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Sublingual or subcutaneous immunotherapy for allergic rhinitis?

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Activity Objectives:

1. To review the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) based on randomized placebo-controlled trials.
2. To compare the efficacy and safety of SCIT versus SLIT based on indirect evidence and evidence from randomized head-to-head comparative trials.

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Allergen immunotherapy is effective in patients with allergic rhinitis (AR) and, unlike antiallergic drugs, has been shown to modify the underlying cause of the disease, with proved long-term benefits. Subcutaneous immunotherapy (SCIT) has been the gold standard, whereas sublingual immunotherapy (SLIT) has emerged as an effective and safe alternative. Previous Cochrane systematic reviews and meta-analyses have confirmed that both SLIT and SCIT are effective in patients with seasonal AR, whereas evidence for their efficacy in patients with perennial disease has been less convincing. Recent large, adequately powered trials have demonstrated reductions in both symptoms and use of rescue medication in patients with seasonal and those with perennial AR. Here we appraise evidence for SCIT versus SLIT based on indirect evidence from Cochrane reviews and recent well-powered double-blind, randomized controlled trials versus placebo and the limited direct evidence available from randomized blind head-to-head comparisons. At present, based on an overall balance of efficacy and side effects, the patient is in equipoise. Pending definitive comparative trials, choice might be determined largely by the local availability of SCIT and SLIT products of proved value and personal (patient) preference. (J Allergy Clin Immunol 2016;137:339-49.)

Key words: *Allergic rhinitis, immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy*

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Allergic rhinitis (AR) is a common disease.[1] Its prevalence in the United States is about 15% based on physician diagnoses and up to 30% based on self-reported symptoms.[2] In Europe the prevalence ranges from 17% to 29%, with an overall prevalence of 23%.[3] AR is frequently associated with bothersome symptoms,

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Abbreviations used
AR: Allergic rhinitis
ARC: Allergic rhinoconjunctivitis
RCT: Randomized controlled trial
SAR: Seasonal allergic rhinitis
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SMD: Standardized mean difference
SR: Systematic review

which can impair quality of life, productive time at work and school, quality of sleep, and decreased involvement in outdoor activities.[2,3] Often, this condition is associated with comorbidities, including asthma.[4] Standard medical therapy consists of allergen avoidance where possible and pharmacotherapy, which generally includes the use of nonsedating oral antihistamines, topical nasal antihistamines, and intranasal corticosteroid sprays.[1,2,5] Suboptimal responses to antiallergic drugs are frequently caused by poor adherence such that patient education on the proper technique and need for regular use of nasal steroid sprays is important. These medications, although effective, must be repeated when symptoms recur because the underlying allergic disease remains unaffected.[1,6] Furthermore, some population surveys have reported that up to 29% of children and 62% of adults have partial or poor relief with pharmacotherapy alone.[7,8]

For patients with AR whose symptoms remain uncontrolled despite a supervised trial of medical treatment, allergen immunotherapy should be considered.[1] Subcutaneous immunotherapy (SCIT) has been shown to be highly effective, particularly for seasonal pollinosis but also for perennial disease in patients with mite allergy.[9,10] Nevertheless, this route of administration can occasionally be associated with allergic side effects and therefore needs to be administered in a specialist setting with access to adrenaline and other resuscitative measures.[11,12] Sublingual immunotherapy (SLIT) has emerged as an effective and safe alternative to the subcutaneous route for patients with seasonal allergic rhinitis (SAR),[1,13] whereas, until recently, evidence for efficacy in perennial mite allergy has been less convincing, particularly in children.[14] Sublingual treatment is commonly associated with local itching and swelling in the mouth, which can occasionally be bothersome and persist for weeks.[11] SLIT has an impressive safety profile in clinical trials[15,16] and postmarketing surveillance of large cohorts.[17] Although there have been isolated reports of more severe allergic side effects, including anaphylaxis, there have been no fatalities.[18] Adherence to sublingual treatment has also been raised as a potential issue,[19] and regular 3-month follow-up for repeat prescriptions has been shown to be effective in improving compliance.[20]

Both SCIT and SLIT, in contrast to antiallergic drugs, have been shown to have disease-modifying properties with clinical benefits that can persist for 2 to 3 years after discontinuation of therapy.[15,21] Three long-term double-blind, placebo-controlled studies of SLIT[6,11,15,16,22-24] and 3 studies of SCIT[21,25-28] for seasonal pollinosis are described in detail in Tables E1 and E2 in this article's Online Repository at www.jacionline.org.[6,11,15,16,21-28] Briefly, 3 years of treatment with sublingual drops of a 5-grass-pollen extract was effective 1 year after discontinuation.[22] Two studies of grass pollen allergen tablet immunotherapy administered daily either pre-coseasonally[16,23,24] or continuously[6,11,15] for 3 years (cumulative annual dose of the Phl p 5

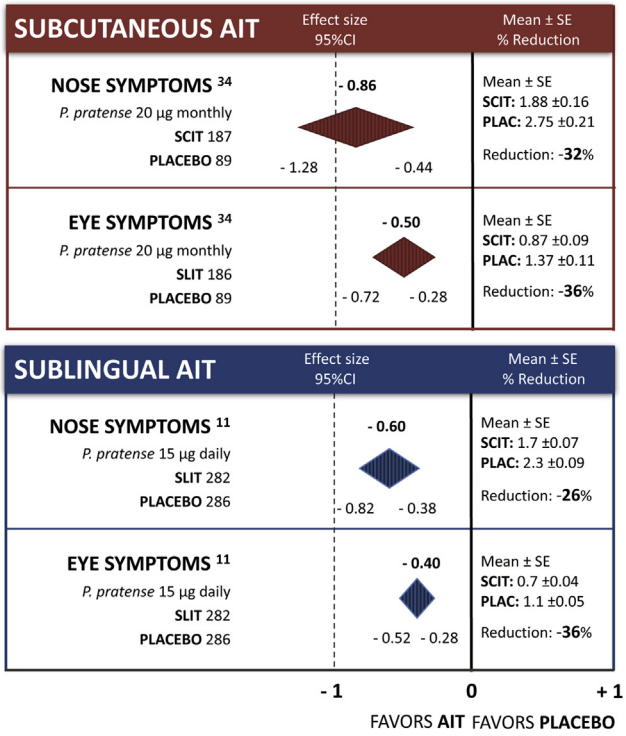

FIG 1. Two well-powered RCTs of SCIT and SLIT for SAR. *AIT,* Allergen immunotherapy.

major allergen for both studies was around 5-6 mg annually) produced remarkably similar results. In both studies there was an approximate 30% to 40% reduction in symptoms and rescue medication use during 3 years of therapy and a 20% to 30% reduction during 2 years off treatment when double-blinding was maintained. Local side effects were common but generally well tolerated, and there were no serious adverse events reported. Three previous double-blind, placebo-controlled trials of subcutaneous ragweed,[25] grass pollen,[21,26,27] and *Parietaria* species[28] immunotherapy produced similar results. Although studies were small (with 10-20 participants per group), 3 to 4 years of treatment resulted in persistent improvement in symptoms and/or reductions in rescue medication at 3 years in 1 study after double-blind withdrawal[21] and in 2 studies at 1 year after discontinuation of immunotherapy.[25,28] There is also evidence that SCIT can prevent disease progression to asthma in children with pollen-induced AR[29] and possibly prevent onset of new allergic sensitizations,[30,31] with similar results for sublingual treatment.[32] