

Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: A comparison based on meta-analyses

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Background: Allergen-specific subcutaneous immunotherapy (SCIT) of seasonal allergic rhinitis (SAR) is usually considered a “second-line,” slow-acting, disease-modifying treatment.

Objective: We sought to test whether SCIT is as effective as antisymptomatic treatment in the control of symptoms in patients with SAR in the first year of treatment.

Methods: We reviewed meta-analyses with 5 or more randomized, double-blind, placebo-controlled trials of SCIT or antisymptomatic treatment in patients with SAR. We then selected trials measuring the total nasal symptom score (TNSS), the total symptom score (TSS), or both during the first pollen season after treatment initiation. Efficacy was determined as the percentage reduction in TSSs and TNSSs obtained with active treatment compared with placebo (relative clinical impact [RCI]) and the standardized mean difference (SMD) of treatment versus placebo (effect size [ES]).

Results: The weighted mean RCI of SCIT on TNSSs ($-34.7\% \pm 6.8\%$) was higher than those of mometasone ($-31.7\% \pm 16.7\%$, $P < .00001$) and montelukast ($-6.3\% \pm 3.0\%$, $P < .00001$). The weighted mean RCI of SCIT on TSSs ($-32.9\% \pm 12.7\%$) was higher than that of desloratadine ($-12.0\% \pm 5.1\%$, $P < .00001$). The overall ES of SCIT in terms of TNSSs (SMD, -0.94 ; 95% CI, -1.45 to -0.43) was similar to that of mometasone (SMD, -0.47 ; 95% CI, -0.63 to -0.32 ; $P > .05$) and higher than that of montelukast (SMD, -0.24 ; 95% CI, -0.33 to -0.16 ; $P < .05$). The overall ES of SCIT in terms of TSSs (SMD, -0.86 ; 95% CI, -1.17 to -0.55) was comparable with that of desloratadine (SMD, -1.00 ; 95% CI, -1.68 to -0.32 ; $P > .05$).

Conclusions: Our data provide indirect but consistent evidence that SCIT is at least as potent as pharmacotherapy in controlling the symptoms of SAR as early as the first season of treatment. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Seasonal allergic rhinitis, allergen-specific immunotherapy, allergen-specific subcutaneous immunotherapy, nasal corticosteroids, antihistamines, leukotriene antagonists

According to the Allergic Rhinitis and its Impact on Asthma 2008 update,¹ allergen-specific immunotherapy (SIT) “is the practice of administering increasing amounts of an allergen extract to an allergic subject to ameliorate symptoms associated with the subsequent exposure to the causative allergen.” The same document states that subcutaneous immunotherapy against allergic rhinitis is indicated in “patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms,” “in patients who do not want to be on constant or long-term pharmacotherapy,” and “in patients in whom pharmacotherapy induces undesirable side effects.”¹ The response to pharmacotherapy appears therefore to be crucial before deciding whether to start SIT in a patient with allergic rhinitis. Most simply, SIT is considered by these guidelines as a sort of “second-line” treatment to be initiated only if pharmacotherapy is unsuccessful, not accepted, or not tolerated. However, pharmacotherapy reduces symptoms of allergic rhinitis without modifying its natural history, whereas SIT would reduce symptoms, especially after some years of treatment.

Clinical guidelines take many parameters into consideration, including costs, safety, acceptance rate, compliance, adherence, and feasibility of different treatments. Is allergen-specific subcutaneous immunotherapy (SCIT), from a merely clinical standpoint, really less efficient than pharmacotherapy in the short-term control of seasonal allergic rhinitis (SAR) symptoms? To answer this question, we analyzed the evidence for the efficacy of SCIT and pharmacotherapy in the control of SAR symptoms.* Unfortunately, only 4 trials directly compared SCIT and antisymptomatic treatment in patients with SAR,²⁻⁵ and they reached conflicting conclusions. Therefore we decided to evaluate a quite large number of double-blind, placebo-controlled trials about SCIT, as well as antisymptomatic treatment, in patients with SAR. To this end, we used 4 meta-analyses published in peer-reviewed journals and examined the efficacy in patients with SAR of SCIT,⁶ 1 nasal corticosteroid (mometasone furoate),⁷ 1 antihistamine (desloratadine),⁸ and 1 leukotriene antagonist (LA; montelukast).⁹ In addition, we reviewed relevant studies of additional antisymptomatic drugs (fexofenadine, loratadine, ebastine, fluticasone propionate nasal spray, and ciclesonide).

*We use the old term *seasonal allergic rhinitis* instead of the new term *intermittent allergic rhinitis*¹ because the old term is used by almost all the trials considered in our review.

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Abbreviations used

ES:	Effect size
LA:	Leukotriene antagonist
MoE:	Magnitude of efficacy
RCI:	Relative clinical impact
SAR:	Seasonal allergic rhinitis
SCIT:	Allergen-specific subcutaneous immunotherapy
SIT:	Allergen-specific immunotherapy
SMD:	Standardized mean difference
TNSS:	Total nasal symptom score
TSS:	Total symptom score
WAO:	World Allergy Organization

METHODS**Selection of meta-analyses, studies, and primary outcomes**

Between August and October 2009, we selected, through a Medline search on PubMed (no time limits), 5 meta-analyses of different treatments belonging to 4 different therapeutic approaches to SAR: SCIT (2 meta-analyses dedicated to the total symptom score [TSS]) and total nasal symptom score [TNSS], respectively),⁶ nasal corticosteroids,⁷ oral antihistamines,⁸ and oral LAs.⁹ Systematic reviews not following the meta-analysis methodology were not included. We focused on meta-analyses that included at least 5 studies on SAR and that allowed a direct or indirect calculation of the average magnitude of efficacy (MoE) of the considered treatment to be made with both measures: relative clinical impact (RCI) and effect size (ES). Most meta-analyses on pharmacologic treatment of allergic rhinitis include trials on both seasonal and persistent allergic rhinitis; we excluded from our analysis studies without natural exposure (eg, studies based on artificial allergen exposure) and studies on persistent allergic rhinitis. We only selected the meta-analysis with a focus on SAR when 2 or more meta-analyses of a given treatment responded to the selection criteria. Primary outcomes are described in the **Methods** section in this article's Online Repository at www.jacionline.org. The vast majority of the examined trials included exclusively or almost exclusively adults. Only 1 trial was limited to children.¹⁰

Analysis of treatment effect

Clinical efficacy in trials of SCIT and trials of antisymptomatic treatment in patients with SAR is generally measured by using different methods (Fig 1). The studies on SCIT commonly evaluate the difference in daily symptom score values recorded throughout the pollen season or during the peak pollen season. By contrast, studies on antisymptomatic treatment of SAR commonly assess baseline values (usually over periods of 1-2 weeks) and treatment values (usually over periods of 2-4 weeks) of the symptom score, and they calculate the absolute and relative improvement of both the placebo and active treatment groups versus baseline values. Efficacy is often estimated as the difference between the percentage of reduction in the active and placebo groups. To compare the efficacy of the 2 therapeutic approaches, we used the means and SDs of the symptom scores recorded during the treatment period (see the **Methods** section in this article's Online Repository).

ES and RCI

Different scales have been used in the 42 trials contributing to the present study to express the primary outcome variables (TSSs and TNSSs). Therefore we followed the criteria suggested by the World Allergy Organization (WAO)¹¹ and used the standardized mean difference (SMD) to calculate the ES of individual studies. The overall ES of each category of treatment was calculated as the DerSimonian and Laird method pooled SMD. Both individual and overall SMD values were reported with 95% CIs. χ^2 Tests were performed to assess heterogeneity between studies, with a *P* value of less than .05 indicating significant differences between studies. Tests of heterogeneity were performed with the I^2 test.

The MoE of treatment versus placebo was also calculated for individual studies and expressed as the percentage reduction in clinical scores (TNSSs or TSSs) in the active versus placebo groups (RCI), as suggested by the WAO.¹¹ The average RCI of treatment for each category of study (SCIT, mometasone, desloratadine, and montelukast) was calculated by using the weighted mean of the values obtained in each of the studies included in the meta-analyses. Crude unadjusted weights were used.

Individual studies

Individual studies on ciclesonide, fluticasone propionate, fexofenadine, loratadine, and ebastine were selected from those available in the literature on the basis of the following criteria: published in the last 10 years (1998 or later); including at least 100 patients; adopting a randomized double-blind, placebo-controlled approach; and included in the Allergic Rhinitis and its Impact on Asthma update document.¹ For this analysis, we also selected the trial with the largest population among those included in each of the meta-analyses of SCIT, mometasone, desloratadine, and montelukast above reported values.

Comparison of ES and RCI

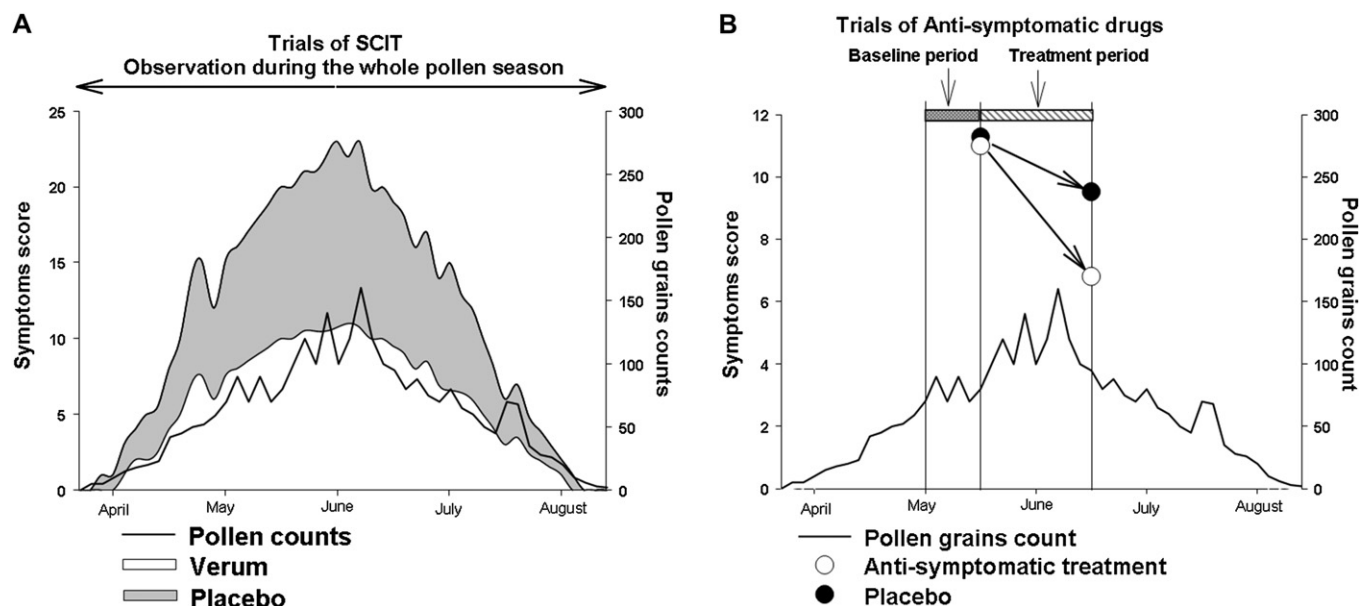
The ES of SCIT in terms of TNSSs was compared with those of nasal corticosteroids, antihistamines, and LAs and in terms of TSSs to antihistamines. A difference was considered significant when the 95% CI of the overall SMD did not overlap. *P* values of less than .05 were considered significant. The RCI of SCIT in terms of TNSSs was compared by means of ANOVA with those of nasal corticosteroids, antihistamines, and LAs and in terms of TSSs with those of antihistamines. The Bonferroni correction was applied to the ANOVA posttests. *P* values of less than .05 were considered significant.

RESULTS**Antisymptomatic effect of SCIT in patients with SAR**

For more information on the antisymptomatic effect of SCIT in patients with SAR, see **Tables I** and **II**.

In 2007, Calderon et al⁶ published a meta-analysis of SCIT for SAR. They examined 276 full-text articles, but only 15 of them¹²⁻²⁶ also met all the criteria for the meta-analysis in terms of the global (nasal, eye, and lung) symptom score. Of these 15 studies, we had to exclude the studies by Walker et al,²⁶ Corrigan et al,²³ and Jutel et al²⁵ because they did not report a complete dataset concerning clinical efficacy during the first season after treatment initiation. We included 12 trials, which included 474 subjects receiving active immunotherapy and 348 receiving placebo. In **Table I** we report the main characteristics of the trials, the TSSs, and the individual and overall RCI and ES values expressed as the SMD. The RCI ranged from -21%¹⁶ to -73%,¹⁵ its weighted mean value was -32.9% (SD, 12.7%; Fig 2, A), and its median value was -37.9%. The ES, expressed as the SMD, ranged from -3.06¹⁹ to -0.27,¹² and its overall value was 0.86 (95% CI, -1.17 to -0.55; Fig 2, B).

