Original Investigation

Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis
A Systematic Review and Meta-analysis

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IMPORTANCE Randomized clinical trials (RCTs) and meta-analyses of sublingual immunotherapy (SLIT) for the treatment of seasonal allergic rhinoconjunctivitis (SARC) have shown a modest clinical benefit compared with placebo. Furthermore, indirect comparison by meta-analyses showed that subcutaneous immunotherapy is more effective than SLIT. Despite these data, SLIT has become the most prescribed treatment of SARC in Europe in recent years, and it was approved by the US Food and Drug Administration for the treatment of SARC to grass pollen in the United States on April 1, 2014.

OBJECTIVE To assess the efficacy and safety of the grass pollen sublingual tablets licensed as drugs in the treatment of patients with SARC to grass pollen.

DATA SOURCES Computerized bibliographic searches of MEDLINE, EMBASE, the Cochrane Library, and ClinicalTrials.gov (from inception to April 30, 2014) were supplemented with a manual search of reference lists.

STUDY SELECTION Randomized clinical trials were included if they compared the grass pollen SLIT tablets approved by regulatory authorities in the European Union and the United States for SARC with placebo.

DATA EXTRACTION AND SYNTHESIS Data on populations, interventions, and outcomes were extracted from each RCT according to the intent-to-treat method by 2 independent observers and were combined using the method by DerSimonian and Laird.

MAIN OUTCOMES AND MEASURES The primary end point was the difference in the symptom score and medication score between SLIT and placebo. We pooled data using random-effects meta-analysis, with standardized mean differences (SMDs) and 95% CIs reported.

RESULTS Data were available in 13 RCTs for the symptom score (4659 patients) and in 12 RCTs for the medication score (4558 patients). We found a small treatment benefit in the symptom score (SMD, −0.28; 95% CI, −0.37 to −0.19; $P < .001$) and in the medication score (SMD, −0.24; 95% CI, −0.31 to −0.17; $P < .001$). Adverse events were reported in 1384 of 2259 patients (61.3%) receiving SLIT and in 477 of 2279 patients (20.9%) receiving placebo. Seven patients in the SLIT group reported treatment-related adverse events requiring epinephrine.

CONCLUSIONS AND RELEVANCE Findings show a small benefit of the grass pollen sublingual tablets in reducing symptoms and in decreasing the use of symptomatic medication (antihistamines and corticosteroids) in patients with SARC. Considering the low magnitude of the benefit, the convenience and easy administration do not seem to be sufficient reasons for the choice of SLIT.

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Allergic rhinoconjunctivitis is a common condition, affecting 5% to 40% of the general population, and there is evidence that its prevalence is increasing.[1-3] To our knowledge, allergen-specific immunotherapy is the only current treatment that modifies the disease process. Allergen-specific immunotherapy for the treatment of allergic respiratory diseases has traditionally been administered by subcutaneous injections. Subcutaneous immunotherapy (SCIT) has proven efficacy in treating allergic rhinitis, but it requires regular injections at a physician's office and carries the risk of potentially serious adverse events.[4] The favorable safety profile and convenience of sublingual immunotherapy (SLIT) are likely factors for its widespread use in Europe, where it is now the preferred route of administration of allergen-specific immunotherapy and was licensed as a drug on September 26, 2009 (Grazax; Alk-Abellò and Oralair; Stallergenes).[5]

On April 1, 2014, the US Food and Drug Administration (FDA) announced approval of the 5-grass pollen sublingual tablet (Oralair; Stallergenes), followed by approval of the timothy grass pollen sublingual tablet (Grazax; ALK-Abellò [marketed by Merck in the United States under the brand name Grastek]).[6,7] Before that date, SLIT with liquid allergen extracts had been used for off-label indications in the United States.[8]

Several clinical trials and meta-analyses have reported the efficacy of SCIT and SLIT compared with placebo for seasonal allergic rhinoconjunctivitis (SARC) to grass pollen.[4,9-12] In our group's previously published meta-analysis[12] of randomized clinical trials (RCTs) on the efficacy, we showed that SLIT was effective for SARC to grass pollen but that its clinical benefit vs placebo was modest. We also showed that SLIT tablets are more effective than drops, likely because of a higher allergen content. All the RCTs of SLIT published at that time had been performed in Europe.[13-23] Since then, 5 additional RCTs have been published, all conducted in North America.[24-28]

Therefore, we performed an expanded systematic review and meta-analysis. Our objective was to provide more reliable and up-to-date evidence on the effect of the grass pollen SLIT tablets approved as drugs in the European Union and the United States.

Methods

The primary sources of the reviewed studies were MEDLINE, EMBASE, the Cochrane Library, and ClinicalTrials.gov (from inception to April 30, 2014), with a specific search strategy (eMethods in the Supplement). Two separate reviewers (M.S.L.-B. and S.L.P.) independently extracted detailed information on the study characteristics, participants, interventions, primary and secondary outcome measures and their methods of ascertainment, and safety outcomes. The accuracy of data extraction was confirmed by 2 other reviewers (D.D.B. and G.D.L.). Disagreements were resolved by consensus adjudication. Studies were included in the meta-analysis if (1) they were RCTs comparing grass pollen SLIT administered as tablets with placebo, (2) they involved patients having a clinical history of SARC to grass pollen with or without mild allergic asthma with a positive grass pollen allergen-specific skin test and elevated serum grass pollen allergen-specific IgE levels, and (3) the symptom score (SS) and medication score (MS) were assessed as outcome measures of the treatment effect, regardless of whether these were the primary end points. In most of the RCTs, the results were reported as the means (SDs). In studies[15,19,22,26,28] that did not report all the values required for the analysis, data were provided by the authors of the original studies or by the pharmaceutical companies.

We used a modification of the Cochrane Collaboration Tool for Assessing Risk of Bias from the Cochrane Handbook for Systematic Reviews of Interventions (eMethods in the Supplement).[29] We used the Jadad score to assess the study quality.[30,31]

The SS and MS were assessed as outcome measures of the treatment effect. The outcome data analyzed were continuous, but different scoring systems and scales for symptoms and medications were used by the authors of the included studies. Therefore, to compare the results, analyses were performed by the method of standardized mean differences (SMDs), expressing the differences in the means between SLIT and placebo in terms of units of the pooled SDs. The overall SMD among patients treated with SLIT and placebo was estimated using models based on fixed-effects and random-effects assumptions, and data were combined using the method by DerSimonian and Laird.[32] The magnitude of the overall effect was classified according to guidelines by Cohen[33]: effect sizes of 0.2, 0.5, and 0.8 correspond to small, medium, and large effects, respectively.

Because 11 of 13 RCTs used as the outcome measure the same SS, ranging from 0 to 18 points (higher scores indicate worse disease severity), we compared the results of these studies using the original SS, reporting the results as the mean difference of SS points. All of our analyses were computed in R (R Foundation) using the Meta (version 2.0.1) and Metafor (version 1.6) statistical packages.[34-36]

A descriptive subgroup analysis was performed on the SS and MS. 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 methodological hypotheses (eMethods in the Supplement). The I^2 statistic, which describes the percentage of variability due to heterogeneity rather than sampling errors, was used to quantify heterogeneity.[37] Publication bias was assessed with funnel plots, Egger test for asymmetry,[38] and the fail-safe calculation (eMethods in the Supplement).

Results

Our search strategy identified 550 unique publications, including more than 80 peer-reviewed studies published from inception of the databases to April 30, 2014, the titles and abstracts of which were screened for inclusion in the study. The

Table 1. Patient Characteristics Among Trials in the Meta-analysis[a]

Source	Country	Intent-to-Treat vs Placebo Participants	Dropout or Withdrawal Rate, %	Male Sex, %	Age, Mean (Range), y	Asthma, %	Poly-Sensitization, %	Severity of SARC	Type of Treatment	Treatment Duration (Preseason + Grass Pollen Season), wk[b]
Pradalier et al,[13] 1999	France (n = 20)	63 vs 63 Randomized, 60 vs 59 completed, 62 vs 61 analyzed	5.6	52	29 (7-58)	34	NR	NR	5-Grass extracts (variable dosage)	8 + 12
Smith et al,[15] 2004[a]	United Kingdom (n = 1)	186 Randomized, 45 vs 55 completed, 50 vs 51 analyzed	28	48	38.5 (18-58)	NR	NR	Severe	5-Grass extracts (variable dosage)	12 + 12
Dahl et al,[16] 2006	8 Countries in Europe (n = 51)	316 vs 318 Randomized, 274 vs 272 completed, 282 vs 286 analyzed	14	59	34.2 (18-65)	NR	NR	Moderate or severe	Phleum p5 extracts (15 µg)	25 + 8
Dahl et al,[17] 2006	Denmark (n = 11), Sweden (n = 4)	74 vs 40 Randomized, 61 vs 32 completed, 61 vs 32 analyzed[c]	18.4	67.5	37.5 (18-64)	100	82	Moderate or severe	Phleum p5 extracts (15 µg)	12 + 8
Durham et al,[18] 2006	8 Countries in Europe and Canada (n = 55)	141 vs 136 Randomized, 131 vs 129 analyzed	4	61.5	36.5 (18-65)	NR	NR	Mild to severe	Phleum p5 extracts (15 µg)	8 + 10
Didier et al,[19] 2007	10 Countries in Europe (n = 42)	155 vs 156 Randomized, 133 vs 146 completed, 136 vs 148 analyzed	9	56.9	28.9 (18-45)	10	54.5	Moderate or severe	5-Grass extracts (variable dosage)	16 + 4
Bufe et al,[21] 2009	Germany (n = 26)	126 vs 127 Randomized, 114 vs 120 completed, 117 vs 121 analyzed	7.5	66	10.1 (5-16)	42	82	Mild to severe	Phleum p5 extracts (15 µg)	17 + 11
Wahn et al,[22] 2009	5 Countries in Europe (n = 29)	139 vs 139 Randomized, 131 vs 135 completed, 131 vs 135 analyzed	4.4	64.3	10.9 (4-17)	21.4	59	Moderate or severe	5-Grass extracts (variable dosage)	16 + 6
Blaiss et al,[24] 2011	United States (n = 41), Canada (n = 8)	175 vs 169 Randomized, 142 vs 140 completed, 149 vs 158 analyzed	18.8	65	12.5 (5-17)	26	89	Moderate or severe[d]	Phleum p5 extracts (15 µg)	16 + 7
Nelson et al,[25] 2011	United States (n = 44), Canada (n = 7)	213 vs 225 Randomized, 175 vs 192 completed, 184 vs 207 analyzed	16.2	50	35.9 (18-65)	23.5	85	Moderate or severe[e]	Phleum p5 extracts (15 µg)	16 + 7
Cox et al,[26] 2012	United States (n = 51)	233 vs 240 Randomized, 207 vs 223 completed, 210 vs 228 analyzed	9	46.6	37.2 (18-65)	20.1	78	Severe	5-Grass extracts (variable dosage)	18 + 6
Murphy et al,[27] 2013	United States (n = 28)	163 vs 166 Randomized, 136 vs 140 completed, 139 vs 150 analyzed	16.2	46.5	35.9 (18-65)	27	85	Moderate or severe[e]	Phleum p5 extracts (15 µg)	16 + 7
Maloney et al,[28] 2014	United States (No. NR), Canada (No. NR)	752 vs 749 Randomized, 603 vs 652 completed, 629 vs 672 analyzed	16.4	52.5	33.5 (5-65)	24.5	85	NR	Phleum p5 extracts (15 µg)	≥12 + 8

