

Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A meta-analysis-based comparison

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Background: Subcutaneous (SCIT) and sublingual (SLIT) immunotherapy are the 2 most prescribed routes for administering allergen-specific immunotherapy. They were shown to be effective in control of symptoms and in reducing rescue medication use in patients with allergic diseases, but their effectiveness has to be balanced against side effects. In recent years, SLIT has been increasingly prescribed, instead of SCIT, because of improved safety and easy administration. **Objective:** We assessed which route is the most effective in the treatment of patients with seasonal allergic rhinitis to grass pollen. **Methods:** An indirect meta-analysis-based comparison between SCIT and SLIT was performed. Treatment efficacy was determined as the standardized mean difference (SMD) in symptom and medication scores obtained with active treatment, SCIT or SLIT, compared with placebo. Studies were included if they were double-blind randomized controlled trials comparing SCIT or SLIT with placebo. Thirty-six randomized controlled trials (3014 patients; 2768 controls) were analyzed.

Results: The overall effect size of SCIT for symptom score (SMD, -0.92 ; 95% CI, -1.26 to -0.58) was significantly higher than SLIT, both administered via drops (SMD, -0.25 ; 95% CI, -0.45 to -0.05) and tablets (SMD, -0.40 ; 95% CI, -0.54 to -0.27). Similar results were reported for medication score (SCIT: SMD, -0.58 ; 95% CI, -0.86 to -0.30 . SLIT drops: SMD, -0.37 ; 95% CI, -0.74 to -0.00 . SLIT tablets SMD, -0.30 ; 95% CI, -0.44 to -0.16).

Conclusions: Our results provide indirect but solid evidence that SCIT is more effective than SLIT in controlling symptoms and in reducing the use of antiallergic medications in seasonal allergic rhinoconjunctivitis to grass pollen. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

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

Abbreviations used

AE: Adverse event
RCT: Randomized controlled trials
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SLIT-D: SLIT administered by drops
SLIT-T: SLIT administered by tablets
SMD: Standardized mean difference

Allergen specific immunotherapy is an established treatment option for allergic disease and the only one able to modify the disease by targeting the underlying immunologic mechanisms. The subcutaneous and the sublingual routes are the most commonly used in clinical practice, with considerable differences worldwide. In the United States subcutaneous immunotherapy (SCIT) is the only route approved by the Food and Drug Administration and is widely prescribed, whereas sublingual immunotherapy (SLIT) is prescribed by only a minority of allergists (<6%). In contrast, in Europe SLIT is prescribed nearly as frequently as SCIT, and, in particular, in southern Europe it is preferred to SCIT, accounting for about 80% of immunotherapies.¹

Seasonal allergic rhinitis to grass pollens is one of the most prevalent allergic diseases in the developed world. The symptoms of the disease can have a pronounced effect on the patient's quality of life, affecting sleep quality, school and work performance, and social activities.²

Several clinical trials have reported the efficacy of both SCIT and SLIT compared with placebo for seasonal allergic rhinitis to grass pollens.³⁻⁵ In a recently published meta-analysis, we showed that SLIT is an effective treatment for seasonal allergic rhinitis to grass pollens, especially in adults, but its clinical benefit was modest.⁶ SLIT was also shown to be safe and well tolerated. The latter advantages explain the increasing use of SLIT seen in Europe in recent years: improved safety and easy administration compared with SCIT.¹ However, the relative efficacy of SCIT and SLIT has not yet been determined. The only published comparative studies, one performed with grass allergens and another with birch pollen, were far too small for a reliable conclusion.^{7,8} Therefore, to clarify this issue, we compared SCIT and SLIT by a meta-analysis of a fairly large number of double-blind, placebo-controlled trials on SCIT and SLIT (updating the previous published meta-analysis)⁶ in patients with seasonal allergic rhinitis to grass pollens.

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,

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rhinosinusitis, and rhinoconjunctivitis), grass, sublingual, subcutaneous, and immunotherapy. The computer search was supplemented with manual searches of reference lists for all available review articles, primary studies, and abstracts from conferences. We selected 38 randomized controlled trials (RCTs),⁹⁻⁴⁷ using the methodology reported in our previous meta-analysis published in this journal.⁶ Detailed descriptions of setting and selection of the studies have been reported (see the **Methods** section in this article's Online Repository at www.jacionline.org).

Statistical analysis

The symptom and medication scores were assessed as outcome measures of the treatment's effect. These data were available in all 36 trials for symptom score^{9-16,19-47} and in 31 RCTs for medication score.^{10-13,15,16,20-35,38-41,43-47} The outcome data analyzed were continuous, but different scoring systems and scales for symptoms and medication were used by the researchers. Therefore, to compare the results, analyses were performed by the method of standardized mean difference (SMD), expressing the differences in means between SLIT or SCIT and placebo in terms of units of the pooled SD. The overall SMD among patients treated with SLIT or SCIT and placebo was estimated with models that were on both fixed effects and random effects assumptions, but we showed in the figures only the results of the random effects model because it is the most conservative.⁴⁸ 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>).⁴⁹⁻⁵¹

A descriptive subgroup analysis was performed on both symptom and medication scores. 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, center (unicenter vs multicenter studies) and evaluation period (peak vs whole pollen season), and 3 dichotomized variables (below or above median): size (sample size of the study), duration of treatment (year), and dropout and withdrawal rate (%). The I^2 statistic, which describes the percentage of variability due to heterogeneity rather than sampling errors, was used to quantify heterogeneity.⁵² Influential analysis—that is, the exclusion of outlying studies until homogeneity has been achieved—was also used to explore heterogeneity. This approach was used to examine the effect of studies identified as being aberrant in either results or methodology.

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 insignificant, unpublished (or missing) studies that would need to be added to a meta-analysis to reduce an overall statistically significant result to insignificance. 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.⁵¹

RESULTS

Features of RCTs

The main features of the studies included in the meta-analysis are shown in **Table I**. The 36 RCTs^{9-16,19-47} (22 for SLIT^{9-14,20-35} and 14 for SCIT^{15,16,36-47}) included a total of 3014 patients treated with immunotherapy and 2768 controls who received placebo. SLIT was administered by sublingual drops in 10 RCTs^{10,12,20-27} and by tablets in 12 RCTs.^{9,11,13,14,28-35} Seven^{11,13,23-25,29,34} of the 22 SLIT^{9-14,20-35} studies enrolled only children (<18 years), another 2 included both adults and children^{25,28}; none of the 14 SCIT studies enrolled children only,^{15,16,36-47} although 5 of them included some patients younger than age 18.^{36,38,41-43} The sample size of the RCTs varied greatly (SLIT: 34²⁰ to 578³⁰ patients; SCIT: 15³⁶ to 943¹⁵ patients).

Seven^{9,14,20-22,26,29} of the 22 SLIT studies^{9-14,20-35} were performed in a single center (or in 2 centers from the same area), whereas 8^{36-41,43,45} of the 14 SCIT RCTs were unicenter studies (or from 2 centers from the same area).^{15,16,36-47} Great variability was observed in the length of the treatment (SLIT: 3²⁰ to 36²³ months; SCIT: 1.5^{42,44} to 36⁴¹ months). High variability was also observed in the dose of allergens administered both for SLIT and for SCIT (**Table I**). Withdrawals and dropout rates varied among studies (0%-11% for SLIT; 0%-21.2% for SCIT).