We also analyzed the effect of SCIT on nasal symptoms only. In the meta-analysis by Calderon et al,⁶ only 8 studies met the criteria for our meta-analysis in terms of nasal symptom scores.^{12,17,21,24,27-30} Of these 8 studies, we had to exclude the studies by D'Amato et al²⁸ and Dolz et al²⁹ because it was not possible to extrapolate the data concerning clinical efficacy during the first season after treatment initiation. We included 6 trials, which included 349 subjects receiving active immunotherapy and 236 receiving with placebo. In **Table II** we report the main characteristics of the trials included, the individual and overall RCI, and the ES values. The RCI ranged from -30%²¹ to



–52%,³⁰ its weighted mean value was –34.7% (SD, 6.8%; Fig 2, C), and its median value was –40.3%. The ES, expressed as the SMD, ranged from –0.53^{21–24} to –2.70,²⁷ and its overall value was –0.94 (95% CI, –1.45 to –0.43; Fig 2, D).

Antisymptomatic effect of desloratadine in patients with SAR

In 2007, Canonica et al⁸ published a meta-analysis of the efficacy of desloratadine delivered through the oral route in the treatment of allergic rhinitis. They screened 229 articles and identified 57 potentially relevant trials, but only 13 of them also met all the criteria for their meta-analysis.⁸ Among those, we further excluded studies on perennial allergic rhinitis and those measuring efficacy after artificial allergen exposure (eg, through chamber test) or after very brief natural exposure (1 day). We examined 6 trials, which included 525 subjects receiving desloratadine and 530 receiving placebo (see Table E1 in this article's Online Repository at www.jacionline.org).^{31–35} The RCI ranged from –9.0%³¹ to –35.6%,³³ its weighted mean value was –12.0% (SD, 5.1%; Fig 2, A), and its median value was –11.3%. The ES of individual studies, expressed as the SMD,⁸ ranged from –4.28³⁴ to –0.17,³² and its overall value was –1.00 (95% CI, –1.68 to –0.32; Fig 2, B).

Antisymptomatic effect of mometasone nasal spray in patients with SAR

In 2008, Penagos et al⁷ published a meta-analysis of the efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. They reviewed 242 articles, but only 16 of them met all the criteria for their meta-analysis.⁷ Among those, we further excluded studies on perennial allergic rhinitis and those measuring efficacy after artificial allergen exposure (eg, through a chamber test) or after very brief natural exposure (1 day). We examined 8 trials, which included 376 subjects receiving mometasone and 257 receiving placebo (see Table E2 in this

article's Online Repository at www.jacionline.org).^{10,36–42} The RCI ranged from –7.8%³⁶ to –56.9%,³⁷ its weighted mean value was –31.8% (SD, 16.7%; Fig 2, C), and its median value was –30.0%. The ES of individual studies, expressed as the SMD,⁷ ranged from –0.18³⁶ to –0.98,³⁷ and its overall value was –0.47 (95% CI, –0.62 to –0.32; Fig 2, D).

Antisymptomatic effect of montelukast in patients with SAR

In 2006, Rodrigo and Yanez⁹ published a meta-analysis of the efficacy of LAs delivered through the oral route in the treatment of SAR. They screened 76 studies, but only 17 of them met all the criteria for their meta-analysis.⁹ Among those, we only considered the studies of oral leukotriene receptor antagonists as monotherapy for SAR. We included 6 trials, which included 1584 subjects treated with montelukast and 1577 treated with placebo (see Table E3 in this article's Online Repository at www.jacionline.org).^{43–48} The meta-analysis by Rodrigo and Yanez⁹ does not report means and SDs of the symptom scores recorded during treatment. However, we were able to calculate these values, as reported in the Methods section in this article's Online Repository, from the data reported in the original articles. The RCI ranged from –3.1%⁴⁸ to –25.4%,⁴⁷ its weighted mean value was –6.3% (SD, 3.0%; Fig 2, C), and its median value was –7.4%. The ES of individual studies, expressed as the SMD,⁹ ranged from –0.48⁴⁵ to –0.16,⁴⁴ and its overall value was –0.24 (95% CI, –0.33 to –0.16; Fig 2, D).

Indirect comparison of SCIT versus antisymptomatic treatment in patients with SAR

We compared the ES of SCIT and desloratadine in terms of TSSs in patients with SAR. The analysis of variance demonstrated that the RCI on the TSS of SCIT was significantly higher than that of desloratadine (Fig 2, A). Similarly, the RCI of SCIT on

TABLE I. Antisymptomatic impact of SCIT in patients with SAR (TSS)

Study Design				Treatment [§]			Control [§]			RCI	SMD (95% CI) [§]	% Weight [*]
name	Allergen	age	SS	N	Mean	SD	N	Mean	SD	(%)		
Balda ¹²	trees	18 - 58	N,E,L	49	6.6	10.4	56	9.1	8.2	-28.0	-0.27 (-0.65, 0.12)	11.41
Bousquet ¹³	grass	11 - 45	N,E,L	20	63.6	32.5	18	108.6	33.2	-41.0	-1.34 (-2.05, -0.63)	7.96
Brewczynski ¹⁴	grass	14 - 34	N,E,L	10	59.5	32.6	8	122.4	85.1	-51.0	-0.98 (-1.97, 0.02)	5.64
Otolani ¹⁵	pellitory	14 - 59	N,E,L	18	0.6	0.1	17	2.3	1.0	-73.0	-2.40 (-3.29, -1.51)	6.40
Drachenberg ¹⁶	grass	18 - 60	N,E,L	74	0.8	0.4	50	0.9	0.4	-21.0	-0.46 (-0.83, -0.10)	11.64
Ferrer ¹⁷	pellitory	15 - 55	N,E,L	22	0.4 [*]	0.3 [*]	20	0.8 [*]	0.6 [*]	-51.2	-0.94 (-1.58, -0.30)	8.66
Meriney ¹⁸	ragweed	21 - 52	N,E,C	10	3.5	3.0	10	8.4	4.2	-58.0	-1.29 (-2.27, -0.30)	5.74
Otolani ¹⁹	grass	15 - 45	N,E,MT,L,O	8	2.0	0.6	7	5.9	1.6	-66.0	-3.06 (-4.69, -1.43)	2.83
Varney ²⁰	grass	19 - 52	N,E,MT,L	19	1531.0	1875.0	16	2230.0	856.0	-31.0	-0.46 (-1.13, 0.22)	8.33
Zenner ²¹	grass, rye	16 - 53	N,E,L	41	82.2 [*]	64.4 [*]	40	116.0 [*]	83.7 [*]	-29.0	-0.45 (-0.89, -0.01)	10.81
Bodtger ²²	birch	19 - 46	N,E,L	16	2.2	1.0	17	3.3	1.4	-33.0	-0.88 (-1.60, -0.16)	7.89
Frew ²⁴	grass	18 - 60	N,E,L	187	3.3	2.4	89	4.6	2.9	-28.0	-0.49 (-0.75, -0.24)	12.69
Overall (I-squared = 70.5%, p = 0.000) [*]											-0.86 (-1.17, -0.55) [*]	100.00