Abbreviation: NR, not reported.

[a] The evaluation period in all studies was the entire grass pollen season.

[b] The study by Smith et al[15] included 2 groups treated with sublingual immunotherapy for 1 year or 2 years, respectively, compared with placebo. Only data from the first year were included in this analysis for consistency with the other studies.

[c] Per-protocol analysis.

[d] In the Methods section, the authors stated that their inclusion criteria were aimed at recruiting participants with moderate to severe seasonal allergic rhinoconjunctivitis.

[e] Likely moderate to severe considering the inclusion criteria (see the Methods sections in the studies).

full text of 16 studies[13-28] was retrieved, of which 13 met the inclusion criteria.[13,15-19,21,22,24-28] We excluded the study by Caffarelli et al[14] because they used an allergoid (Lais; Lofarma SpA), the study by Horak et al[20] because it used an allergen challenge chamber, and the study by Halken et al,[23] which is a secondary analysis of a previously published data set[22] (eFigure 1 in the Supplement).

Table 1 summarizes descriptive data for the 13 qualifying trials.[13,15-19,21,22,24-28] All studies except for one[17] reported the results of an intent-to-treat analysis.

The methodological quality of the studies included in the meta-analysis was good (eTable 1 in the Supplement). The risk of bias was estimated as high in one study,[15] medium in 4 RTCs,[13,16,21,27] and low in the remaining 8 RCTs[17-19,22,24-26,28] (eTable 2 in the Supplement). A rigorous method of randomization was explicitly described in 8 studies,[17-19,22,24-26,28] and allocation concealment was not reported in any studies. In the remainder, this information was absent or unclear (eTable 2 in the Supplement).

Data on the SS were available in all 13 trials,[13,15-19,21,22,24-28] and data on the MS were available in 12 studies.[13,16-19,21,22,24-28] The 13 RCTs included a total of 4659 patients (Table 1). Seven studies[13,15-17,19,21,22] were conducted in Europe, 5 studies[24-28] in North America, and one study[18] in Europe and Canada. Only one study[15] was conducted in a single center. The sample size of the studies varied greatly (range, 114 in the study by Dahl et el[17] to 1501 in the study by Maloney et al[28]). Three studies[21,22,24] enrolled only individuals 17 years or younger, and 2 other studies[13,28] included mainly adults, with few children. The study completion rate ranged from 72% to 96%.[15,18] The median percentage of male participants was 56.9% (range, 46.5% in the study by Murphy et al[27] to 67.5% in the study by Dahl et al[17]). The median of the mean age of patients in the adult studies was 35.9 years (range, 28.9 years in the study by Didier et al[19] to 38.5 years in the study by Smith et al[15]). The percentage of patients with mild to moderate asthma was reported in 10 of 13 studies (range, 10% in the study by Didier et al[19] to 100% in the study by Dahl et al[17]). The percentage of patients sensitized to allergens other than grass pollen was reported in 9 of 13 studies[17,19,21,22,24-28] (range, 59%-85%). Eight studies clearly reported the severity of SARC among the enrolled population (severe,[15,26] moderate to severe,[16,17,19,22] or mild to severe with few mild cases[18,21]), 3 other studies[24,25,27] likely included individuals with moderate to severe SARC, and the remaining 2 studies[13,28] did not define the severity of SARC. Eight studies (4 in Europe[16-18,21] and 4 in North America[24,25,27,28]) used the grass pollen allergen extract tablets at the same dosage (75 000 standard quality units-tablet, 2800 bioequivalent allergy units, approximately 15 µg of Phleum p5) with a comparable treatment duration (mean length of preseasonal treatment, 14.3 weeks and mean length of coseasonal treatment, 8.5 weeks). Four studies (3 in Europe[13,19,22] and one in the United States[26]) used tablets containing 5-grass pollen allergen extracts at the same dosage standardized in index of reactivity units (IR) (concentration, 300 IR/mL, corresponding to approximately 25 µg of the group of 5 major allergens) for similar duration of treatment (mean length of preseasonal treatment, 16.7 weeks and mean length of coseasonal treatment, 5.7 weeks). The remaining RCT used tablets containing 5-grass pollen allergen extracts administered at a lower concentration (100 IR/mL, approximately 8.5 µg of the group of 5 major allergens).[13]

