptom and medication scores were assessed as outcome measures of the treatment effect. The search, limited only to English language literature published through January 2010, identified 119 abstracts, of which 88 were considered unsuitable for inclusion (review articles, observational studies, RCTs that were not double-blind, analysis of other outcomes such as costs and IgE profile). Among the studies reviewed, 33 RCTs met the inclusion criteria, and 19⁶⁻²⁴ were included in the meta-analysis. Six studies were excluded because they were duplicate studies,²⁵⁻³⁰ 1 because a mixture with nongrass allergens was used for SLIT,³¹ 1 because the outcome was the asthma symptom score,³² 4 because of insufficient data,³³⁻³⁶ and 2 because they used allergoid for SLIT.^{37,38}

Review of the trials

The trials were first reviewed using a list of predefined pertinent issues that concerned the characteristics of patients and treatments. Each RCT was evaluated and classified by 2 independent investigators (D.D.B., G.D.L.). Discrepancies among reviewers were infrequent (overall interobserver variations, 10%) and were resolved by discussion.

Statistical analysis

The symptom and medication scores were assessed as outcome measures of the treatment's effect. These data were available in all 19 trials for symptom score and in 17 RCTs for medication score.

The outcome data analyzed were continuous, but different scoring systems and scales for symptoms and medication were used by the authors. Therefore, to compare the results, analyses were performed by the method of standardized mean difference (SMD), expressing the differences in means between SLIT and placebo in terms of units of the pooled SD. The overall SMD among patients treated with SLIT and placebo was estimated with models based on both fixed effects and random effects assumptions.³⁹

We in turn excluded each study to ensure that no single study would be solely responsible for the significance of any result (so-called *robust analysis*).

All our analyses were computed in R by using the Meta and Metafor statistical packages, package version 1.1-8 (<http://www.R-project.org>).⁴⁰⁻⁴² A descriptive subgroup analysis was carried out on both symptom and medication score. A graphical procedure was preferred to a meta-regression because of the likelihood of false-positive results positively correlated with the number of characteristics investigated. The selection of characteristics defining subgroups was motivated by clinical and methodologic hypotheses. We selected 2 categorical variables, age (children vs adults) and type of treatment (drops vs tablets); 3 dichotomized variables (below or above median), duration of treatment (months), length of preseasonal treatment (weeks), and dropout and withdrawal rate (%); and 1 categorized variable, monthly dose (below first quartile, between first and third quartile, above third quartile).

The I^2 statistic, which describes the percentage of variability because of heterogeneity rather than sampling errors, was used to quantify heterogeneity.⁴³

Influential analysis—that is, the exclusion of outlying studies until homogeneity has been achieved—was also used to explore heterogeneity.

This method was used to examine the effect of studies identified as being aberrant in either results or conduct.

To handle publication bias, we used the fail-safe calculation, a simple procedure by which one can estimate whether publication bias (if it exists) may be safely ignored. A fail-safe number indicates the number of nonsignificant, unpublished (or missing) studies that would need to be added to a meta-analysis to reduce an overall statistically significant result to nonsignificance. If this number is large relative to the number of observed studies, one can feel fairly confident in the summary conclusions. Here the fail-safe numbers were computed following the Rosenberg approach by means of the R Metafor package.⁴²

RESULTS

Features of RCTs

The main features of the studies included in the meta-analyses are shown in Table I. The 19 RCTs included a total of 2971 patients, 1518 of whom received SLIT. Five studies enrolled only children,^{9,11,13,20,21} and 2 studies included both adults and children, but with a vast majority of adults.^{6,18} The sample size of the studies varied greatly, ranging from 34¹⁶ to 578²² patients. The median percentage of males was 59.0%, ranging from 47.0%¹⁷ to 67.5%.²³ The median of the mean ages of patients in 15 studies was 29.4 years, ranging from 9.3²¹ to 38.5,¹⁵ but mean age was not reported in 4 studies.^{8,14,16,20}

The percentage of patients affected by mild-moderate asthma was reported only in 11^{6,7,9-13,18,20,21,23} of 19 studies and ranged from 10.0%⁷ to 100%²³ (median, 34%). In 10 studies, the treatment and placebo were administered by sublingual drops,^{6,8-10,12,16,17,19,20,21} in the remaining 9 by tablets.^{7,11,13-15,18,22-24} Great variability was observed in the duration of treatment (range, 3¹⁶ to 36²¹ months) as well as in the length of preseasonal treatment (range, 4¹⁶ to 30¹⁹ weeks; no preseasonal treatment in 2 RCTs^{12,14}). High variability was also observed in the monthly dose of allergens administered by SLIT (range, 6²⁰ to 1200¹⁰ μ g). The number of antigens used in the different SLIT pharmaceutical preparations ranged from 1^{13,19,21-24} to 6.¹⁰ The median monthly amount of the major allergen group 5 (Phl p 5) among the different pharmaceutical preparations was 450 μ g.

All RCTs reported dropouts and withdrawals and analyzed patients who completed the study. The median rate of dropouts and withdrawals was calculated to be 11.1%, ranging from 0%^{8,14,16} to 51.5%.¹⁰

Symptom score

The effect of grass pollen SLIT on symptom score (19 RCTs: 1518 patients receiving SLIT, 1453 placebo) is shown in Fig 1. Sixteen studies showed a reduction of nasal symptoms compared with placebo, but only 9 of them achieved statistical significance. The pooled SMD for the treatment effect was -0.32 (95% CI, -0.44 to -0.21 ; $P < .0001$), indicating a significant reduction in symptoms in subjects receiving SLIT compared with those receiving placebo. Sensitivity analysis showed that these results were robust when we used a fixed-effects model (-0.34 ; 95% CI, -0.41 to -0.27 ; $P < .0001$). Robust analysis showed that evaluation of the 18 studies remaining after the exclusion of the largest trial²³ resulted in a similar effect size without loss of significance (SMD, -0.30 ; 95% CI, -0.43 to -0.18 ; $P < .0001$).

Significant heterogeneity between the results of individual studies was reported ($Q = 40.95$; $df = 18$; $P = .002$; $I^2 = 55.8\%$).

TABLE I. Patient and study characteristics of the randomized controlled trials in the meta-analysis

Study	N	Male (%)	Mean or mean $\pm$ SD age (range)	Adults or child (%)	Asthma (%)	Type of treatment	Allergens	Monthly dose	Length of preseasonal treatment (wk)	Duration (mo)
¹⁶ Feliziani 1995	T 18 -> 18 P 16 -> 16	NR	NR (14-48)	NR	NR	Drops	5*	120 μ g of 5 grass pollen	<4	3
¹⁷ Hordijk 1998	T 27 -> 24 P 30 -> 30	47	27.5 (18-45)	Adults	NR	Drops	5†	168 μ g of Lol p 5	12	10
¹⁸ Pradalier 1999	T 63 -> 62 P 63 -> 61	52	29 $\pm$ 11 (7-58)	Adults (86.5)	34	(Drops) Tablet	5‡	255 μ g of Phl p 5	8	5
¹⁹ Torres-Lima 2002	T 28 -> 26 P 28 -> 23	57	34 (21-55)	Adults	NR	Drops	1§	900 μ g of Phl p 5	8-30	12-18
¹⁵ Smith 2004	T 62 -> 45 P 62 -> 51	48	38.5 (18-58)	Adults	NR	(Drops) Tablet	5‡	867 μ g Lol p 1 504 μ g Dac g 5	12	24
²⁰ Rolinck-Werninghaus 2004	T 49 -> 39 P 48 -> 38	67	NR (3-14)	Children	40	Drops	5‡	6 μ g major allergen group 5	4	32
²¹ Bufe 2004	T 82 -> 68 P 79 -> 64	NR	9.3 $\pm$ 3 (NR)	Children	42	Drops	1§	273 μ g of Phl p 5	20	36
²² Dahl 2006a	T 316 -> 282 P 318 -> 286	59	34.2 $\pm$ 9.8 (18-65)	Adults	NR	Tablets	1§	450 μ g of Phl p 5	16	6
²³ Dahl 2006b	T 74 -> 61 P 40 -> 32	67.5	35.7 $\pm$ 10.2 (18-64)	Adults	100%	Tablets	1§	450 μ g of Phl p 5	10-14	5
²⁴ Durham 2006	T 153 -> 131 P 150 -> 129	61.5	36.5 (18-65)	Adults	NR	Tablets	1§	450 μ g of Phl p 5	8	6
⁶ de Blay 2007	T 61 -> 53 P 57 -> 51	66.3	25 $\pm$ 7.5 (12-41)	Adults (89.4)	27.9	Drops	3¶	275 μ g major allergen group 5	32	10
⁷ Didier 2007	T 155 -> 136 P 156 -> 148	56.9	29.4 $\pm$ 7.3 (18-45)	Adults	10	Tablets	5‡	750 μ g major allergen group 5	20	6
⁸ Mösges 2007	T 48 -> 48 P 53 -> 53	NR	NR (18-50)	Adults	NR	Drops	5‡	600 μ g of Phl p 5	16	9
⁹ Röder 2007	T 108 -> 91 P 96 -> 77	56.5	12.7 $\pm$ 2.7 (6-17)	Children	58.3	Drops	5	168 μ g of Lol p 5	24	24
¹⁰ Pfaar 2008	T 94 -> 42 P 91 -> 48	62.5	33.1 (17-59)	Adults	29.2	Drops	6#	1200 μ g of Phl p 5	16	24
¹¹ Wahn 2009	T 139 -> 131 P 139 -> 135	64.3	10.9 $\pm$ 3.22 (5-17)	Children	21.4	Tablets	5‡	600 μ g of Phl p 5	16	8
¹² Ott 2009	T 123 -> 99 P 60 -> 46	59	33.3 $\pm$ 10.4 (7.9-64.7)	NR	13.1	Drops	5‡	600 μ g of Phl p 5	NR	3 $\times$ 3
¹³ Bufe 2009	T 126 -> 117 P 127 -> 121	66	10.1 (5-16)	Children	42	Tablets	1§	450 μ g of Phl p 5	8	6
¹⁴ Horak 2009	T 45 -> 45 P 44 -> 44	NR	NR (18-50)	Adults	NR	Tablets	5‡	600 μ g of Phl p 5	NR	4

NR, Not reported; P, placebo; SD, Standard Deviation; T, SLIT.

**Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, *Phleum pratense*, and *Poa pratensis*.†*Anthoxanthum odoratum*, *Cynodon dactylon*, *Dactylis glomerata*, *Holcus lanatus*, and *Phleum pratense*.‡*Dactylis glomerata*, *Poa pratensis*, *Lolium perenne*, *Anthoxanthum odoratum*, and *Phleum pratense*.§*Phleum pratense*.¶*Dactylis glomerata*, *Phleum pratense*, and *Lolium perenne*.||*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*, and *Holcus lanatus*.#*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Holcus lanatus*, *Poa pratensis*, and *Festuca elatior*.

Influence analysis identified the study from Ott et al¹² as the influential study. The I^2 value for heterogeneity excluding this study decreased from 55.8% to 45.9% with a similar effect size (SMD, -0.35; 95% CI, -0.46 to -0.24; $P < .0001$).

The fail-safe number was 390, high enough to confirm the robustness of the results against publication bias.

We performed subgroup analysis to evaluate whether there was evidence of a different effect of SLIT in predefined subgroups of patients (Fig 2). When we analyzed studies of adults and children separately, we showed that the median SMD was -0.47 in adults and -0.16 in children (Fig 2). Notably, only 1¹¹ of the 5 children

studies showed a statistically significant difference between SLIT and placebo.

Analysis by monthly dose of allergens administered by SLIT showed that the median SMD was -0.47 and -0.38, respectively, in subjects receiving medium (276-600 μ g) and high (>600 μ g) monthly doses of allergens compared with placebo, whereas the SMD was -0.16 in patients treated with a low monthly dose (≤ 275 μ g; Fig 2).

Analysis by duration of SLIT treatment showed that the median SMD was -0.43 in studies with patients receiving SLIT <12 months and -0.11 in studies with patients treated ≥ 12 months