NOTE: Weights are from random effects analysis

[§]Data from Calderon et al.⁶ if not otherwise indicated
^{*}Data from the original paper, ^{*}calculated on the basis of studies included in this table

SS= symptom score, based on symptoms of the target organs: N=nasal, E=eye, L=lung, MT=mouth and throat, O=others (headache, tiredness)

the TNSS was significantly higher than those of mometasone and montelukast (Fig 2, C). The ES of SCIT in terms of the TSS was not significantly different from that of desloratadine (Fig 2, B). The ES of SCIT in terms of the TNSS was not significantly different from that of mometasone, and it was significantly greater than that of montelukast (Fig 2, D).

We expanded this comparison by selecting studies of other molecules and treatments, including fexofenadine,⁴⁹ loratadine,⁵⁰ ebastine,⁵⁰ ciclesonide,⁵¹ and fluticasone propionate nasal spray.⁵² In this descriptive analysis we also reported one of the trials (the largest for population size) included in the meta-analyses of SCIT,²⁴ mometasone,¹⁰ desloratadine,³⁵ and montelukast.⁴⁴ We selected 9 studies and calculated the RCI in terms of total (Fig 3, A) or nasal (Fig 3, B) symptoms of SAR. SCIT had a maximal effect (−29%); nasal corticosteroids had a high (−10% to −22%), antihistamines an intermediate (−5% to −18%), and montelukast a lower (−7%) RCI.

DISCUSSION

Nasal corticosteroids, oral antihistamines, and other drugs are normally proposed as a “first-line” and fast-acting antisymptomatic treatment for SAR. By contrast, SCIT is usually considered a “second-line” treatment, the purpose of which is to modify the natural history of the allergic disease. According to

international guidelines, SCIT is indeed suggested especially when pharmacotherapy is not effective, accepted, or tolerated.¹ However, our analysis shows that SIT is at least as effective as pharmacotherapy in the control of symptoms in patients with SAR as early as in the first season after treatment initiation.

Before accepting this conclusion, we should take into account a couple of questions on the methods adopted in this study: (1) Were the measures of efficacy appropriate enough and validated? (2) Were the trials properly selected and homogeneous enough? (3) What is the role of a different use of rescue medications? (4) What is the role of differences in the population size? (5) What is the role of differences in the follow-up duration? (6) What is the role of differences in disease severity? Each of these questions deserves a clear answer.

First, we measured the MoE according to the suggestions of the WAO¹¹ (ie, as the percentage reduction in global clinical scores in the active vs placebo group [RCI]). However, we measured the overall ES also as the SMD (ie, the standard approach adopted by the Cochrane Collaboration). Interestingly, these 2 universally accepted methods led to similar conclusions (ie, that SCIT is not inferior to pharmacotherapy as an antisymptomatic treatment of SAR; Fig 2).

Second, it should be noted that some of the trials of SCIT included in our analysis were performed more than 2 decades ago on small sample sizes. However, their quality was judged high enough to justify their admission in a Cochrane meta-analysis.⁶

TABLE II. Antisymptomatic impact of SCIT in patients with SAR (TNSS)

name	Study Design			Treatment [§]			Control [§]			RCI (%)	SMD (95% CI) [§]	% Weight*
	Allergen	age	SS	N	Mean	SD	N	Mean	SD			
Balda ¹²	trees	18 - 58	n.r	49	2.8	4.3	56	4.4	4.4	-37.0	-0.37 (-0.76, 0.02)	18.75
Ferrer ¹⁷	pellitory	15 - 55	I,S,R,O	22	0.5 ^A	0.4 ^A	20	0.9 ^A	0.6 ^A	-47.0	-0.88 (-1.51, -0.24)	15.84
Zenner ²¹	grass,rye	16 - 53	n.r	41	44.5 ^A	32.2 ^A	40	63.3 ^A	38.3 ^A	-30.0	-0.53 (-0.97, -0.08)	18.14
Frew ²⁴	grass	18 - 60	n.r	187	2.0	1.5	89	2.9	1.9	-30.0	-0.53 (-0.78, -0.27)	19.95
Bousquet ¹³	grass	n.r.	n.r	39	61.0	17.9	19	109.0	16.8	-44.0	-2.70 (-3.45, -1.95)	14.48
Mirone ³⁰	ragweed	23 - 60	I,S,R,O	11	4.0	3.3	12	8.3	4.2	-52.0	-1.09 (-1.98, -0.20)	12.84
Overall (I-squared = 85.0%, p = 0.000)*											-0.94 (-1.45, -0.43)*	100.00

NOTE: Weights are from random effects analysis

§Data from Calderon et al.⁶ if not otherwise indicated
^AData from the original paper, *calculated on the basis of studies included in this table

SS= symptom score, based on nasal symptoms: I=itchy, S=sneezing, R=rhinorrhea, O=occlusion

Similarly, the high quality of all the trials of desloratadine, mome-tasone, and montelukast included in our analyses is reflected by their admission in meta-analyses published in peer-reviewed journals.⁷⁻⁹ Trials with SCIT were rather heterogeneous with regard to the composition of the administered allergenic extract and to the sensitization pattern of their study populations. However, the outcome of our analysis did not change when only trials of grass pollen SCIT were taken into consideration (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org).

Third, a comparison between SCIT versus pharmacotherapy in the treatment of SAR might be inappropriate because of a different use of rescue medication. Indeed, trials of antisymptomatic treatment compare drugs against placebo (or placebo plus antihistamines), whereas trials on SCIT compare immunotherapy plus antisymptomatic treatment against placebo plus antisymptomatic treatment. We believe that this heterogeneity does not reduce the reliability of our comparison because (1) we have taken into consideration the symptom scores only and excluded the medication scores; (2) the medication score was invariably reduced among patients receiving SCIT compared with that in patients receiving placebo in the trials examined⁶; and (3) therefore the difference of the MoE of SCIT compared with placebo would have been even bigger if antisymptomatic treatment in patients receiving placebo would have been reduced to the same extent as in patients receiving SCIT. However, we cannot rule out a synergistic effect between SCIT and antisymptomatic drugs;

we consider this possibility to be unlikely because the mechanisms of the 2 categories of treatment are different.

Fourth, the sample sizes examined in most trials of SCIT are smaller than those examined in most drug trials. The power calculation and related sample size is dependent on the ES and distribution. As long as the sample size is according to the statistical plan and power calculation, a small sample size is of no disadvantage. Nevertheless, in the largest trial of SCIT, which involved more than 200 patients,²³ the MoE was almost identical to the overall weighted mean of the 14 studies included in our analysis. Interestingly, the comparison of the outcomes of the studies with the largest sample size for each category provided similar results as those obtained through the meta-analyses (Fig 3).

Fifth, the observation period of trials of SCIT in patients with SAR usually covers the whole pollen season, whereas the observation period of pharmacotherapy trials usually covers the peak pollen season only. However, the difference in the MoE of SCIT compared with that of placebo is even stronger when the analysis is limited to the peak season only.^{24,52}

Sixth, trials of SCIT might have evaluated patients with more severe symptoms than those examined in trials of antisymptomatic drugs. On the one hand, from a mathematic standpoint, this might have led to the observation of a wider improvement of disease in trials of SCIT; on the other hand, from a clinical standpoint, a more severe disease might be less susceptible to

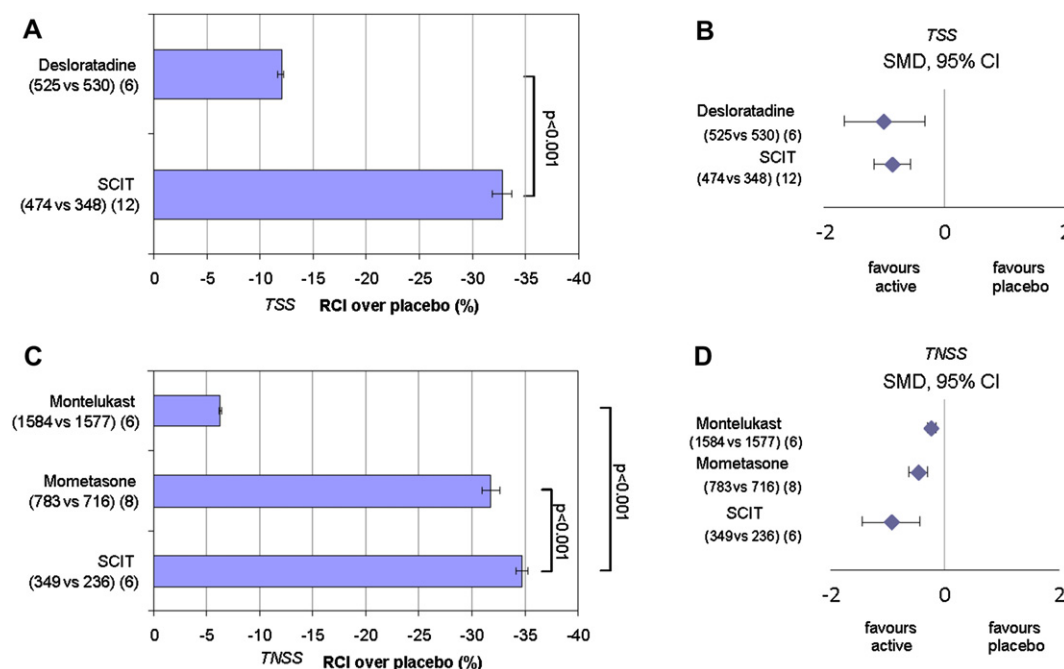


FIG 2. Comparison of efficacy between SCIT and antisymptomatic treatment. **A** and **C**, Comparison of the RCI among treatment categories. Each *bar* represents the weighted mean value from a set of individual studies. *Lines* represent 95% confidence limits. Fig 2, **A**, Studies considering TSSs (Tables I and E1). Fig 2, **C**, Studies considering TNSSs (Tables II, E2, and E3). The number of patients (active vs placebo groups) and the number of studies contributing to each category is given in brackets. **B** and **D**, Comparison of the ES among different categories of treatments. Each *point* represents the overall (weighted) average SMD of values from a set of individual studies. *Lines* represent 95% confidence limits. Fig 2, **B**, Studies considering TSSs (Tables I and E1). Fig 2, **D**, Studies considering TNSSs (Tables II, E2, and E3).

symptom improvement. On the basis of the published data, an influence of heterogeneity in terms of disease severity on our findings cannot be ruled out.

It should be highlighted that we found a kind of hierarchy of the RCI among different antisymptomatic treatments (ie, inhaled corticosteroids >> antihistamines >> LAs; Fig 2, **A** and **B**). A similar hierarchy was already reported in a specific meta-analysis comparing the clinical efficacy of these 3 drug categories in patients with allergic rhinitis⁵¹ and in a recent review looking at the efficacy of intranasal steroids, nasal antihistamines, and oral antihistamines in patients with SAR.⁵³ This consistency with previous studies supports the robustness of our methodological approach. In addition, the outcome of our meta-meta-analysis was supported by the outcome of the analysis based on single studies testing other antihistamines (Fig 3, **A**), inhaled nasal corticosteroids, and LAs (Fig 3, **B**).

Nevertheless, it should be noted that the evidence provided by our study is indirect because it is based on trials performed in different populations and settings. On the other hand, only 4 trials have directly compared SCIT and antisymptomatic treatment in patients with SAR,²⁻⁵ and they reached conflicting conclusions. In a randomized, double-blind, comparative study with birch pollen SCIT and nasal corticosteroids (budesonide, 400 µg daily) in 41 patients with birch pollen allergy affected by SAR with or without asthma, budesonide was more effective than short-course, preseasonal SCIT in reducing the symptoms of rhinoconjunctivitis; the 2 therapies were equivalent in terms of the need for rescue medication.² SCIT with a grass pollen extract was more efficient in the first year of treatment than cetirizine, mometasone furoate, and

levocabastine eye drops in controlling symptoms and use of rescue drug medication in an open trial involving 30 patients with SAR.³ In a prospective randomized study of 48 patients with SAR to grass, rye pollen, or both, short-term SCIT was more effective than a standard antisymptomatic treatment (local or systemic antihistamines, disodium cromoglycate eye drops and nasal sprays, local glucocorticosteroid, and nasal decongestants) in reducing symptoms and drug use during season.⁴ By contrast, in a double-blind, parallel-group trial in 60 ragweed-sensitive adults, preseasonal SCIT was markedly less efficient than budesonide nasal spray used throughout the season in controlling symptoms of SAR.⁵

Our results are therefore consistent with the positive conclusions of 2 trials^{2,4} and in conflict with the negative conclusions of the other 2 trials.^{3,5} More trials directly comparing the antisymptomatic effect of pharmacotherapy versus SCIT in patients with SAR in the same study population are needed to confirm our indirect evidence. Such trials are not easy to design because rescue medication must be given for ethical reasons.^{2-5,49}

With this limitation, we can conclude that SCIT has not only a disease-modifying and long-term effect, creates a reduction in drug consumption, and has a preventive effect on asthma and new sensitizations⁵⁴⁻⁵⁷ but also has a rather powerful antisymptomatic effect starting as early as the first season after treatment onset. Actually, the additional efficacy of SCIT is superior to that obtained with antihistamines and is well above the critical threshold (at least 20% less symptoms than placebo) established by the WAO's recommendations.^{11,58}

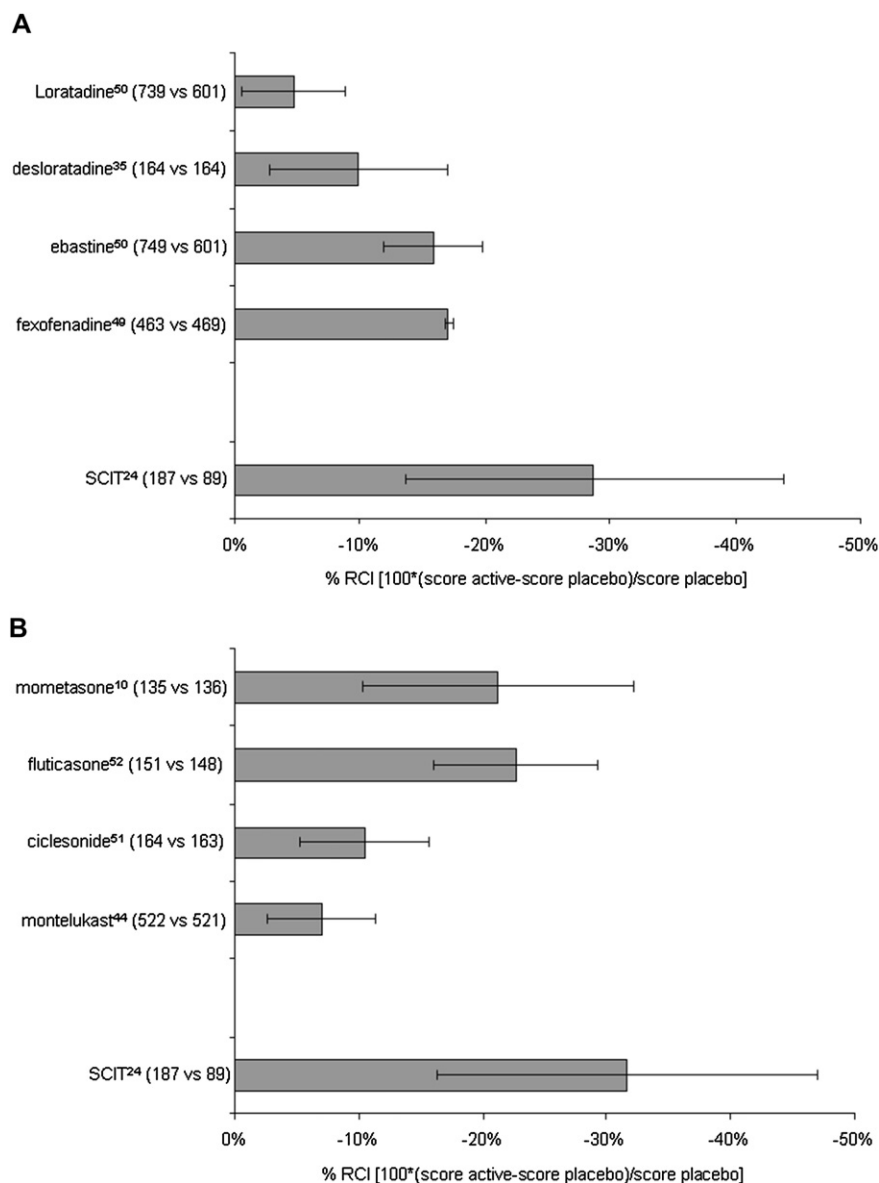


FIG 3. Comparison of the RCI among different treatments. *Meta-analysis of 3 highly homogeneous trials. The numbers of patients receiving active treatment or placebo are reported in *parentheses*. $RCI = [100 \times (\text{score active} - \text{score placebo}) / \text{score placebo}]$; treatment period. Differences between SCIT and other treatments were not significant after Bonferroni correction for multiple comparisons.

Our results support the novel concept that cost/benefit analysis of specific immunotherapy in patients with SAR should take into account not only its long-term efficacy⁵⁹ but also its short-term effect on symptoms. The respective value of pharmacotherapy and SCIT in such a cost/benefit analysis of the treatment options in patients with SAR could then be revised. However, therapeutic algorithms do not depend exclusively on the efficacy of treatments. Many other factors, such as safety, costs, feasibility, acceptance rates, adherence, and compliance contribute to the characterization of the role of different therapeutic options in the disease management plan of a chronic disease.

In conclusion, our data provide indirect evidence that SCIT is an antisymptomatic treatment in patients with SAR, which is at

least as potent as drugs, even in the first season of treatment. Trials directly comparing the antisymptomatic effect of pharmacotherapy versus SCIT in patients with SAR are needed to confirm this indirect evidence.

We thank Ms Sabine Mussler for her help with the literature search.

Clinical implications: SCIT is effective not only in the long-term but also in the short-term treatment of SAR.

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METHODS

Primary outcomes

To compare the efficacy of the 2 therapeutic approaches, we used the means and SDs of symptom scores recorded during the treatment period. These values were already reported for each trial in 3 of the 4 meta-analyses used in this review.^{E1-E3} The meta-analysis on LAs in patients with SAR^{E4} reported only the average changes in symptoms score from baseline induced by the treatment or placebo. We then calculated the mean of symptom scores recorded during the treatment period from the data reported in the original articles. Within each meta-analysis, we selected as primary outcomes data of efficacy expressed either as the TSS (nasal and eye symptoms plus lung symptoms, throat/oral symptoms, or both) or the TNSS (nasal pruritus or itch, nasal discharge or rhinorrhea, nasal blockage or obstruction or stiffness, and sneezing). Differences in the methodology of measuring the TSS or the TNSS among studies were accepted.