Figure 1 shows the results of the meta-analysis. All studies showed a beneficial effect of SLIT on the SS compared with placebo, but 6 of them did not achieve statistical significance.[13,15,18,21,25,27] The pooled SMD for the treatment effect was −0.28 (95% CI, −0.37 to −0.19; $P < .001$), indicating a statistically significant reduction in symptoms in patients receiving SLIT compared with placebo (Figure 1A). Significant heterogeneity between the results of individual studies was reported ($Q_{12} = 26.18$, $P = .01$, $I^2 = 54.2\%$, $\tau^2 = 0.0142$), but it decreased to 28% ($Q_{11} = 15.21$, $P = .17$, $\tau^2 = 0.0049$), with a similar effect size (pooled SMD, −0.24, 95% CI, −0.32 to −0.16; $P < .001$), with exclusion of an influential study[16] (eMethods in the Supplement). This low between-study heterogeneity reported for the SS after exclusion of the influential study ($I^2 = 28.0\%$, $\tau^2 = 0.0049$) explains the observation that the results between the random-effects (pooled SMD, −0.24; 95% CI, −0.32 to −0.16; $P < .001$) and fixed-effects (pooled SMD, −0.22; 95% CI, −0.28 to −0.16; $P < .001$) models are almost overlapping.

All studies used as the outcome measure an SS ranging from 0 to 18 points except for the studies by Pradalier et al[13] and Smith et al,[15] which used a score range of 0 to 21. Excluding these 2 studies, we could compare the studies using the original SS, which is easier to interpret. With this method, the mean difference between SLIT and placebo was −0.83 (95% CI, −1.03 to −0.63; $P = .001$), without significant heterogeneity ($I^2 = 16.4\%$) (Figure 1B). The SMD that excluded 2 studies did not change (SMD, −0.28; 95% CI, −0.39 to −0.18; $P < .001$), indicating that an SMD of −0.28 corresponds to a mean difference of −0.83 SS point.

Data on the MS were obtained for 12 RCTs[13,16-19,21,22,24-28] (4558 patients). A statistically significant difference between SLIT and placebo was observed in only 7 RCTs[16-19,22,26,28] (Figure 1C). The pooled estimate of treatment on the MS was statistically significant (SMD, −0.24; 95% CI, −0.31 to −0.17; $P < .001$). An analysis using the original MS was not performed owing to the different scoring systems used.

Funnel plots and Egger test for the SS and MS did not show substantial evidence of bias toward positive results, suggesting no selective reporting (eFigure 2 in the Supplement). The fail-safe numbers were 237 for the SS and 172 for the MS, high enough to confirm the robustness of the results against publication bias.

Subgroup analyses suggested a greater benefit in European vs American studies, in studies using the 5-allergen grass pollen extract tablets vs studies using the 1-allergen grass pollen extract tablets, and in smaller studies. No age effect was found. These results are summarized in **Figure 2** and in the eResults in the Supplement.

A sensitivity analysis that excluded the 5 studies at high[15] or moderate[13,16,21,27] risk of bias and the study[17] using a per-protocol analysis produced similar results (SMD, −0.25; 95% CI, −0.34 to −0.15; $P < .001$). These results suggested that trial quality affects outcomes only marginally.

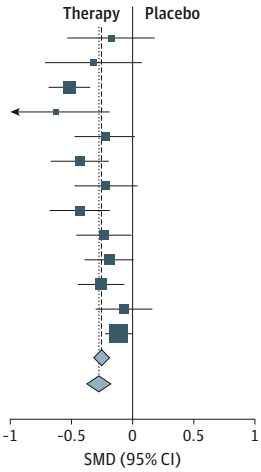
In total, 1817 of 2597 patients (70.0%) receiving SLIT vs 1137 of 2555 patients (44.5%) receiving placebo reported adverse events (**Table 2** and eTable 3 in the Supplement). Probable treatment-related adverse events were reported in 9 of 13 studies, and there were 3 times as many adverse events in patients receiving SLIT (1384 of 2259 [61.3%]) compared with those receiving placebo (477 of 2279 [20.9%]). Most adverse events were moderate in severity for both groups. The withdrawal rate for adverse events was higher in the SLIT group (159 patients [6.0%]) than in the placebo group (58 patients [2.2%]). No

Figure 1. Meta-analysis of the Efficacy of Sublingual Immunotherapy vs Placebo for Seasonal Allergic Rhinoconjunctivitis