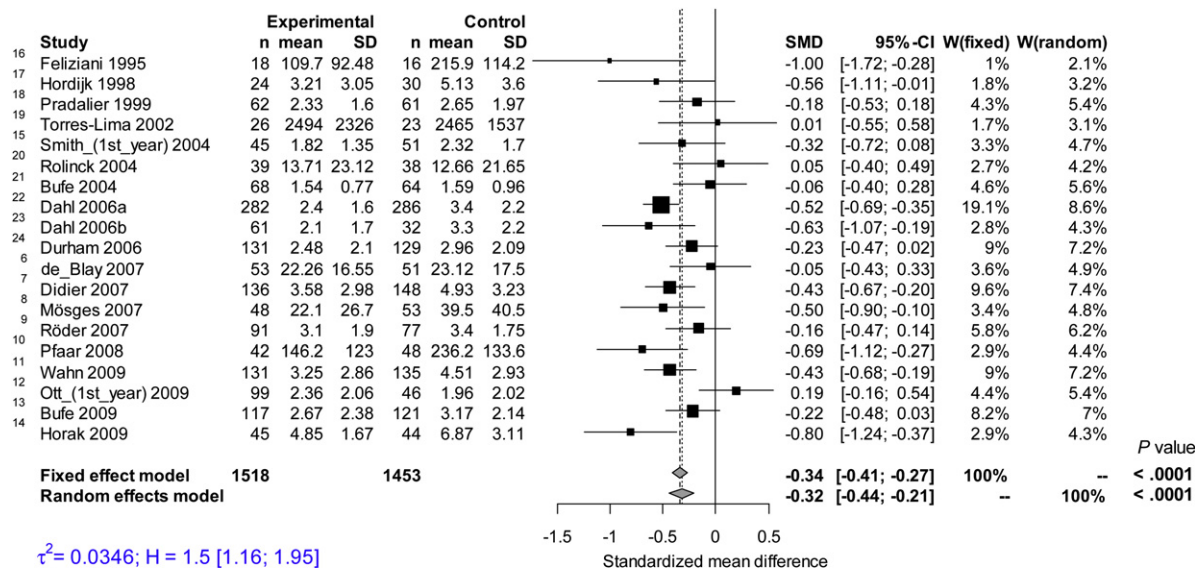


FIG 1. Meta-analysis of 19 randomized controlled trials of SLIT versus placebo for seasonal allergic rhinosinusitis, using both the random and fixed effects models. The SMD and 95% CI for the effect of SLIT on symptom score are plotted on the graph. Studies are arranged chronologically based on the year of publication. For the study by Pfaar and Klimek,¹⁰ the combined symptom-medication score was used.

(Table II). Analysis by length of preseasonal treatment showed that the effect of SLIT compared with placebo was higher in patients receiving a preseasonal treatment ≥ 12 weeks (median SMD, -0.44) than in those receiving SLIT for < 12 weeks (median SMD, -0.22; Fig 2).

Analysis by type of treatment showed that the effect of SLIT compared with placebo was higher in subjects who received tablets (median SMD, -0.43) than in those receiving drops (median SMD, -0.11). This difference is mainly a result of children studies using drops for SLIT, showing no difference between SLIT and placebo (data not shown).

Analysis by rate of dropout and withdrawals of individual studies showed that in studies with a dropout and withdrawal rate below the median value of 11.1%, the median SMD of SLIT compared with placebo was -0.50, with a low degree of heterogeneity ($I^2 = 28\%$), considerably different than in those with high dropout and withdrawal rate (median SMD, -0.11; Fig 2). This difference was statistically significant.

Analyses by (1) mean age of patients (below/above the median value of 29.4 years), (2) percentage of male patients (below/above the median value of 59%), and (3) percentage of patients with allergic asthma (below/above the median value of 34%) did not show any difference in the overall effect (data not shown).

Medication score

Data on medication score were obtained for 17 RCTs (1430 patients receiving SLIT and 1358 receiving placebo). Although 15 studies showed a reduction of rescue medication for nasal symptoms compared with placebo, a significant difference was observed in only 7 (Fig 3). The pooled estimate of treatment on medication score was significant (SMD, -0.33; 95% CI, -0.50 to -0.16; $P < .0001$; Fig 3). Similar results were obtained using a

fixed-effects model (-0.32; 95% CI, -0.40 to -0.25; $P < .0001$). In all the robust analyses, the pooled estimate of the treatment effect was significant.

A significant between-study heterogeneity ($Q = 73.72$; $df = 16$; $P < .0001$; $I^2 = 78.5\%$) was reported. Influence analysis showed a reduction of heterogeneity and a similar pooled estimate (SMD, -0.29; 95% CI, -0.38 to -0.20; $P < .001$) after exclusion of the RCTs of Röder et al⁹ and Bufo et al²¹ ($Q = 16.83$; $df = 14$; $P = .26$; $I^2 = 17.5\%$).

The fail-safe number was high enough to exclude other analyses for publication bias ($n = 298$).

Subgroup analysis showed that the effect of SLIT on medication score is more evident in adults (median SMD, -0.35; heterogeneity, $I^2 = 22.7\%$) than in children (median SMD, -0.12; heterogeneity, $I^2 = 93.0\%$; Fig 4).

Analysis by monthly dose of allergens administered for SLIT showed that the median SMD between SLIT and placebo was higher in subjects receiving a medium (median SMD, -0.30) or high (median SMD, -0.35) monthly dose of allergens than in those receiving a low monthly dose (median SMD, -0.17; Fig 4).

Analysis by duration of SLIT treatment showed that the median pooled SMD was -0.33 ($I^2 = 13.0\%$) in patients who received SLIT for < 12 months and -0.17 ($I^2 = 93.0\%$) in those receiving SLIT for ≥ 12 months (Fig 4).

Analysis by length of preseasonal treatment showed that the effect of SLIT compared with placebo was higher in patients receiving a preseasonal treatment ≥ 12 weeks (median SMD, -0.35) than in those treated for < 12 weeks (median SMD, -0.13; Fig 4).

Analysis by type of treatment did not show any difference in the effect of SLIT compared with placebo between patients who received tablets (median SMD, -0.30) and those receiving drops (median SMD, -0.28; Fig 4).