Symptom score

The effect of grass pollen immunotherapy on symptom score is shown in **Fig 1**, in which SLIT via drops (SLIT-D; group 1) or tablets (SLIT-T; group 2) and SCIT (group 3) are compared with placebo, is plotted on the graph. All the studies, except one,¹² showed a reduction of symptom score in actively treated patients compared with placebo, but it was statistically significant in 3^{10,20,27} of the 10 studies performed with SLIT-D^{10,12,20-27} in 8^{11,14,29-31,33-35} of the 12 studies with SLIT-T,^{9,11,13,14,28-35} and in 12^{15,16,36-38,40-42,44,47} of the 14 SCIT studies.^{15,16,36-47} The pooled SMD for the treatment effect was -0.25 (95% CI, -0.45 to -0.05 ; $P < .01$) for SLIT-D, -0.40 (95% CI, -0.54 to -0.27 ; $P < .001$) for SLIT-T, and -0.92 (95% CI, -1.26 to -0.58 ; $P < .0001$) for SCIT, indicating a statistically significant and considerable clinical benefit in patients treated with SCIT and a mild-to-moderate benefit for patients treated with SLIT, both drops and tablets, compared with placebo.⁵² All the studies were performed in European countries, except 2 for SLIT-T,^{34,35} which were performed in the United States and Canada, and 1 for SCIT,¹⁵ which was mainly performed in the United States and Canada, with a minority of European patients (9 European, 75 North American centers). Excluding these latter studies the pooled SMD increased to -0.43 (95% CI, -0.59 to -0.26 ; $P < .00001$) for SCIT-T and to -1.05 (95% CI, -1.44 to -0.65 ; $P < .00001$) for SCIT, showing a remarkable difference, in particular for SCIT, for the treatment effectiveness between the European and American studies.

The fail-safe number was 530 for SLIT studies and 232 for SCIT studies, high enough to confirm the robustness of the results against publication bias.

A remarkable degree of heterogeneity between the results of individual studies was reported, both for SLIT (SLIT-D: $Q = 17.32$; $df = 9$; $P = .04$; $I^2 = 48\%$; SLIT-T: $Q = 31.89$; $df = 11$; $P = .008$; $I^2 = 66\%$) and SCIT ($Q = 109.35$; $df = 13$; $P = .00001$; $I^2 = 88\%$). The highest degree of heterogeneity was reported for SCIT, but the effect of SCIT reported by the individual studies lies on the same side of the reference line.

The subgroup analysis performed to evaluate whether there was evidence of a different effect of both SLIT and SCIT in predefined subgroups of patients is reported in **Fig 2**.

Medication score

Data on medication score were obtained for 20 SLIT RCTs^{10-13,20-35} and 11 SCIT RCTs.^{15,16,38-41,43-47} Although almost all the studies showed a reduction of rescue medication score compared with placebo, a statistically significant difference was observed only in 10 RCTs for SLIT^{10,11,20,26,27,29-33} and in 5 for SCIT^{16,39-41,47} (**Fig 3**). The pooled estimate of treatment on medication score was statistically significant both for SLIT

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

Study (year)	Country (no. of centers)	Participants	Male (%)	Age (y), mean (range)	Asthma (%)	Type of treatment	Cumulative dose	Treatment duration (mo)*	Evaluation period
SLIT drops									
Feliziani (1995) ²⁰	Italy (1)	T 18 → 18 P 16 → 16	NR	NR (14-48)	NR	5 Grass extracts	480 µg of 5 grass pollens†	4	Peak pollen season
Hordijk (1998) ²¹	Netherlands (2)	T 27 → 24 P 30 → 30	47	27.5 (18-45)	NR	5 Grass extracts	2,250 µg of Lol p5†	13	Whole pollen season
Torres-Lima (2002) ²²	UK (2)	T 28 → 26 P 28 → 23	57	34 (21-55)	NR	Phl p 5	17,000 µg of major allergen Phl p 5†	14-24	Peak pollen season
Bufe (2004) ²³	Germany (33)	T 82 → 68 P 79 → 64	NR	9.3 ± 3 (NR)	42	Phl p 5 extracts	9.6 mg of major allergen Phl p 5	41	Whole pollen season
Rolinck-Werninghaus (2004) ²⁴	Germany (4)	T 49 → 39 P 48 → 28	67	NR (3-14)	40	5 Grass extracts	188 µg of group 5 major allergen	33	Peak pollen season
de Blay (2007) ²⁵	France (15)	T 61 → 53 P 57 → 51	66.3	25 ± 7.5 (12-41)	27.9	3 Grass extracts		18	
Mösges (2007) ¹⁰	Germany (14)	T 48 → 48 P 53 → 53	NR	NR (18-50)	NR	5 Grass extracts	3,500 µg of Phl p 5	13	Peak pollen season
Röder (2007) ²⁶	Netherlands (2)	T 108 → 91 P 96 → 77	56.5	12.7 ± 2.7 (6-17)	58.3	5 Grass extracts	4.5 mg equivalent Lol p 5	30	Whole pollen season
Pfaar (2008) ²⁷	Germany Poland Macedonia (11)	T 94 → 42 P 91 → 48	62.5	33.1 (17-59)	29.2	6 Grass extracts	20.23 ± 4.60 mg	28	Peak pollen season
Ott (2009) ¹²	Germany (multi-center)	T 123 → 99 P 60 → 46	59	33.3 ± 10.4 (7.9-64.7)	13.1	5 Grass extracts	1,500 µg of group 5 major allergen	3 for 2 consecutive years	Whole pollen season
SLIT tablets									
Pradaliere (1999) ²⁸	France (20)	T 63 → 62 P 63 → 61	52	29 ± 11 (7-58)	34	5 Grass extracts	935 µg of group 5 major allergen	7	Whole pollen season
Caffarelli (2000) ²⁹	Italy (1)	T 24 → 24 P 24 → 20	57	8.4	98	Allergoid, 3 pollens	37,250 AU	3	Peak pollen season
Smith (2004) ⁹	UK (1)	T 62 → 45 P 62 → 51	48	38.5 (18-58)	NR	5 Grass extracts	6,264 mg of Lol p 1; 3,654 mg of Dac g 5	28	Whole pollen season
Dahl (2006) ³⁰	Europe (58)	T 316 → 282 P 318 → 286	59	34.2 ± 9.8 (18-65)	NR	Phl p 5 extracts	4,500 µg of major allergen Phl p 5†	10	Whole pollen season
Dahl (2006) ³¹	Denmark (11) Sweden (4)	T 74 → 61 P 40 → 32	67.5	37.5 ± 10.2 (18-64)	100	Phl p 5 extracts	3,600 µg of major allergen Phl p 5†	8	Whole pollen season
Durham (2006) ³²	Europe, Canada (55)	T 153 → 131 P 150 → 129	61.5	36.5 (18-65)	NR	Phl p 5 extracts	3,600 µg of major allergen Phl p 5†	8	Whole pollen season
Didier (2007) ³³	Europe (10)	T 155 → 136 P 156 → 148	56.9	29.4 ± 7.3 (18-45)	10	5 Grass extracts	7,500 µg of major allergen Phl p 5†	11	Whole pollen season
Wahn (2009) ¹¹	Europe (29)	T 139 → 131 P 139 → 135	64.3	10.9 ± 10.2 (5-17)	21.4	5 Grass extracts	7,200 µg of major allergen Phl p 5†	12	Whole pollen season
Bufe (2009) ¹³	Germany (26)	T 126 → 117 P 127 → 121	66	10.1 (5-16)	42	Phl p 5 extracts	3,600 µg of major allergen Phl p 5†	8	Whole pollen season
Horak (2009) ¹⁴	Austria (1)	T 45 → 45 P 44 → 44	NR	NR (18-50)	NR	5 Grass extracts	2,400 µg of major allergen Phl p 5†	4	Whole pollen season‡
Blaiss (2011) ³⁴	USA (41) Canada (8)	T 173 → 149 P 167 → 158	65	5-17	26	Phl p 5 extracts	2,500 µg of major allergen Phl p 5†	5.5	Whole pollen season
Nelson (2011) ³⁵	USA (44) Canada (7)	T 213 → 208 P 225 → 225	50	18-65	23	Phl p 5 extracts	3,600 µg of major allergen Phl p 5†	7	Whole pollen season
SCIT									
Ortolani (1984) ³⁶	Italy (1)	T 8 → 8 P 7 → 7	40	22.5 (15-45)	100%	3 Grass pollen extracts	18,000 RAST-U	8	Pollen season
Bousquet (1987) ³⁷	France (1)	T 40 → 39 P 20 → 20	NR	25.2 ± 12.1	NR	Allergoid, 6 pollens	25,649.5 ± 17,704.3 PNU	1.5	Peak pollen season
Bousquet (1990) ³⁸	France (1)	T 20§ → 20 P 18 → 18	42.1	26.8 ± 10.4 (11-45)	>50%	Allergoid, 6 pollens	45,433 ± 14,001 PNU	1.5	1.5 mo (May 1 to June 15)
Varney (1991) ³⁹	UK (2)	T 20 → 19 P 20 → 16	55	35	45%	Grass pollen extracts/depot	840,000 BU	5	Whole pollen season
Pastorello (1992) ⁴⁰	Italy (1)	T 10 → 10 P 9 → 9	26.3	27.4 (18-56)	NR	Allergoid/depot	116,045 PNU	5	1 mo (May)

(Continued)

TABLE I. (Continued)

Study (year)	Country (no. of centers)	Participants	Male (%)	Age (y), mean (range)	Asthma (%)	Type of treatment	Cumulative dose	Treatment duration (mo)*	Evaluation period
Dolz (1996) ⁴¹	Spain (1)	T 20→18 P 10→10	NR	19.1 (15-35)	21.4	Grass pollen extracts/depot	2,125,150 USQ	36	1 mo (May 15 to June 15)
Zenner (1997) ⁴²	Germany (12)	T 45→41 P 41→40	68.6	28.5 (16-53)	34.9	Grass pollen extracts/depot	3 µg of major allergen group 5	1.5	Pollen season (10 wk)
Brewczynski (1999) ⁴³	Poland (1)	T 10→10 P 10→8	50	22.1 (14-34)	25	Alleroid/depot	120,000 AU-equivalents	12	Pollen season
Drachemberg (2001) ⁴⁴	Germany(13) Austria (1)	T 81→74 P 60→50	54	28.7	NR	Allergoid/depot	60 µg of group 1 grass pollen allergen	1.5	1 mo (May 15 to June 15)
Jutel (2005) ⁴⁵	Poland (1)	T 31→29 P 31→28	64.9	24.7	19.3	Recombinant allergens/depot	490 µg of total protein‡	20-21	Peak after 18 mo
Corrigan (2005) ⁴⁶	Germany (8) UK (2)	T 77→66 P 77→62	41.6	34.5 (18-60)	27.3	Allergoid/depot, 6 pollens	20,000 TU	4.5 for 2 consecutive y	Peak pollen season
Frew (2006) ⁴⁷	UK (26)	T 203§→187 P 103→89	56.2	38.2 (18-60)	NR	Grass pollen extracts/depot	80 of µg Phl p5	6	Whole pollen season
DuBuske (2011) ¹⁵	USA (58) Canada (17) Europe (9)	T 514→473 P 514→470	50.8	35.5 ± 11	14	Allergoid/depot, 13 pollens	21.5 µg of Lol p1	3	Peak and whole pollen season
Pfaar (2012) ¹⁶	Germany (30)	T 126→98 P 53→44	NR	33 (11-69)	NR	Allergoid	160 µg of Phl p5	1.5	Whole pollen season

NR, Not reported; P, placebo; T, treated; UK, United Kingdom; USA, United States of America.

*Treatment duration up to the evaluation period.

†The cumulative dose was not reported in the original article and was calculated by the authors of the present meta-analysis.

‡The efficacy of SLIT was evaluated in patients exposed to pollens in an allergen challenge chamber.

§Only high-dose group was analyzed.

||Median.

(SLIT-D: SMD, -0.37 ; 95% CI, -0.7 to -0.00 ; SLIT-T: SMD, -0.30 ; 95% CI, -0.44 to -0.16) and for SCIT (SMD, -0.58 ; 95% CI, -0.86 to -0.30).

The fail-safe number was high enough to exclude other analyses for publication bias both for SLIT (384) and for SCIT (66).

Significant between-study heterogeneity was reported (SLIT-D: $Q = 68.6$; $df = 9$; $P = .0001$; $I^2 = 86.9\%$; SLIT-T: $Q = 25.2$; $df = 9$; $P = .0028$; $I^2 = 64.3\%$; SCIT: $Q = 53$; $df = 10$; $P = .0001$; $I^2 = 81.1\%$; Fig 3).

Subgroup analysis is shown in Fig 4. Additional analysis and an expanded version of the analyses shown above both for symptom and medication scores are available (see the Methods section in this article's Online Repository).

Safety

A total of 960 treatment-emerged adverse events (AEs) was reported for patients who received SCIT (0.86 AEs/patient), less than one-half of those receiving SLIT (4046 AEs; 2.13 AE/patient; Table II). Most AEs were modest in severity for both the treatment and placebo groups. The withdrawal rate for AEs was higher in the SLIT group (78 patients; 0.04%) than in the SCIT group (18 patients; 0.019%). Twelve episodes of anaphylaxis requiring epinephrine treatment were reported in SCIT-treated patients, only 1 in patients receiving SLIT. Notably, 2 episodes of anaphylaxis were also reported in patients treated with placebo in the SCIT studies (Table II).

DISCUSSION

This meta-analysis of data from 36 RCTs, representing a pooled total of 3014 patients treated with immunotherapy and

2768 controls who received placebo, provides indirect evidence that, in patients with seasonal allergic rhinoconjunctivitis to grass, SCIT is more effective than SLIT in the control of symptoms and in the reduction of antiallergic medication use. The evidence has to be considered indirect because it is based on trials that compared immunotherapy with placebo, not on a direct comparison between the 2 different treatments. No comparative RCTs between SCIT and SLIT with grass pollen for allergic rhinitis have been published to date. The only small study that compared these 2 routes for grass allergens is not a randomized study and had unreliable results.⁷

Significant heterogeneity exists among the results of individual RCTs, in particular for SCIT studies, and this may raise some concerns. Indeed, any amount of heterogeneity is acceptable, providing both that the predefined eligibility criteria for the meta-analysis are sound and that the data are correct.⁵³ Although in particular some of the SCIT trials included in our analysis were performed more than 2 decades ago on small sample sizes, their quality has been considered sufficient to justify their admission not only in ours but also in different Cochrane meta-analyses.⁵⁴⁻⁵⁶ Moreover, something to be considered to understand if heterogeneity is too high is the observed directions of effects,⁵³ and in this case all the effects lie on the same side of the reference line (Fig 1 and Fig 2).

The benefit of SCIT is likely to be even greater if we consider only the European population. Indeed, excluding the largest trial by DuBuske et al,¹⁵ mainly performed on North American patients, we reported an increased efficacy of SCIT, with a pooled summary SMD of -1.05 (95% CI, -1.44 to -0.65). By contrast, it must be noted that the 2 SLIT studies conducted on the North American population also showed a small benefit compared

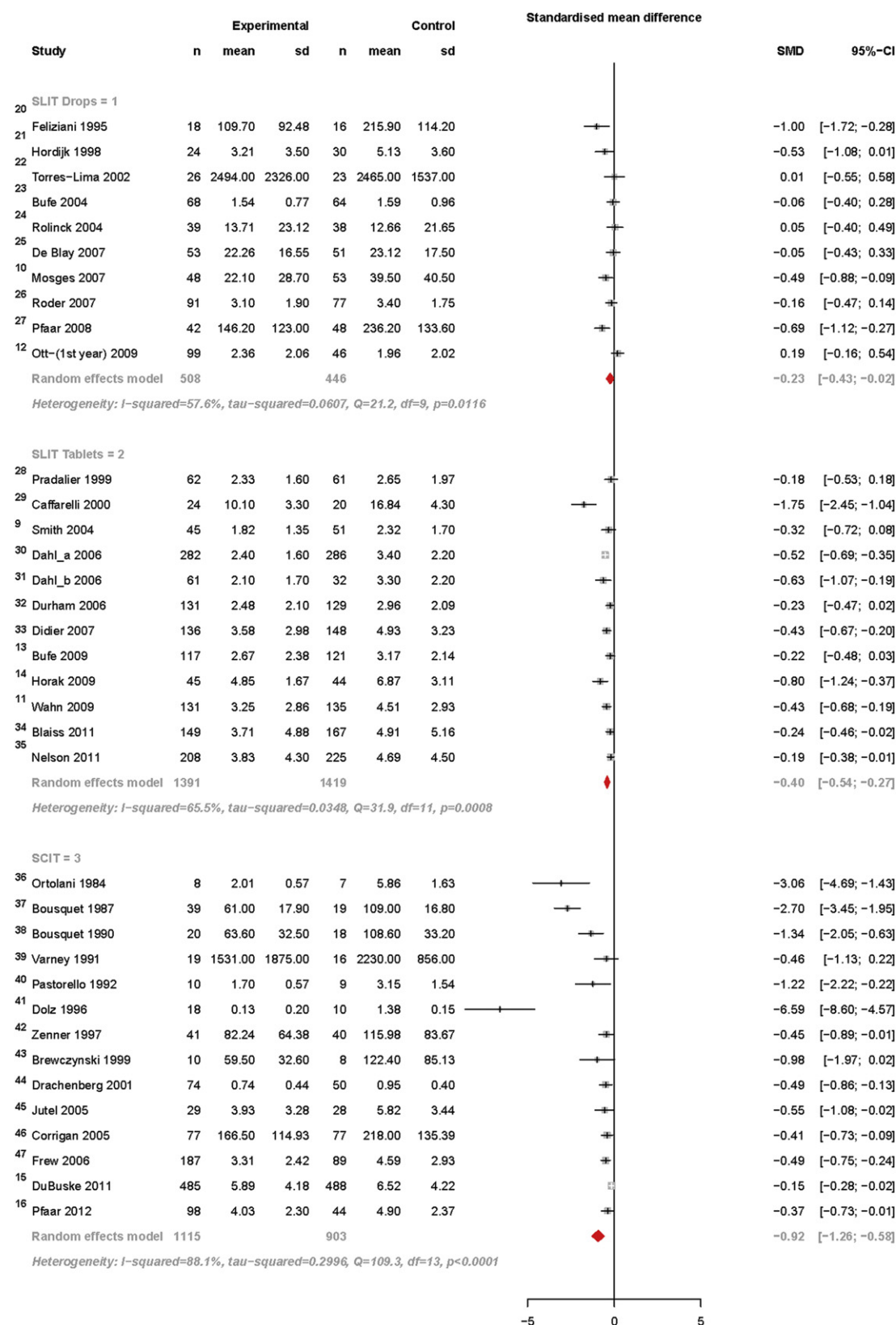


FIG 1. Meta-analysis of 36 RCTs of allergen specific immunotherapy versus placebo for seasonal allergic rhinosinusitis: 10 RCTs of SLIT-D (group 1), 12 RCTs of SLIT-T (group 2), and 14 RCTs of SCIT, using the random effects model. The SMD and 95% CI for the effect of allergen specific immunotherapy on symptom score are plotted on the graph. Studies of each group are arranged chronologically on the basis of the year of publication. For the studies by Pfaar and Klimek²⁷ and Pastorello et al,⁴⁰ the combined symptom-medication score was used.

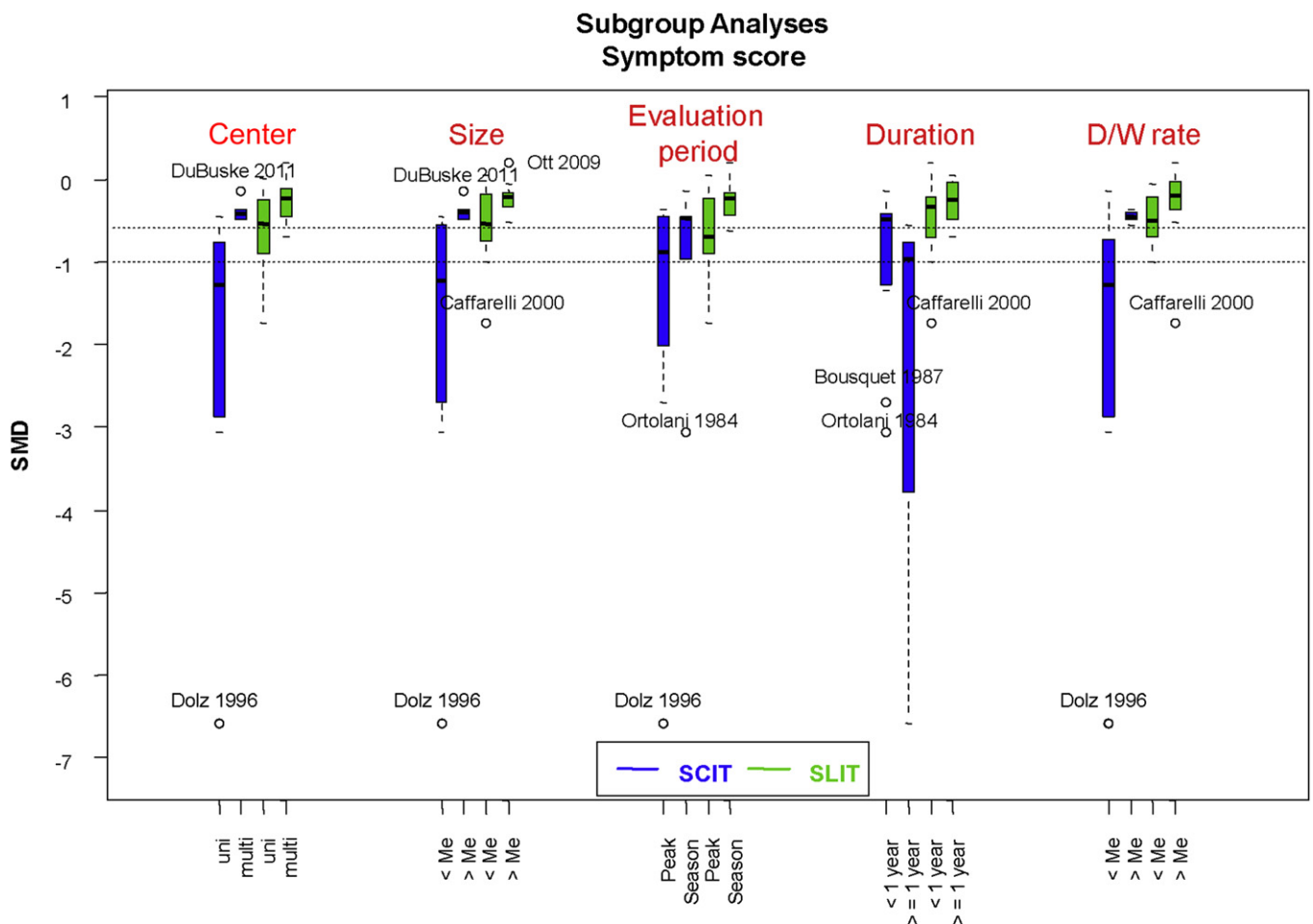


FIG 2. Descriptive subgroup analysis for symptom score of the 36 RCTs of allergen specific immunotherapy versus placebo for seasonal allergic rhinosinusitis. Box plots include the middle 50% of the data. The horizontal bars inside the boxes represent the median SMDs. The dotted lines to the whiskers extend to the most extreme data points, which are no more than 1.5 times the interquartile range from the box. Unicenter versus multicenter studies: SCIT median SMD unicenter, -1.28 ; SCIT median SMD multicenter, -0.42 ; SLIT median SMD unicenter, -0.53 ; SLIT median SMD multicenter, -0.22 . Sample size [below/above the median sample size (MSS) of all the studies]: SCIT median SMD below MSS, -1.28 ; SCIT median SMD above MSS, -0.40 ; SLIT median SMD below MSS, -0.53 ; SLIT median SMD above MSS, -0.22 . In some studies the symptom score was evaluated during the whole pollen season, in others during the week with the highest pollen count (peak): SCIT median SMD at peak, -0.89 ; SCIT median SMD whole season, -0.47 ; SLIT median SMD at peak, -0.69 ; SLIT median SMD whole season, -0.23 . Duration of treatment: SCIT median SMD <12 months, -0.49 ; SCIT median SMD ≥ 12 months, -0.97 ; SLIT median SMD <12 months, -0.33 ; SLIT median SMD ≥ 12 months, -0.24 . Rate of dropout and withdrawal (D/W) of individual studies (below/above the median value of 9.2%): SCIT median SMD $<9.2\%$, -1.28 ; SCIT median SMD $\geq 9.2\%$, -0.45 ; SLIT median SMD $<9.2\%$, -0.51 ; SLIT median SMD $\geq 9.2\%$, -0.20 .

with the overall population, confirming the different response to immunotherapy from European and American studies. The reason for this difference is unknown, but it may be related to environmental conditions. This hypothesis is strengthened by more evidence. Subgroup analysis by center showed that the effectiveness was considerably higher in the unicenter compared with multicenter studies. A possible explanation could be that the population under study in a single center is exposed to more homogeneous environmental conditions, compared with those in a multicenter study, enrolling subjects living in different countries, or even different continents¹⁵ in some cases.

The results of the subgroup analysis by sample size of the studies could also be interpreted in this light. The better results were shown in the smallest studies because they are mainly

unicenter studies, obviously including a lower number of patients than multicenter studies. The findings from the subgroup analyses, which are stronger effects in small, single center studies and weaker effects in large, multicenter studies, could be suggestive of potential publication bias. The high fail-safe number reported for both SCIT and SLIT ruled out this possibility, even though the asymmetric funnel plot shown for SCIT studies (data not shown) leaves some doubts for the latter. However, a publication bias, if any, is unlikely to influence the results of the subgroup analysis about the differences between multi/unicenter and small/big studies. In fact, the results were the same both for SLIT studies, with no evidence of publication bias at all, and SCIT studies, with asymmetrical funnel plot, but a very high fail-safe number; if publication bias was responsible for the observed effect in the

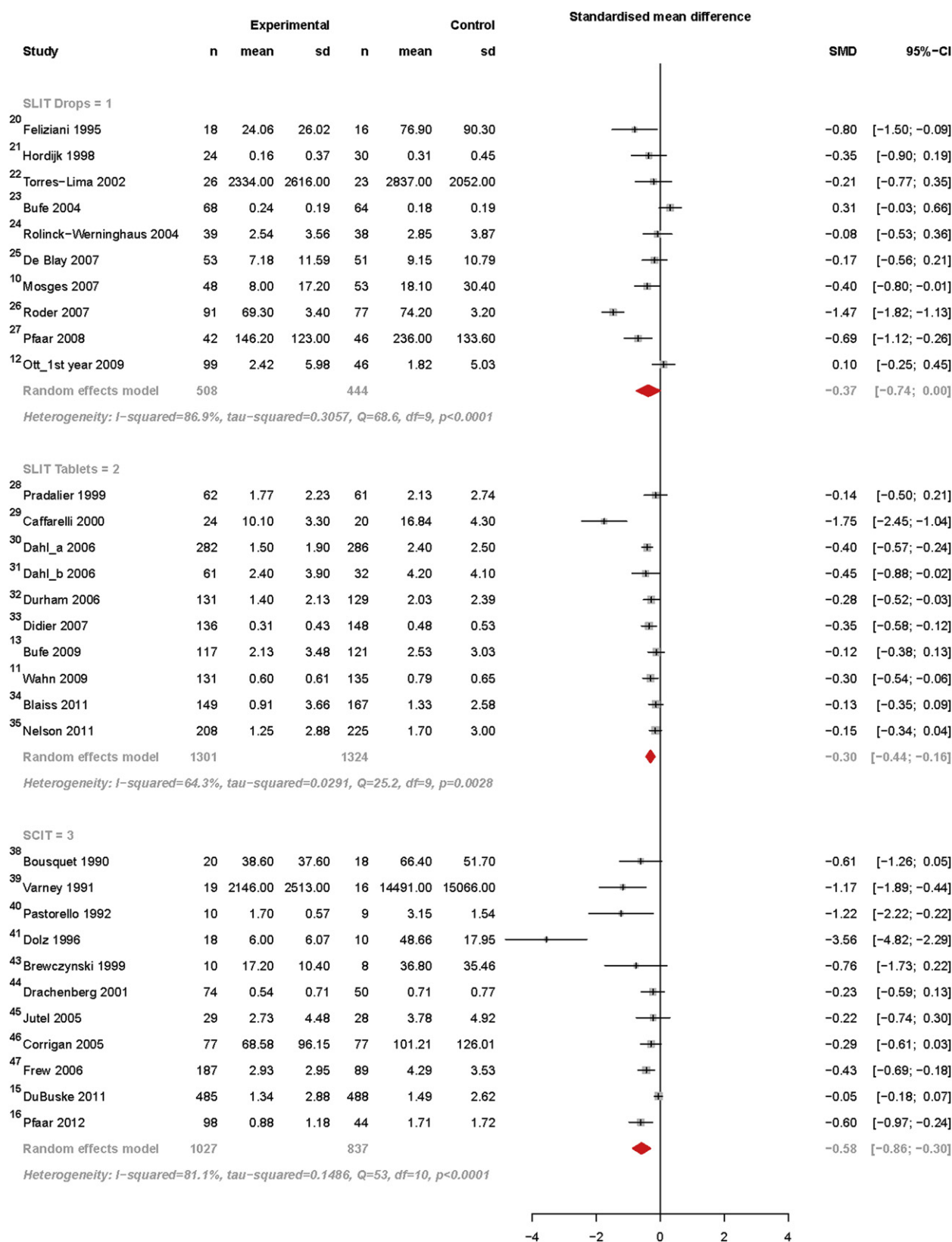


FIG 3. Meta-analysis of 34 RTCs of allergen specific immunotherapy versus placebo for seasonal allergic rhinosinusitis: 10 RCTs of SLIT-D (group 1), 10 RCTs of SLIT-T (group 2), and 14 RCTs of SCIT, using the random effects models. The SMD and 95% CI for the effect of SLIT on medication score are plotted on the graph. Studies are arranged chronologically on the basis of the year of publication. For the studies by Pfaar and Klimek²⁷ and Pastorello et al⁴⁰ the combined symptom-medication score was used.

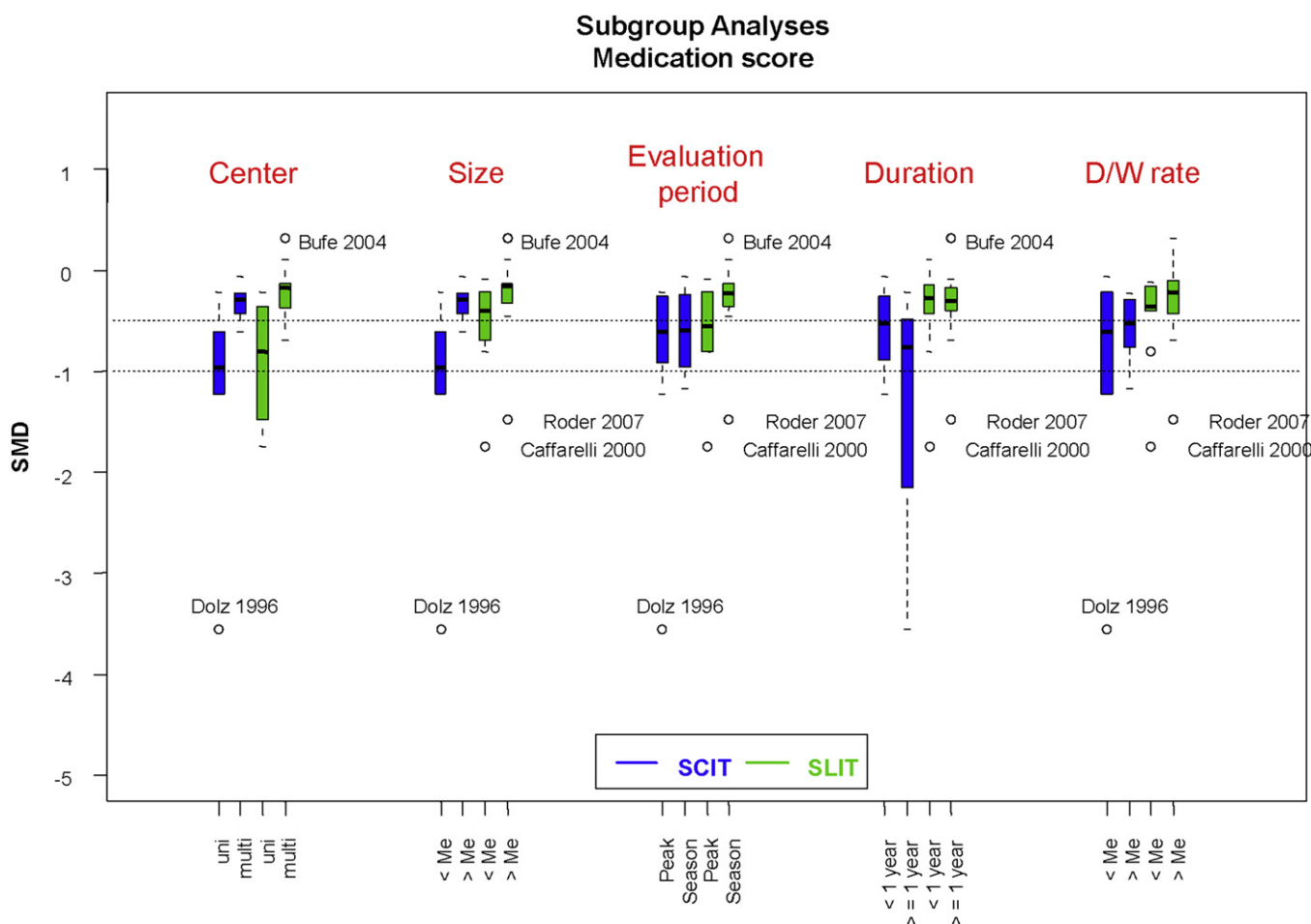


FIG 4. Descriptive subgroup analysis for medication score of the 34 RCTs of allergen specific immunotherapy versus placebo for seasonal allergic rhinosinusitis. Box plots include the middle 50% of the data. The *horizontal bars* inside the boxes represent the median SMDs. The *dotted lines* to the whiskers extend to the most extreme data points, which are no more than 1.5 times the interquartile range from the box. Unicenter versus multicenter studies. SCIT median SMD: unicenter, -0.96 ; multicenter, 0.29 . SLIT median SMD: unicenter, -0.79 ; multicenter, -0.17 . Sample size [below/above the median sample size (MSS) of all the studies]: SCIT median SMD below MSS, -0.96 ; SCIT median SMD above MSS, -0.28 ; SLIT median SMD below MSS, -0.40 ; SLIT median SMD above MSS, -0.15 . Peak/whole pollen season: SCIT median SMD at peak, -0.60 ; SCIT median SMD whole season, -0.51 ; SLIT median SMD at peak, -0.54 ; SLIT median SMD whole season, -0.22 . Duration of treatment: SCIT median SMD <12 months, -0.51 ; SCIT median SMD ≥ 12 months, -0.75 ; SLIT median SMD <12 months, -0.28 ; SLIT median SMD ≥ 12 months, -0.30 . Rate of dropout and withdrawal (D/W) of individual studies (below/above the median value of 9.2%): SCIT median SMD $<9.2\%$, -0.60 ; SCIT median SMD $\geq 9.2\%$, -0.51 ; SLIT median SMD $<9.2\%$, -0.53 ; SLIT median SMD $\geq 9.2\%$, -0.20 .

subgroup analyses, we would have shown the effect only in the SCIT subgroup, as the result of a potential publication bias, but not in the SLIT subgroup.

Another consideration must be taken into account to better appraise the difference in effectiveness between SCIT and SLIT. The studies showing the highest benefit of SLIT-T are (1) the study from Caffarelli et al,²⁹ which is the only one performed with an allergoid and enrolling almost all asthmatic patients; (2) the study from Dahl et al,³¹ performed on asthmatic patients, with allergic rhinitis analyzed as secondary outcome; and (3) the study from Horak et al,¹⁴ performed in an allergen challenge chamber. Excluding these 3 studies with such peculiar characteristics, the pooled SMD decreased to -0.32 (95% CI, -0.42 to -0.23), showing that SLIT-T is even much less effective than SCIT compared with placebo. SLIT-T was more effective than SLIT-D, so

the same conclusions are also valid for the latter. Indeed, it must be noted that the difference between SLIT-D and SLIT-T is likely because of the child studies. In fact, limiting the analysis only to the adult studies, we reported the same pooled SMD compared with placebo for studies with drops (SMD, -0.37) and tablets (SMD, -0.38). As we showed in our previous meta-analysis,⁶ a possible explanation for this different effect between adults and child studies could be the low dose of allergen administered in the child studies. In fact, we previously showed that a monthly dose ≤ 275 μg of the main allergen, the one mostly used in children studies, was insufficient to obtain a clinically significant response to treatment and that the ideal dose was between 276 and 600 μg .⁶ Unfortunately, we could not analyze the same issue for SCIT studies. In fact, different units of measure were used in different studies to report the allergen content of each

TABLE II. Total AEs related to SCIT and SLIT

	SCIT		SLIT	
	Treated	Placebo	Treated	Placebo
Total AEs, no.	960	456	4046	1856
Total AEs/patients, %	0.86	0.5	2.13	0.99
Withdrawals for AE, no.	18	5	78	25
Withdrawals for AE/patient, %	0.019	0.005	0.04	0.013
Anaphylactic reactions, no.	12	2	1	0

pharmaceutical preparation and most of them (8 of 14) were not comparable. Only in 6 of 14 studies was the allergen content of the vaccines expressed as micrograms, but these studies are insufficient for a reliable subgroup analysis.

Another important source of heterogeneity between the results of individual studies is the evaluation period. In some studies symptom and medication scores are assessed during the peak weeks of the pollen season, in others during the whole pollen season. This different criteria used for the evaluation of the treatment benefit led to different results, with a clearly higher benefit for symptom score reported in the studies that evaluated the treatment effect during the peak pollen season, when patients complain the most of severe allergic symptoms, notably with similar median values of SMD for SCIT and SLIT (Fig 2) (see the [Methods](#) section in this article's Online Repository).

The subgroup analysis by duration of treatment showed that a SCIT treatment lasting at least 1 year is associated with a better response both for treatment and medication scores. This result is consistent with the conclusion of the observational study by Walker et al,⁵⁷ showing that clinical improvement of symptoms was maintained with continued immunotherapy during 3 or 4 years of treatment. However, most RCTs published to date used a short treatment schedule for SCIT, probably to confront the problem of compliance to a treatment considered by patients long and uncomfortable compared with SLIT, which can be self-administered by the patient at home, without the observation period needed after the administration of the subcutaneous vaccine at the physician's office. It is also possible that the long-term treatment with placebo injections could hamper the SCIT trials. This might be true for adults, but in particular for children.

Considering the results of our analysis safety is the most important reason for the choice of SLIT as the preferential form of immunotherapy. Both RCTs and nonrandomized or observational studies reported major adverse events, such as anaphylaxis, after vaccination, although adequately managed by the physician and rapidly resolved. In the RCTs included in the present meta-analysis we reported 12 episodes of anaphylaxis that required epinephrine, of the 960 patients treated with SCIT, and only 1 of the 4046 patients treated with SLIT, confirming that SLIT is associated with a negligible number of major adverse events, but also confirming that they are rare in the SCIT group. Paradoxically, the number of total AEs, mild to severe, is higher in the SLIT than in the SCIT group. For SCIT, no difference was observed in the prevalence of significant adverse events between build-up/induction and maintenance periods, but data from most RCTs, especially the older ones, are insufficient to draw firm conclusions (collectively only 3 of 14 studies reported in which phase, induction or maintenance, the adverse events occurred, and it appeared they were prevalent in the induction phase).

The dropout/withdrawal rate varies greatly among the studies. This could represent a methodologic limit of many studies, potentially biasing the statistical analysis. By subgroup analysis we showed that the studies with a low dropout/withdrawal rate show a higher benefit of the treatment than studies with a high number of dropout/withdrawals. This is more evident for symptom score in patients treated with SCIT. Besides the considerations of the quality of the studies with a possibly inappropriate handling of dropout or withdrawals, we can also hypothesize that the adherence to the treatment could influence the final results, with the highest benefit in studies with high degree of adherence to treatment.

A limit of this analysis is that the studies have different rescue medication scores. This could suggest that the antiallergic medication use could have influenced the results of each study about the symptom score reduction. However, the direction of the effect is the same for both symptom and medication scores, although, in contrast to symptom score, for medication score the difference between SCIT and SLIT was not statistically significant. However, compared with the symptom score analysis, data from 3 studies are missing,^{36,37,42} and this could have partially influenced the final result.

The subgroup analyses also seem to confirm the previous hypothesis. In fact, the results of each subgroup analysis showed the same direction of the effect both for symptom and medication score for all the stratifying variables except for the treatment duration. The discrepancy for treatment duration could be explained by our previous findings⁶ on the importance of the length of the preseasonal treatment (>16 weeks) to achieve the best SLIT efficacy instead of the length of treatment during the season.

The results of this retrospective analysis are subject to limitations, for differences in patient (such as differences in the baseline severity of the disease and the different prevalence of other comorbidities such as asthma) and study characteristics. 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, variations because they reflect group averages rather than individual data.

In conclusion, the available data provide indirect evidence that for seasonal allergic rhinoconjunctivitis SCIT with grass allergens is more effective than SLIT in the control of symptoms and in the reduction of antiallergic medications. Trials directly comparing these 2 routes of immunotherapy are needed to confirm this evidence.

On the basis of the findings from this and the previous meta-analysis,⁶ an ideal comparative study should be a randomized, placebo-controlled, double-blind, double-dummy study that enrolls a large number of patients from a single center or a single country or a few countries with similar pollen exposure and with people of similar ethnicity. The treatment should be started at least 16 weeks before the expected beginning of the pollen season and should last 1 or 2 years. A vaccine with a dose of the main extract ≥ 275 μ g for SLIT should be used. The ideal dose for SCIT vaccines has still to be defined.

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Clinical implications: SCIT with grass allergens is more effective than SLIT for adult patients with rhinoconjunctivitis. Trials directly comparing these 2 routes of immunotherapy are needed to confirm this evidence.

REFERENCES

1. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockett RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;62:317-24.
2. Bousquet J, Schünemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, et al. In collaboration with the WHO Collaborating Center of Asthma and Rhinitis (Montpellier). Development and implementation of guidelines in allergic rhinitis – an ARIA-GA2LEN paper. *Allergy* 2010;65:1212-21.
3. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
4. Cox L, Wallace D. Specific allergy immunotherapy for allergic rhinitis: subcutaneous and sublingual. *Immunol Allergy Clin North Am* 2011;31:561-99.
5. Calderón MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol* 2011;127:30-8.
6. Di Bona D, Plaia A, Scafidì V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010;126:558-66.
7. Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996;26:1253-61.
8. Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59:45-53.
9. Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831-7.
10. Mösges R, Brüning H, Hessler HJ, Götz G, Knaussmann HG. Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial. *Acta Dermatovenereol Alp Panonica Adriat* 2007;16:143-8.
11. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6.
12. Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:1394-401.
13. Bufer A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73.
14. Horak F, Jaeger S, Worm M, Melac M, Didier A. Implementation of pre-seasonal sublingual immunotherapy with a five-grass pollen tablet during optimal dosage assessment. *Clin Exp Allergy* 2009;39:394-400.
15. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultra-short-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc* 2011;32:239-47.
16. Pfaar O, Urry Z, Robinson DS, Sager A, Richards D, Hawrylowicz CM, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. *Allergy* 2012;67:272-9.
17. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
18. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME, et al. Clinical efficacy and safety of pre-seasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients: a double-blind, placebo-controlled study. *Allergol Immunopathol (Madr)* 2006;34:194-8.
19. Bousquet PJ, Calderón MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. The Consolidated Standards of Reporting Trials (CONSORT) statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA2)LEN article. *J Allergy Clin Immunol* 2011;127:49-56.
20. Feliziani V, Lattuada G, Parmiani S, Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts: a double blind study. *Allergol Immunopathol (Madr)* 1995;23:224-30.
21. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardized grass pollen extract: a double-blind placebo-controlled study. *Allergol Immunopathol (Madr)* 1998;26:234-40.
22. Torres-Lima M, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002;32:507-14.
23. Bufer A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004;59:498-504.
24. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59:1285-93.
25. de Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, Tunon de Lara JM, et al. SUBLIM Group. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2007;99:453-61.
26. Röder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007;119:892-8.
27. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2008;100:256-63.
28. Pradaliere A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999;54:819-28.
29. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000;55:1142-7.
30. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
31. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90.
32. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
33. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
34. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
35. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80.
36. Ortolani C, Pastorello E, Moss RB, Hsu YP, Restuccia M, Joppolo G, et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. *J Allergy Clin Immunol* 1984;73:283-90.
37. Bousquet J, Frank E, Soussana M, Hejjoui A, Maasch HJ, Michel FB. Double-blind, placebo-controlled immunotherapy with a high-molecular-weight, formalinized allergoid in grass pollen allergy. *Int Arch Allergy Appl Immunol* 1987;82:550-2.
38. Bousquet J, Hejjoui A, Soussana M, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol* 1990;85:490-7.
39. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:265-9.
40. Pastorello EA, Pravettoni V, Incorvaia C, Mambretti M, Franck E, Wahl R, et al. Clinical and immunological effects of immunotherapy with alum-adsorbed grass allergoid in grass-pollen-induced hay fever. *Allergy* 1992;47:281-90.
41. Dolz L, Martínez-Cócerca C, Bartolomé JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
42. Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:23-9.
43. Brewczynski PZ, Kroon AM. Efficacy and safety of immunotherapy with modified grass pollen allergens. Results of a placebo controlled study [Wirksamkeit und verträglichkeit einer immuntherapie mit modifizierten grasperpollenallergenen]. *Allergologie* 1999;22:411-20.

44. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;56:498-505.
45. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;116:608-13.
46. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Study Group. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;60:801-7.
47. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25.
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177-88.
49. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2009. ISBN 3-900051-07-0. Available at: <http://www.R-project.org>.
50. Guido Schwarzer. meta: Meta-Analysis with R. R package version 1.1-8. 2010. Available at: <http://CRAN.R-project.org/package=meta>.
51. Wolfgang Viechtbauer. metafor: Meta-Analysis Package for R. R package version 1.0-1. 2010. Available at: <http://CRAN.R-project.org/package=metafor>.
52. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
53. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008;37:1158-60.
54. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;1:4-12.
55. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010;12:CD002893.
56. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007;1:CD001936.
57. Walker SM, Varney VA, Gaga M, Jacobson MR, Durham SR. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. *Allergy* 1995;50:405-13.