A SMD for symptom score

Source	Experimental No.	Experimental Mean (SD)	Control No.	Control Mean (SD)	SMD (95% CI)	Weight, % Fixed	Weight, % Random	P Value
Pradalier et al,[13] 1999	62	2.33 (1.60)	61	2.65 (1.97)	-0.18 (-0.53 to 0.18)	2.7	4.7	
Smith et al,[15] 2004 (first year)	50	1.82 (1.35)	51	2.32 (1.70)	-0.32 (-0.72 to 0.07)	2.2	4.1	
Dahl et al,[16] 2006	282	2.40 (1.60)	286	3.40 (2.20)	-0.52 (-0.69 to -0.35)	12.0	10.3	
Dahl et al,[17] 2006	61	2.10 (1.70)	32	3.30 (2.20)	-0.63 (-1.07 to -0.19)	1.7	3.5	
Durham et al,[18] 2006	131	2.48 (2.10)	129	2.96 (2.09)	-0.23 (-0.47 to 0.02)	5.6	7.5	
Didier et al,[19] 2007	136	3.58 (2.98)	148	4.93 (3.23)	-0.43 (-0.67 to -0.20)	6.0	7.8	
Bufe et al,[21] 2009	117	2.67 (2.38)	121	3.17 (2.14)	-0.22 (-0.48 to 0.03)	5.1	7.1	
Wahn et al,[22] 2009	131	3.25 (2.86)	135	4.51 (2.93)	-0.43 (-0.68 to -0.19)	5.7	7.5	
Blaiss et al,[24] 2011	149	3.71 (4.88)	158	4.91 (5.16)	-0.24 (-0.46 to -0.01)	6.6	8.1	
Nelson et al,[25] 2011	184	3.83 (4.30)	207	4.69 (4.50)	-0.19 (-0.39 to 0.00)	8.4	9.1	
Cox et al,[26] 2012	210	3.73 (3.16)	228	4.65 (3.82)	-0.26 (-0.45 to -0.07)	9.4	9.5	
Murphy et al,[27] 2013	139	5.69 (4.98)	150	6.06 (5.15)	-0.07 (-0.30 to 0.16)	6.3	7.9	
Maloney et al,[28] 2014	629	3.11 (4.01)	672	3.58 (4.15)	-0.12 (-0.22 to -0.01)	28.2	12.9	
Fixed-effects model	2281		2378		-0.25 (-0.31 to -0.20)	100.0	NA	<.001
Random-effects model					-0.28 (-0.37 to -0.19)	NA	100.0	<.001

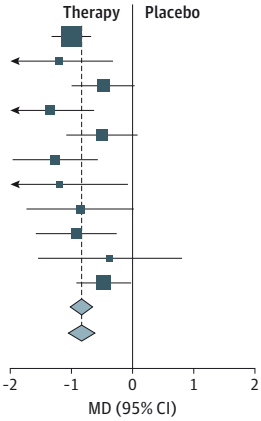
Heterogeneity: $I^2 = 54.2\%$, $\tau^2 = 0.0142$, $P = .01$, $Q_{12} = 26.18$



B MD for symptom score

Source	Experimental No.	Experimental Mean (SD)	Control No.	Control Mean (SD)	MD (95% CI)	Weight, % Fixed	Weight, % Random	P Value
Dahl et al,[16] 2006	282	2.40 (1.60)	286	3.40 (2.20)	-1.00 (-1.32 to -0.68)	30.9	23.9	
Dahl et al,[17] 2006	61	2.10 (1.70)	32	3.30 (2.20)	-1.20 (-2.07 to -0.33)	4.0	4.9	
Durham et al,[18] 2006	131	2.48 (2.10)	129	2.96 (2.09)	-0.48 (-0.99 to 0.03)	11.9	12.4	
Didier et al,[19] 2007	136	3.58 (2.98)	148	4.93 (3.23)	-1.35 (-2.07 to -0.63)	5.9	6.9	
Bufe et al,[21] 2009	117	2.67 (2.38)	121	3.17 (2.14)	-0.50 (-1.08 to 0.08)	9.3	10.2	
Wahn et al,[22] 2009	131	3.25 (2.86)	135	4.51 (2.93)	-1.26 (-1.96 to -0.56)	6.4	7.4	
Blaiss et al,[24] 2011	149	3.71 (4.88)	158	4.91 (5.16)	-1.20 (-2.32 to -0.08)	2.4	3.1	
Nelson et al,[25] 2011	184	3.83 (4.30)	207	4.69 (4.50)	-0.86 (-1.73 to 0.01)	4.0	4.9	
Cox et al,[26] 2012	210	3.73 (3.16)	228	4.65 (3.82)	-0.92 (-1.57 to -0.27)	7.2	8.2	
Murphy et al,[27] 2013	139	5.69 (4.98)	150	6.06 (5.15)	-0.37 (-1.54 to 0.80)	2.3	2.9	
Maloney et al,[28] 2014	629	3.11 (4.01)	672	3.58 (4.15)	-0.47 (-0.91 to -0.03)	15.7	15.3	
Fixed-effects model	2169		2266		-0.83 (-1.01 to -0.66)	100.0	NA	<.001
Random-effects model					-0.83 (-1.03 to -0.63)	NA	100.0	<.001

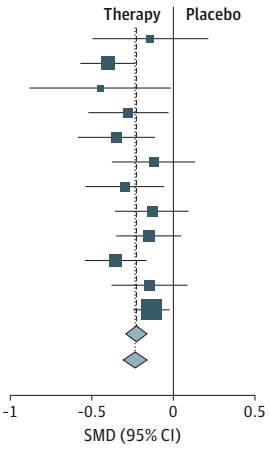
Heterogeneity: $I^2 = 16.4\%$, $\tau^2 = 0.0187$, $P = .29$, $Q_{10} = 11.96$