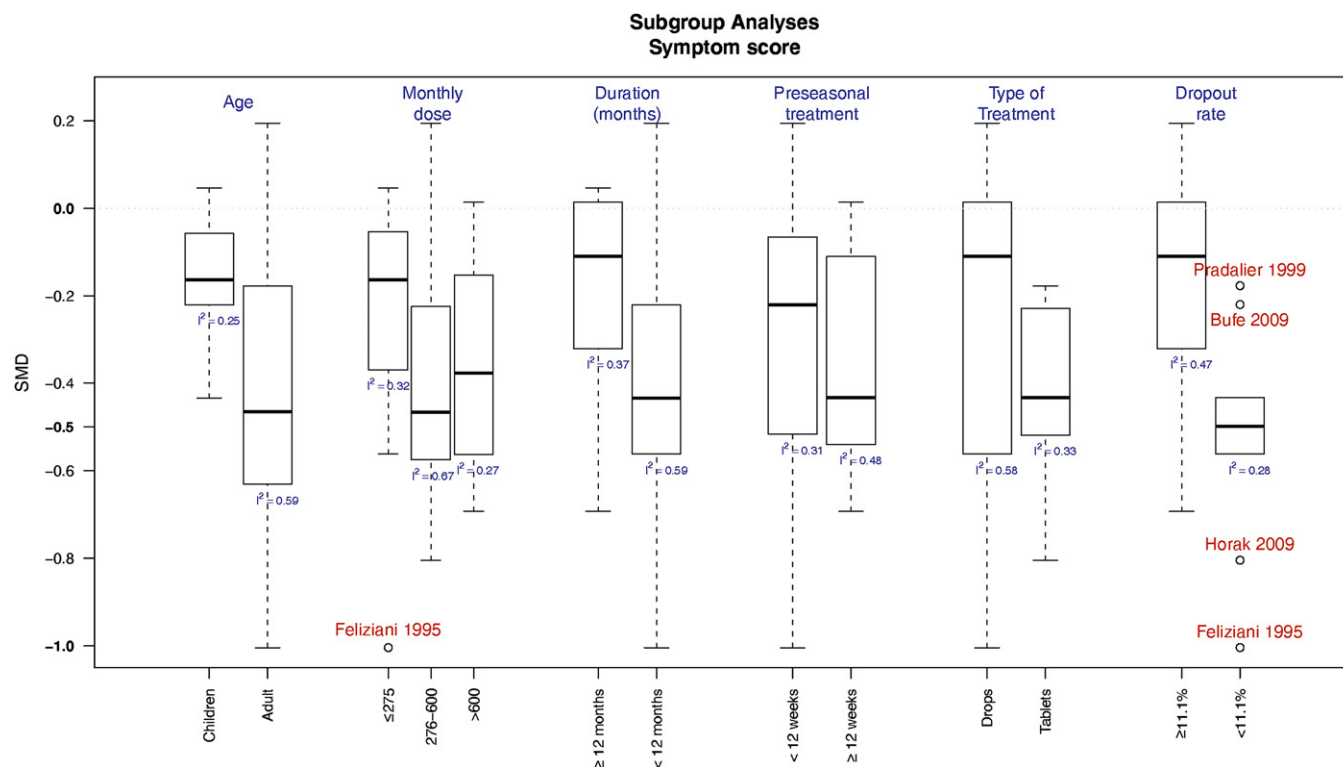


FIG 2. Descriptive subgroup analysis for symptom score of the 19 RCTs of SLIT versus placebo for seasonal allergic rhinosinusitis. Box plots include the middle 50% of the data. The horizontal bars inside the boxes represent the median SMDs. The dotted lines to the whiskers extend to the most extreme data points, which are no more than 1.5 times the interquartile range from the box. The degree of heterogeneity for each subgroup is plotted on the graph (I^2).

Analysis by dropout/withdrawal rate showed that the effect of SLIT compared with placebo was higher in studies with a low (<11.1%) dropout/withdrawal rate (median SMD, -0.35; heterogeneity, $I^2 = 0\%$) than in those with high ($\geq 11.1\%$) dropout/withdrawal rate (median SMD, -0.21; heterogeneity, $I^2 = 88\%$; Fig 4).

Analyses by (1) mean age of patients (below/above the median value of 29.4 years), (2) percentage of male patients enrolled (below/above the median value of 59%), and (3) percentage of patients with allergic asthma (below/above the median value of 34%) did not show any difference in the overall effect (data not shown).

Safety

A total of 4856 treatment-emergent adverse events (AEs) was reported, 3286 (2.6 AEs/patient) in the SLIT group and 1570 (1.34 AEs/patient) in the placebo group (Table II). The majority of AEs were modest in severity for both treatment and placebo groups. Fifty-four patients (3%) in the SLIT group and 12 patients (0.7%) in the placebo group were withdrawn from the studies for treatment-related AEs.