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), grass, sublingual, subcutaneous, and immunotherapy. 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 most 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.^{E1-E8} Studies were included in the meta-analysis if (1) they were RCTs comparing grass pollen SCIT or SLIT with placebo; (2) they included patients of any age with at least a 2-year history of allergic rhinitis (AR) to grass pollen with or without mild allergic asthma and/or conjunctivitis with a positive grass allergen-specific skin prick test, and elevated serum grass allergen-specific IgE; and (3) symptom and medication scores were assessed as outcome measures of the treatment effect. The search, limited to literature published through March 2012, identified 483 abstracts, of which 303 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, 38 RCTs met the inclusion criteria, and 2 were excluded because of insufficient data.^{E9,E10}

Review of the trials

The trials were first reviewed with a list of predefined pertinent issues that concerned the characteristics of patients and treatments.^{E11} Each RCT was evaluated and classified by 2 independent investigators (D.D.B. and G.D.L.). Discrepancies among reviewers were infrequent (overall interobserver variations, 10%) and were settled by discussion.

ADDITIONAL RESULTS AND COMMENTS

To assess if a rapid or rush immunotherapy buildup could have influenced the results of the individual studies, we performed a subgroup analysis that compared studies with and without the ultra-rush protocol (ultra-rush protocol SMD, -0.82 ; 95% CI, -1.31 to -0.32 ; non-ultra-rush protocol SMD, -1.13 ; 95% CI -1.70 to -0.57), showing a slightly better efficacy for the studies without an ultra-rush protocol, suggesting that this approach did not likely affect the final result. Moreover, it must also be noted that the most effective study, the Dolz study, used the rush ultra-short buildup schedule of immunotherapy followed by a 3-year maintenance treatment. However, in that study the efficacy of the treatment was shown only at the end of the first (1991) and the second (1992) years of treatment not after the first pollen season (1990), suggesting that the duration of treatment is more important than the ultra-rush protocol to obtain a response.

For the symptom score it was possible to analyze differences both in SLIT and SCIT related to the different number of pollens included in the pharmaceutical preparations. In this case, the subgroup analysis showed a better reduction of both symptom and medication score for SLIT and only a better reduction of symptom score, but not for medication score for SCIT with the use of more than 1 allergen as follows. For the symptom score, number of allergens: SCIT with 1 pollen vaccine median SMD, -0.52 ; SCIT with >1 pollen vaccine median SMD, -0.85 ; SLIT with 1 pollen vaccine median SMD, -0.22 ; SLIT with >1 pollen vaccine median SMD, -0.43 . For the medication score, Number of allergens: SCIT with 1 pollen vaccine median SMD, -0.59 ; SCIT with >1 pollen vaccine median SMD, -0.60 ; SLIT with 1 pollen vaccine median SMD, -0.18 ; SLIT with >1 pollen vaccine median SMD, -0.35 .

For the discrepancy between symptom and medication scores in the SCIT studies, it must be noted that, compared with symptom score subgroup analysis in the medication score subgroup analysis, we were unable to include 2 of 5 SCIT studies, because those authors did not report the medication score as an outcome measure. This is likely the reason why the data from the 2 analyses are inconsistent.

Because many trials include some information about exposure to pollen, we tried to understand if the degree of pollen exposure could also have influenced the results. Most studies plotted the daily changes in symptom and medication scores together with the changes in the daily pollen count. Unfortunately, the mean pollen count of the whole season or at the peak of the pollen exposure is not frequently reported in the text; therefore, we can only obtain this data from the graphs without a precise estimate. Taking into account this limitation in the accuracy of the analysis, we observed that the 4 SCIT studies that reported the highest pollen count during the season (Corrigan, Frew, Dolz, Pastorello) showed the highest treatment benefit (symptom score) compared with the remaining studies (high pollen count studies SMD, -1.40 ; 95% CI, -2.31 to -0.50 ; low pollen count studies SMD, -0.48 ; 95% CI, -0.75 to -0.21 ; the 2 studies from Bousquet were not included in any analysis because data on the pollen exposure were not reported). Moreover, in the multicenter Zenner study, the benefit of immunotherapy was shown only in the subgroup of patients exposed to a moderate pollen concentration not in the subgroup of patients exposed to a low pollen concentration.

Similar results were reported for SLIT. In fact, the studies with the highest pollen exposure showed the best efficacy of immunotherapy (high pollen exposure studies SMD, -0.50 ; 95% CI, -0.83 to -0.18 ; low pollen exposure studies SMD, -0.32 ; 95% CI, -0.42 to -0.21).

To better analyze the importance of pollen exposure on the results of the individual studies we evaluated if there was a difference in the placebo scores during the whole and the peak of the pollen season. Because most of the individual studies either report data on the whole pollen season or data on the peak pollen season, not data on both the observation periods, it was impossible to evaluate a difference between the placebo scores during the peak or during the whole season in the same study.

We could only compare the differences in the placebo scores among different studies. Because studies used different scoring systems, we standardized the placebo scores by dividing the mean scores by its own SD, to compare peak and whole season scores of the individual studies. As expected, we found median standardized placebo peak scores higher than median standardized placebo whole season scores (standardized placebo mean: SCIT peak = 2.22; SCIT whole season = 1.55; SLIT peak = 1.77; SLIT whole season = 1.43).

This difference is responsible for heterogeneity between the results of the individual studies. However, at the same time, the higher decrease in the symptom score observed at the peak of the pollen season allows a more accurate evaluation of the true effect of the immunotherapy, whereas this appears to be less evident if we compare the mean results of the whole pollen season, likely including many days with low pollen exposure.

A certain number of children patients were included in a few of SCIT studies; the number of children included was not reported, but, given the mean age of the study population in these studies, this number is likely to be low. Therefore, it is possible to compare SCIT studies, mainly including adult patients, with the

subgroup of SLIT (both drops and tablets) adults studies. When we excluded the children studies, the SMD of SLIT-D increased from -0.23 (95% CI, -0.43 to -0.02) to -0.37 (95% CI, -0.65 to -0.08), whereas the SMD of SLIT-T did not significantly change (-0.38 ; 95% CI, -0.52 to -0.25) for symptom score. The overall SMD for SLIT was -0.38 (95% CI, -0.51 to -0.25), still very low compared with SCIT (less than one-half of SCIT SMD [-0.92 ; 95% CI -1.26 to -0.58]), with a statistically significant difference. In contrast, no significant difference excluding children studies was reported for medication score SLIT-D SMD (-0.32 ; 95% CI, -0.55 to -0.08 ; SLIT-T SMD, -0.30 ; 95% CI, -0.39 to -0.23).

The lower efficacy of SLIT children studies is mainly because of those performed with drops. As shown in our previous meta-analysis,^{E12} this effect is likely due to the lower allergen dose administered with drops in these studies.

REFERENCES

- E1. Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831-7.
- E2. Mösges R, Brüning H, Hessler HJ, Götz G, Knaussmann HG. Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial. *Acta Dermatovenerol Alp Panonica Adriat* 2007;16:143-8.
- E3. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6.
- E4. Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:1394-401.
- E5. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73.
- E6. Horak F, Jaeger S, Worm M, Melac M, Didier A. Implementation of pre-seasonal sublingual immunotherapy with a five-grass pollen tablet during optimal dosage assessment. *Clin Exp Allergy* 2009;39:394-400.
- E7. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultra-short-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc* 2011;32:239-47.
- E8. Pfaar O, Urry Z, Robinson DS, Sager A, Richards D, Hawrylowicz CM, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. *Allergy* 2012;67:272-9.
- E9. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
- E10. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients: a double blind, placebo-controlled study. *Allergol Immunopathol (Madr)* 2006;34:194-8.
- E11. Bousquet PJ, Calderón MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. The Consolidated Standards of Reporting Trials (CONSORT) statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA(2)LEN) article. *J Allergy Clin Immunol* 2011;127:49-56.
- E12. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010;126:558-66.