Calculation of the average symptom scores recorded during treatment (LAs)

In a meta-analysis of trials of LAs in patients with SAR,^{E4} as well as in the 6 original trials contributing to the meta-analysis itself,^{E5-E10} the means and SDs of the clinical scores recorded during treatment are not reported. However, the average changes from baseline are reported so that we calculated the average symptom scores registered during treatment by subtracting the average changes from the average baseline values. Adjusted mean (analysis of covariance) were available in the studies and used by us instead of rough means. In one study^{E7} baseline values were also not reported. However, this study reports the changes in average symptom scores during treatment with respect to the baseline values as both absolute values and percentages of reduction. From these data, we could then calculate the average symptom score (SS) recorded during treatment by using the following formula:

$$\text{Average SS during treatment} = \frac{100 \times \text{average change in SS}}{\% \text{ reduction in SS}} - \text{average change in SS}.$$

Calculation of the RCI of treatment versus placebo

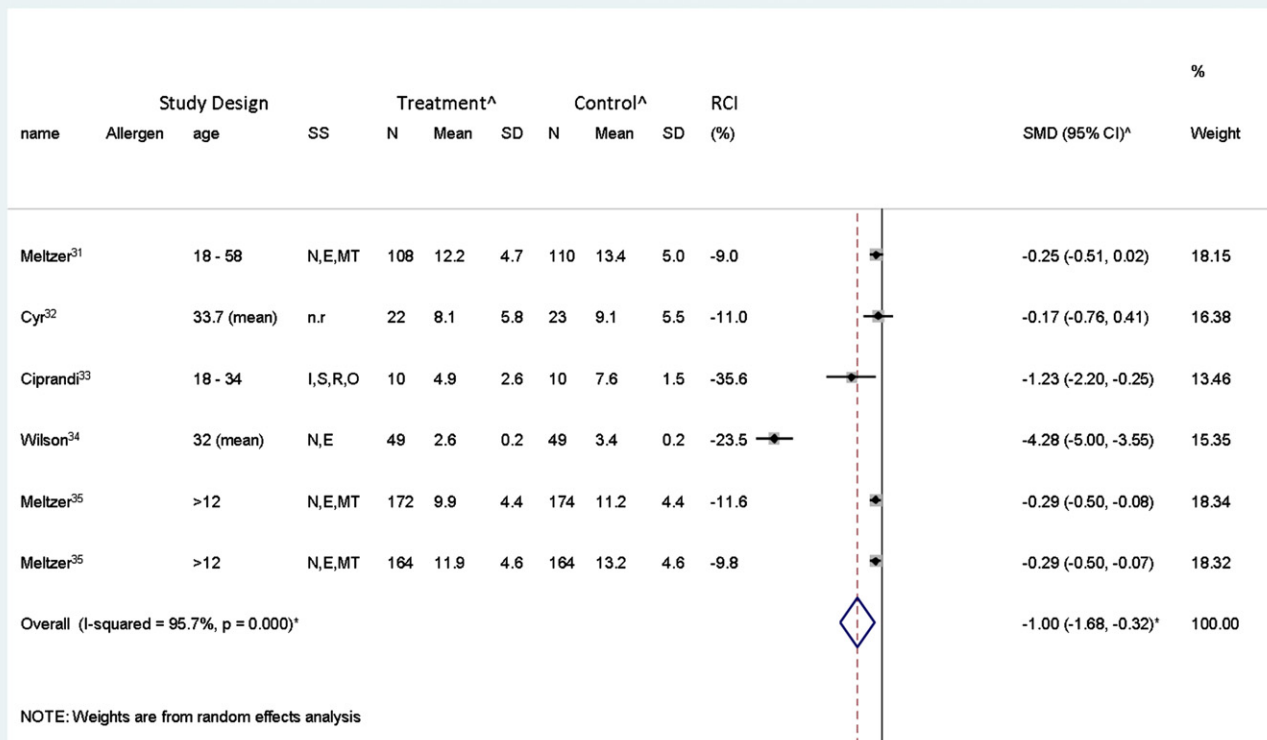
The relative effect of treatment versus placebo was calculated according to the following formula, which is derived from the one reported above:

where *SSa* is defined as the symptom score for the active group, and *SSp* is defined as the symptom score for the placebo group.

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$$\text{RCI} = \frac{100 \times [(\text{average baseline SSa} + \text{average change in SSa}) - (\text{average baseline SSp} + \text{average change in SSp})]}{(\text{average baseline SSp} + \text{average change SSp})},$$

TABLE E1. The antisymptomatic effect of desloratadine in patients with SAR (TSS)[^]Data from Canonica et al.⁸^{*}calculated on the basis of studies included in this table

SS= symptom score, based on symptoms of the target organs: N=nasal, E=eye, L=lung, MT=mouth and throat, O=others (headache, tiredness)

In the study by Ciprandi et al., TSS is based on nasal symptoms only: I=itchy, S=sneezing, R=rhinorrhoea, O=obstruction

TABLE E2. The antisymptomatic effect of mometasone nasal spray in patients with SAR (TNSS)

name	Study Design		SS	Treatment [^]			Control [^]			RCI (%)	SMD (95% CI) [^]	Weight
	Allergen	age		N	Mean	SD	N	Mean	SD			
Gawchick ³⁶		12 - 74	I,S,R,O	122	5.9	2.8	123	6.4	2.9	-7.8	-0.18 (-0.43, 0.07)	15.29
Stuck ³⁷		27.3 + 4.9	n.r	13	8.8	7.6	11	20.4	14.8	-56.9	-0.98 (-1.84, -0.12)	2.85
Berkowitz ³⁸		12 - 59	I,S,R,O	101	5.1	2.2	99	6.8	2.2	-25.0	-0.77 (-1.06, -0.48)	13.56
Meltzer ¹⁰		6 - 11	I,S,R,O	135	4.3	2.8	136	5.5	2.9	-21.2	-0.41 (-0.65, -0.17)	15.81
Meltzer ³⁹		12 - 65	I,S,R,O	80	4.4	2.6	41	6.0	2.6	-27.2	-0.63 (-1.01, -0.24)	9.84
Bronsky ⁴⁰		18 - 65	I,S,R	96	5.9	4.6	95	8.8	4.6	-32.7	-0.63 (-0.92, -0.34)	13.42
Graft ⁴¹		36 (mean)	n.r	114	1.1	3.7	101	2.4	3.7	-54.2	-0.35 (-0.62, -0.08)	14.37
Hebert ⁴²		18 - 67	I,S,R,O	122	1.7	5.8	110	3.7	5.8	-53.8	-0.34 (-0.60, -0.08)	14.86
Overall (I-squared = 51.0%, p = 0.046)*											-0.47 (-0.63, -0.32)*	100.00

NOTE: Weights are from random effects analysis

[^]Data from Penagos et al.⁷

*calculated on the basis of studies included in this table

SS= symptom score, based on nasal symptoms: I=itchy, S=sneezing, R=rhinorrhoea, O=occlusion

-1.84 0 1.84
Favours treatment Favours control

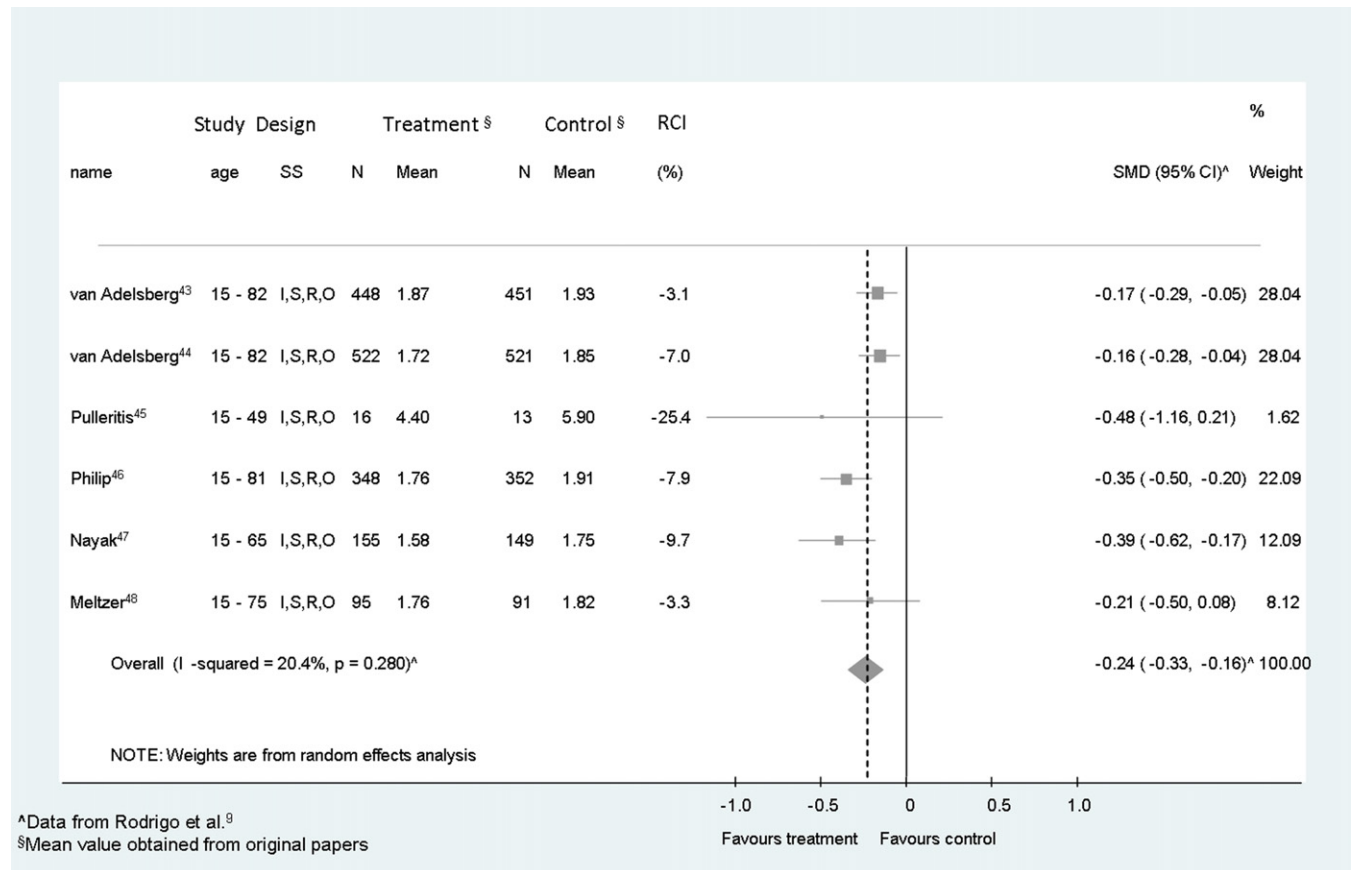
TABLE E3. The antisymptomatic effect of montelukast in patients with SAR (TNSS)

TABLE E4. The antisymptomatic effect of SCIT in patients with SAR caused by grass pollen allergy (TSS)

name	Study Design			Treatment [§]			Control [§]			RCI (%)		SMD (95% CI) [§]	% Weight
	Allergen	age	SS	N	Mean	SD	N	Mean	SD				
Bousquet ¹³	grass	11 - 45	N,E,L	20	63.6	32.5	18	108.6	33.2	-41.0		-1.34 (-2.05, -0.63)	12.14
Brewczynski ¹⁴	grass	14 - 34	N,E,L	10	59.5	32.6	8	122.4	85.1	-51.0		-0.98 (-1.97, 0.02)	7.86
Drachenberg ¹⁶	grass	18 - 60	N,E,L	74	0.8	0.4	50	0.9	0.4	-21.0		-0.46 (-0.83, -0.10)	20.90
Ortolani ¹⁵	grass	15 - 45	N,E,MT,L,O	8	2.0	0.6	7	5.9	1.6	-66.0		-3.06 (-4.69, -1.43)	3.57
Varney ²⁰	grass	19 - 52	N,E,MT,L	19	1531.0	1875.0	16	2230.0	856.0	-31.0		-0.46 (-1.13, 0.22)	12.89
Zenner ²¹	grass, rye	16 - 53	N,E,L	41	82.2 [^]	64.4 [^]	40	116.0 [^]	83.7 [^]	-29.0		-0.45 (-0.89, -0.01)	18.66
Frew ²⁴	grass	18 - 60	N,E,L	187	3.3	2.4	89	4.6	2.9	-28.0		-0.49 (-0.75, -0.24)	23.99
Overall (I-squared = 60.6%, p = 0.019)*												-0.71 (-1.04, -0.38)*	100.00

NOTE: Weights are from random effects analysis

[§]Data from Calderon et al.⁶ if not otherwise indicated[^]Data from the original paper *calculated on the basis of studies included in this table

-4.69 0 4.69

Favours treatment Favours control

SS= symptom score, based on symptoms of the target organs: N=nasal, E=eye, L=lung, MT=mouth and throat, O=others (headache, tiredness)

TABLE E5. The antisymptomatic effect of SCIT