DISCUSSION

This meta-analysis of data from 19 RCTs shows that in seasonal allergic rhinoconjunctivitis, SLIT with grass allergens provides a significant improvement of symptoms and a significant reduction of antiallergic medication use compared with placebo. The results, representing a pooled total of 1518 patients receiving

TABLE II. Total and treatment-related AEs

	SLIT	Placebo
Total AE, no.	3286	1570
Total AE/patients, %*	2.6	1.34
Treatment-related AE, no.	1322	436
Related AE/patients, %†	0.94	0.33
Withdrawal for AE‡		
No.	54	12
Percent	3	0.7

*Data available for 15 of 19 RCTs.

†Data available for 16 of 19 RCTs.

‡Data available for 17 of 19 RCTs.

SLIT and 1453 receiving placebo, indicate a high degree of statistical significance of the treatment effect with no evidence of publication bias, but the benefit of SLIT compared with placebo is modest (SMD < -0.50).

Significant heterogeneity exists among the results of individual studies. Because several potential sources of heterogeneity are present in this set of data, several steps were considered in the investigation of the causes. Influence analysis, in which 1 study is excluded at a time, was performed to ascertain the impact of removing each of the studies on the between-study heterogeneity. This analysis identified the study by Ott et al¹² as largely responsible for the heterogeneity of symptom score results. The study by Ott et al¹² is the only one showing a better response to placebo after treatment (data kindly provided by Stallergenes, Antony, France on January 2010), although the authors concluded that

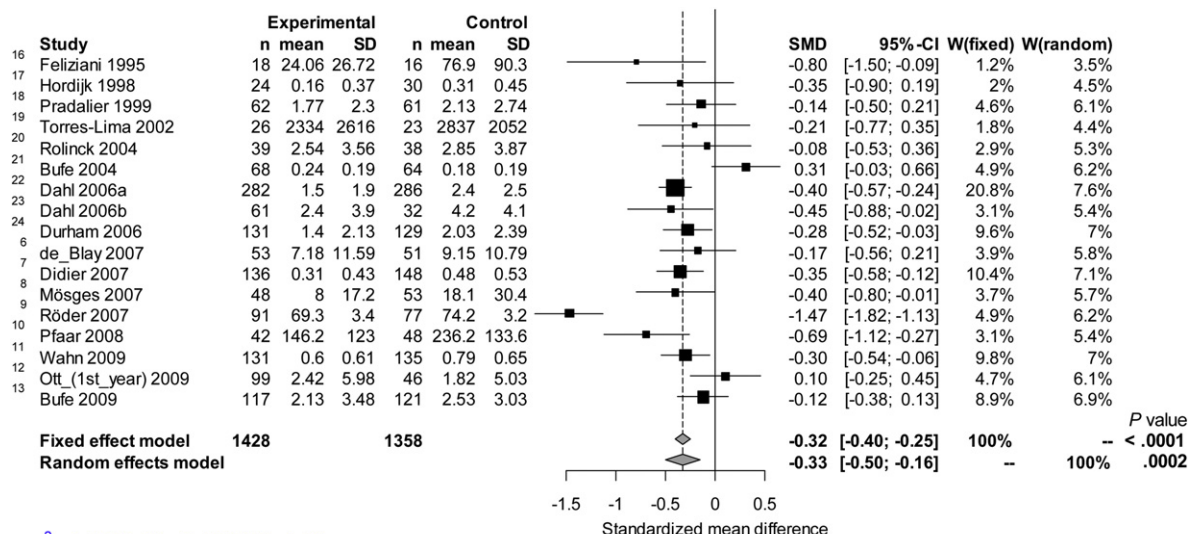


FIG 3. Meta-analysis of 17 randomized controlled trials of SLIT versus placebo for seasonal allergic rhinosinusitis. The SMD and 95% CI for the effect of SLIT on medication score are plotted on the graph. Studies are arranged chronologically based on the year of publication. For the study by Pfaar and Klimek,¹⁰ the combined symptom-medication score was used.

SLIT is efficacious in reducing symptom score. This apparent discrepancy stems from the fact that Ott et al¹² based their analysis on the comparison of symptom score within each group, SLIT and placebo groups, before and after treatment, not on a comparison between SLIT and placebo at the end of treatment. This analysis is flawed by the fact that patients included in the placebo group at baseline had a lower mean symptom score than those included in the SLIT group (data kindly provided by Stallergenes, Antony, France on January 2010), probably because of problems related to the randomization process or to the effect of a high dropout/withdrawal rate. Removing the study by Ott et al¹² from the overall analysis reduced the degree of heterogeneity within acceptable limits ($I^2 = 46.4\%$) and led to an improvement of the treatment effect for symptoms (median SMD, -0.50), confirming the robustness of the general conclusions of the efficacy of SLIT for AR.

Many RCTs have been conducted to identify the optimal SLIT regimen that would increase the cost-effectiveness of treatment. There was considerable variation in SLIT protocols among the studies we evaluated regarding dose of allergens, duration of treatment, length of preseasonal treatment, and pharmaceutical preparations. Our analysis suggests that a course of treatment no longer than 12 months is better than long-term treatment (>12 months). Long-term studies confirm the results of this analysis. The study by Smith et al¹⁵ showed that subjects treated with SLIT during the first year and placebo during the second year had a bigger reduction in symptom score compared with placebo than subjects treated with SLIT for 2 consecutive years. The studies by Dahl et al²⁷ and Durham et al,³⁰ representing the extension of the first study by Dahl et al,²² showed similar differences between SLIT and placebo for symptom score over 3 years of treatment and the first year of follow-up. The study by Ott et al¹² showed similar differences between SLIT and placebo over the 3 years

of treatment and over the 2 years of follow-up. These studies also show that the effect of SLIT is maintained over time after cessation of treatment.

Exploratory analysis by length of pretreatment suggested that a preseasonal treatment ≥ 12 weeks is associated with a better response rate both for symptom reduction and antiallergic medication, suggesting that starting the treatment at least 3 months before the beginning of the pollen season is more important than the duration of the treatment itself for a better clinical response.

Subgroup analysis by allergen dose suggested that clinical response to treatment was better for patients who received a monthly allergen dose higher than 276 μg . No difference was found comparing the 450 μg dose to doses ≥ 600 μg , suggesting that a monthly dose of 450 μg might be the best cost-effective dose. Our results are consistent with what Durham⁴⁴ observed, showing that the effects of SLIT were dependent on both allergen dose and length of preseasonal treatment.

The data of this meta-analysis suggest that SLIT with grass allergens is not of particular benefit for children, showing a small effect both for reduction of rhinitis symptoms and antiallergic medication compared with placebo. Different conclusions were drawn by the meta-analysis by Penagos et al,⁴⁵ showing SLIT as highly effective for AR in children compared with placebo, but they are based on studies using allergens other than grass. One possible explanation for the different effect of SLIT with grass allergens between adults and children could be the different dose of allergen administered. Three^{9,20,21} of 5^{11,13} child studies using an allergen dose <276 μg did not show any difference between SLIT and placebo. The only RCT showing a statistically significant benefit of SLIT is the trial with the highest dose of grass allergen administered (600 μg).¹¹ Our data emphasize the need for future trials in children to identify the best antigen dose to achieve effective treatment.