C SMD for medication score

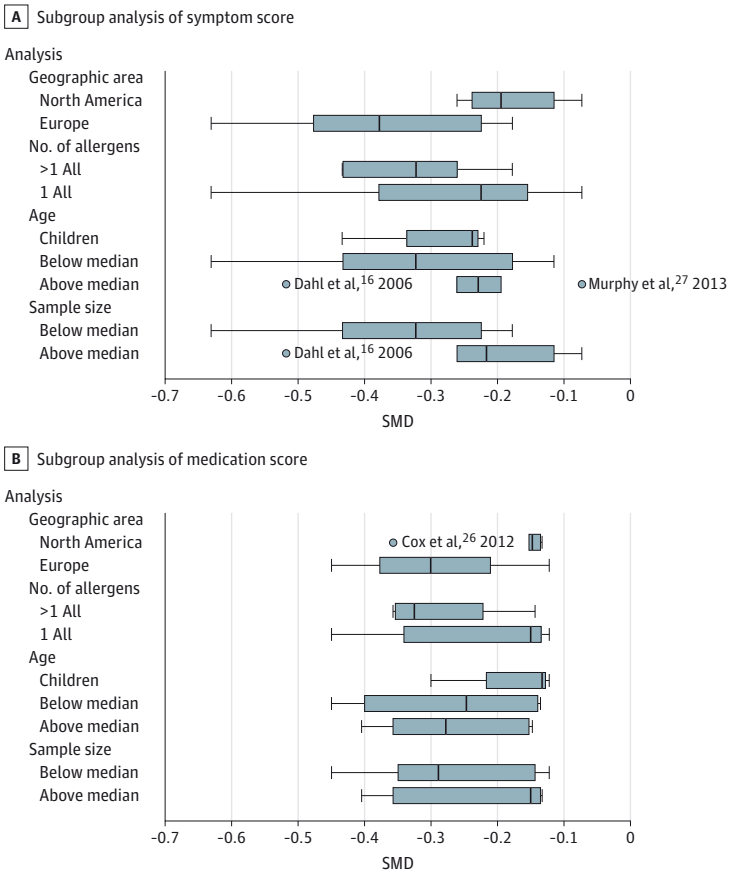
Source	Experimental No.	Experimental Mean (SD)	Control No.	Control Mean (SD)	SMD (95% CI)	Weight, % Fixed	Weight, % Random	P Value
Pradalier et al,[13] 1999	62	1.77 (2.23)	61	2.13 (2.74)	-0.14 (-0.50 to 0.21)	2.7	3.5	
Dahl et al,[16] 2006	282	1.50 (1.90)	286	2.40 (2.50)	-0.40 (-0.57 to -0.24)	12.3	12.2	
Dahl et al,[17] 2006	61	2.40 (3.90)	32	4.20 (4.10)	-0.45 (-0.88 to -0.02)	1.8	2.4	
Durham et al,[18] 2006	131	1.40 (2.13)	129	2.03 (2.39)	-0.28 (-0.52 to -0.03)	5.7	6.7	
Didier et al,[19] 2007	136	0.31 (0.43)	148	0.48 (0.53)	-0.35 (-0.58 to -0.12)	6.2	7.2	
Bufe et al,[21] 2009	117	2.13 (3.48)	121	2.53 (3.03)	-0.12 (-0.38 to 0.13)	5.3	6.3	
Wahn et al,[22] 2009	131	0.60 (0.61)	135	0.79 (0.65)	-0.30 (-0.54 to -0.06)	5.8	6.9	
Blaiss et al,[24] 2011	149	0.91 (3.66)	158	1.33 (2.58)	-0.13 (-0.36 to 0.09)	6.8	7.8	
Nelson et al,[25] 2011	184	1.25 (2.88)	207	1.70 (3.00)	-0.15 (-0.35 to 0.05)	8.6	9.4	
Cox et al,[26] 2012	210	0.12 (0.22)	228	0.23 (0.37)	-0.36 (-0.55 to -0.17)	9.5	10.1	
Murphy et al,[27] 2013	139	1.07 (2.56)	150	1.47 (2.83)	-0.15 (-0.38 to 0.08)	6.4	7.4	
Maloney et al,[28] 2014	629	0.88 (2.76)	672	1.36 (4.15)	-0.14 (-0.24 to -0.03)	28.8	20.2	
Fixed-effects model	2231		2327		-0.23 (-0.29 to -0.17)	100.0	NA	<.001
Random-effects model					-0.24 (-0.31 to -0.17)	NA	100.0	<.001

Heterogeneity: $I^2 = 21.7\%$, $\tau^2 = 0.0031$, $P = .23$, $Q_{11} = 14.05$



MD indicates mean difference; NA, not applicable; SMD, standardized mean difference.

Figure 2. Descriptive Subgroup Analysis



Analyses of symptom score (A) and medication score (B) for the efficacy of sublingual immunotherapy in seasonal allergic rhinoconjunctivitis. The boxplots include the middle 50% of the data. The horizontal bars inside the boxes represent the median standardized mean difference (SMD). 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. Outliers in panel A include the study by Murphy et al[27] and a study by Dahl et al.[16] The outlier in panel B is a study by Cox et al.[26]

Table 2. Adverse Events During Treatment

Variable	Sublingual Immunotherapy	Placebo	Odds Ratio	*P* Value
Patients, No./total No. (%)				
Total adverse events[a]	1817/2597 (70.0)	1137/2555 (44.5)	2.91	<.001
Treatment-related adverse events[b]	1384/2259 (61.3)	477/2279 (20.9)	5.98	<.001
Withdrawals[c]	159/2658 (6.0)	58/2587 (2.2)	2.77	<.001
Anaphylactic reactions	0	0	0.63	.82
Adverse events requiring epinephrine	9	3	9.39	.13
Treatment-related adverse events requiring epinephrine	7	0	1.88	.35

[a] A study by Dahl et al[17] did not report data on safety and was not included in this analysis.

[b] Studies by Pradalier et al,[13] Smith et al,[15] Dahl et al,[17] and Didier et al[19] were not included in this analysis because they did not report data on treatment-related adverse events.

[c] All 13 studies[13,15-19,21,22,24-28] were included in the analysis.

episode of anaphylaxis was reported in the RCTs; however, 9 adverse events requiring epinephrine were reported in the SLIT group, of which 7 were treatment related. Three serious adverse events requiring epinephrine were reported in the placebo group, but none of them were treatment related.

Discussion

This meta-analysis provides evidence of a small benefit of grass pollen allergy immunotherapy tablets in the treatment of SARC. The low level of heterogeneity after exclusion of the influential study[16] suggests that the results are not influenced by uncertainties about study quality or publication bias.

Most of the studies included in this meta-analysis enrolled patients with reported moderate or severe SARC, which are the inclusion criteria as recommended by the World Allergy Organization,[39] corresponding to a mean SS without any treatment of 12.5 on an 18-point SS scale. On average, the SS during the treatment period reported in the RCTs is 3 to 4 points, with a SLIT vs placebo difference of −0.83 SS point. This means that, of a mean SS reduction of approximately 8 to 9 points, SLIT is responsible for only about 10% (<1 SS point). Therefore, the symptomatic treatment (antihistamines or cor-

ticosteroids) administered on demand is likely responsible for most of the relief of the symptoms in both groups. Some critics might assert that the higher use of rescue medication to alleviate symptoms in the placebo group decreases the mean difference between SLIT and placebo. However, with this set of data, we observed no substantial role of rescue medication in modifying the SS because the MS difference between SLIT and placebo was small (SMD, −0.23).[33]

Besides a statistically significant difference between SLIT and placebo, the FDA requires for drug approval that SLIT studies must demonstrate at least a 15% improvement in the total combined score (TCS [the SS plus the MS]) compared with placebo (the World Allergy Organization recommends a 20% improvement).[39,40] Most of the studies analyzed herein seem to fulfill these requirements. However, the group difference is less than 1 SS point, which is not significant in clinical practice according to the criteria by Cohen.[33] Despite the limits of Cohen's threshold for clinical effectiveness, comparisons with other treatments such as SCIT for grass pollen allergen (SMD, −0.92)[4] or oral antihistamines or nasal corticosteroids[41,42] showing higher benefits confirm that the clinical benefit of the SLIT tablets reported in our meta-analysis is small. This is likely due to several methodological defects in the analysis of the data.

First, the calculation of the percentage of improvement in the TCS of 15% or 20% between active and placebo as a measure of SLIT efficacy reported in the RCTs is questionable because the TCS is the sum of different clinical outcomes. Therefore, a distinct evaluation for each of them would be more appropriate from a clinical point of view.

Second, the SS and MS are calculated using different scales (0-18 points for the SS and up to 36 points for the MS), and the results of these 2 different scales are summed to obtain the TCS. This is incorrect from a statistical point of view because scales have different weights depending on their range. However, there is a more serious statistical problem: the MS is a qualitative variable, and it can be considered on an ordinal scale but cannot be treated as interval data because intervals between each value (ie, 1 point for antihistamines, 2 points for nasal corticosteroids, and 3 points for oral corticosteroids, as arbitrarily assigned by investigators,) are not equal. Therefore, a TCS cannot be computed. The comparison would be valid only if limited to the SS.

The third and most important concern is that the calculation of the percentage of improvement in the SS between SLIT and placebo shown in the individual studies does not take into account the SS scale range and consequently does not reflect the real clinical difference between the groups. The difference in the mean daily SS between SLIT and placebo recorded during the pollen season is the primary outcome of each study. This difference is also expressed as the percentage of improvement and is calculated as the placebo score minus the SLIT score, divided by the placebo score. For example, in the study by Cox et al,[26] reporting the highest efficacy among North American studies, the difference between SLIT and placebo is −0.95 (3.21 minus 4.16) SS point, corresponding to a 22.8% (3.21 minus 4.16, divided by 4.16) improvement in the SLIT group compared with the placebo group (eTable 4 in the Supplement). This seems to fulfill the FDA requirement for SLIT efficacy (difference of ≥15%), but an improvement of only 0.95 SS point is observed in the SLIT group compared with the placebo group. This difference is not clinically significant according to the criteria by Cohen[33] because it corresponds to −0.26 SMD (Figure 1A), a value close to the assumed subjective threshold of inefficacy (−0.20 SMD). A different calculation must be made to reflect the real clinical difference between the groups. The correct evaluation of an improvement between SLIT and placebo cannot take into account only the SS values during the treatment period but should compare these SS values with the SS values that are retrospectively reported in the absence of any treatment for each group. This approach allows us to incorporate the scale range in the evaluation of the clinical improvement. We considered again the study by Cox et al,[26] which is the only included study that precisely reports all the data useful for an accurate comparison between SLIT and placebo (eTable 4 in the Supplement). In their study, the severity of SARC is defined by the retrospective rhinoconjunctivitis SS, which is comparable between SLIT and placebo owing to the randomization (14.90 SS points for each group). Therefore, patients receiving SLIT have an improvement of 11.69 (14.9 minus 3.21) SS points, which corresponds to a 78% improvement compared with the retrospective SS while patients receiving placebo have an improvement of 10.74 (14.9 minus 4.16) SS points, corresponding to a 72% improvement. Although the difference between SLIT and placebo in SS points remains unchanged at −0.95 (10.74 minus 11.69) SS point, the percentage of improvement decreases to 6% (78% minus 72%), which is much less than the 22.9% reported in the study (an analysis that includes all the studies is shown in eFigure 3 in the Supplement). Computing the improvement according to the method described above, we take into account the actual scale of the SS, thus mirroring the true clinical difference (<1 SS point on a scale of 0-18). In contrast, using the method of the authors of each study, a 1-point difference between 2 groups is the same percentage whether a 10-point scale or a 100-point scale is used.

Subgroup analysis showed that the treatment efficacy was lower in North American studies[24-28] than in European studies.[13,15-19,21,22] The reason for this difference is unclear. North American RCTs are the most recent, feature larger sample sizes on average, and are unaffected by bias owing to study quality, suggesting that these studies likely provide a more reliable estimation of the treatment effect. On the other hand, the proportion of polysensitized participants was higher in North American studies than in European studies. This may mask the treatment effect, although researchers tried to control for the geographic- and weather-related variability of pollen seasons, as well as the negative influence of confounding allergens.

Four of five North American SLIT studies[24,25,27,28] used a tablet containing an extract of a single grass pollen (Phleum p5). However, in North America a 5-grass pollen allergen extract can be expected to better represent natural exposure and sensitization conditions encountered by patients with grass pollen allergy than an extract of a single grass pollen. This may explain the greater benefit, particularly in the MS, reported in

the study by Cox et al,[26] which used a 5-grass pollen allergen extract. However, this evidence was not found in European studies, which showed the same efficacy between the 1-grass pollen and 5-grass pollen allergen extracts.

There are limitations of this meta-analysis owing to imperfections in all single studies, including the participation of sponsor companies in the study design and interpretation of data.[43,44] Other limitations include potential conflicts of interest by 1 or more authors in studies, the fact that some studies did not describe the randomization or the allocation concealment method, the use of a low dosage of allergens in one study, the small sample sizes in some studies, and the use of a per-protocol analysis by one study. However, our study also has strengths, including the following: the total number of participants is large for assessment of the treatment effect, many individual studies are well powered, most studies used similar treatment regimens and similar allergen dosages, the risk of publication bias is low and unlikely to influence the final result, and the level of heterogeneity is minimal after exclusion of the influential study.[16] Therefore, we believe that the results showing a small clinical benefit of SLIT administered as tablets likely represent a valid finding. Furthermore, in contrast to previous meta-analyses,[4,12,45,46] RCTs using the same 18-point SS scale were included in this meta-analysis (except for 2 studies[13,15]). This allowed us to report the results as SS units (mean differences), which are much easier to interpret than SMDs.

The overall results of our analysis are consistent with previous investigations. Lin et al[47] reported a moderate level of evidence to support the effectiveness of SLIT for the treatment of allergic rhinitis. Dretzke et al[46] reported a mild reduction in the SS with SLIT compared with placebo. Our review, which is the most comprehensive to date because it analyzes studies up to 2014, indicates that the benefit is even lower than previously assessed owing to inclusion of the most recent and powerful SLIT studies. Moreover, in contrast to previous reviews that analyzed studies with extreme variability in the type of allergens, dosing, and treatment schedules, this review included studies with standardized high dosages of grass pollen only, which have been established as the most effective by previous studies.

The clinical implication of our findings is that the continued widespread use of SLIT in Europe, as well as future use of the treatment in the United States, is questionable. As shown by previous meta-analyses[4,46] indirectly comparing SCIT and SLIT, SCIT seems to be the most effective treatment. The main reasons for the choice of SLIT have been the convenience and safety profile. However, in the studies included in this meta-analysis, there were 7 patients in the SLIT group with treatment-related adverse events requiring epinephrine. For this reason, the FDA requires that patients who commence SLIT treatment must be provided with epinephrine for self-injection.[6,7] Furthermore, the number of episodes of anaphylaxis reported in SCIT RCTs is negligible[4]; in contrast, the total number of adverse events is higher in SLIT than in SCIT.[4] In addition, serious complications such as eosinophilic esophagitis with the use of SLIT for grass pollen allergens have been reported.[48]

On the other hand, it is important to emphasize that no fatality has been reported with the use of SLIT. However, there are reports of systemic reactions, including those resulting in death, associated with SCIT.[49]

Regarding the convenience, factors such as the availability of therapy (in some areas it would be impossible for patients to receive injections weekly) and the ability to tolerate therapy (particularly in children, who tolerate SLIT at a much younger age than SCIT) may be important reasons for the choice of SLIT. This cannot be discounted because it represents a substantial benefit of SLIT compared with placebo.

Conclusions

The results of this meta-analysis are sufficient to conclude that the grass pollen allergy immunotherapy tablets show an allergen-specific effect, but its magnitude is small and is complicated by adverse events. Therefore, the convenience and ease of administration do not seem to be sufficient reasons for the choice of SLIT. However, SLIT can be appropriate for certain patients. Our data suggest that further studies are needed to identify variables to predict the response to SLIT,[50,51] permitting the targeting of this treatment to individuals who are likely to respond.

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Study concept and design: All authors.
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