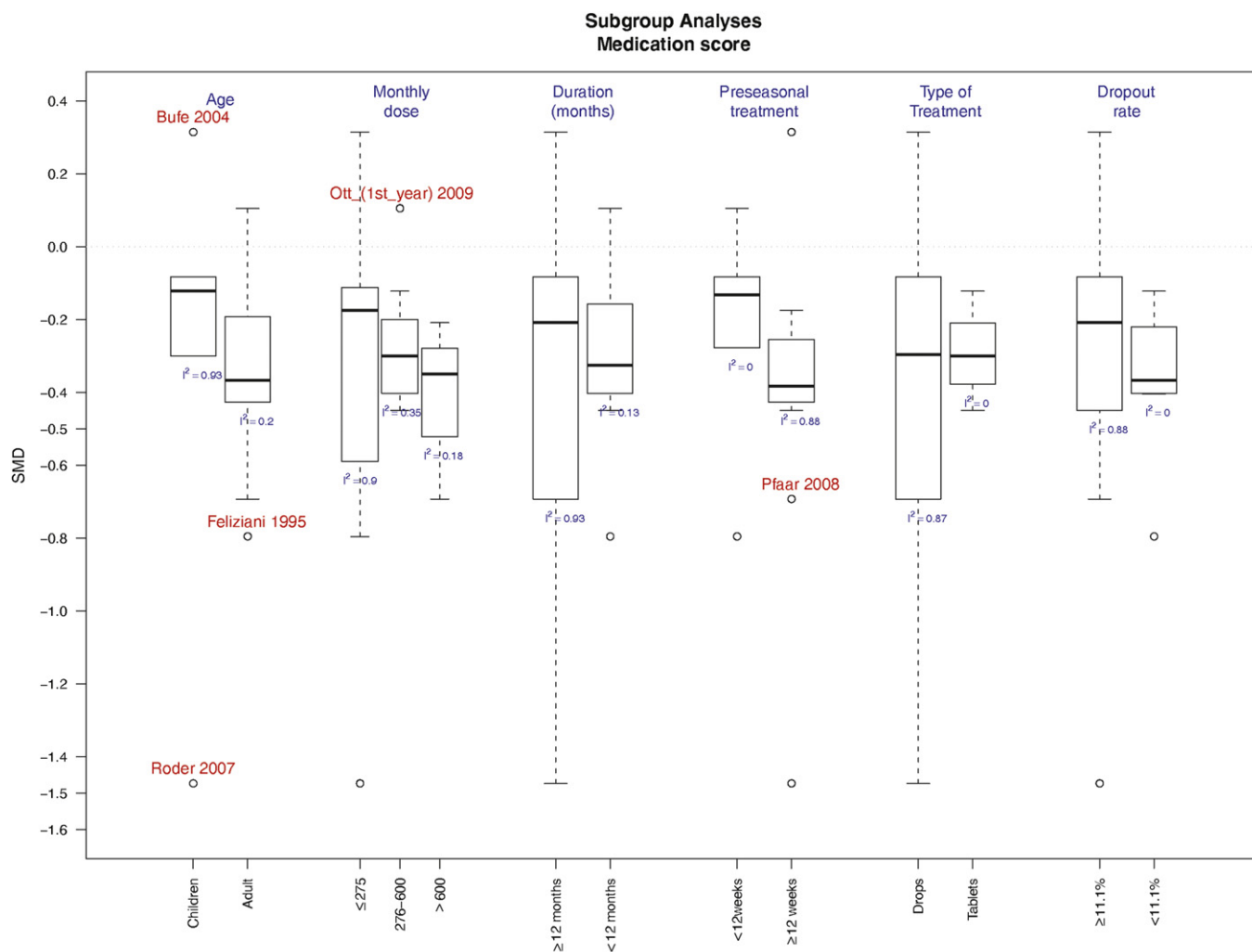


FIG 4. Descriptive subgroup analysis for medication score of the 17 RCTs of SLIT versus placebo for seasonal allergic rhinosinusitis. Box plots include the middle 50% of the data. The horizontal bars inside the boxes represent the median SMDs. The dotted lines to the whiskers extend to the most extreme data points, which are no more than 1.5 times the interquartile range from the box. The degree of heterogeneity for each subgroup is plotted on the graph (I^2).

Regarding the different pharmaceutical preparations, our analysis showed that tablets are more efficacious than drops for reducing symptoms. This difference is mainly a result of the child studies. However, in child studies using drops for SLIT, a low monthly dose of antigen was administered, suggesting that the low efficacy of drops compared with tablets could be related to the low allergen dose used.

Besides the study and patient characteristics, some methodologic issues inherent in the analysis of data in the individual studies could also be responsible for the inconsistency of the results. The most important criticism of the studies is the handling of dropouts/withdrawals. The dropout/withdrawal rate varies greatly among the studies, potentially hampering the reliability of the results. Moreover, some studies analyze data according to the intention-to-treat method, and some others per protocol. We use the dropout/withdrawal rate as a surrogate marker of study quality. When we included in a subgroup analysis studies with a low dropout/withdrawal rate, we observed an increase in the treatment effect for symptom score with a relevant reduction of

heterogeneity, showing that the quality of individual studies affects the final results.

Only a minority of serious side effects leading to withdrawal were reported by the studies included in the meta-analysis, confirming SLIT as a safe procedure with limited, mostly mild, side effects. Nevertheless, significant systemic side effects were reported after SLIT both in patients previously treated with SCIT and in patients previously untreated with SCIT at the first dose of SLIT.⁴⁶⁻⁴⁹

The results of this retrospective analysis are subject to several limitations. Differences in the baseline severity of the disease; different prevalence of patients with other comorbidities such as asthma, conjunctivitis, and atopic dermatitis; difficulties in the comparability of different scores used; differences in the pharmaceutical preparations; and differences in the SLIT protocols among studies may have limited the accuracy of this meta-analysis. We attempted to control for these differences by including covariates that described the patients studied and the study design features. However, these summary results describe

only between-study, not between-patient, variation because they reflect group averages rather than individual data.

We could not identify with this set of data any clinical characteristics able to predict the response in the individual patient. The only predictor identified was age, but for the reason mentioned, caution must be exercised when interpreting results based on the child studies.

Regarding publication bias, the high fail-safe number together with the personal contacts made directly with principal investigators and pharmaceutical companies make us confident that no important published trials were overlooked. Publication bias was probably not substantial and was considered unlikely to change the direction of our pooled estimate of treatment effect.

The available evidence is sufficient for us to conclude the following: (1) SLIT with grass allergens improves the rhinosinusitis symptoms and reduces the use of antiallergic medications compared with placebo, (2) the overall effect is clinically modest, (3) a prolonged preseasonal treatment significantly increases the response rate, and (4) a course of treatment no longer than 12 months with a monthly allergen dose of 450 μ g seems to be the best treatment option. Further studies are needed to define clearly the role of SLIT with grass allergens in children.

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Clinical implications: SLIT with grass allergens is effective in reducing rhinoconjunctivitis symptoms and medication use in adults. The best results are after preseasonal treatment ≥ 12 weeks at 1 year.

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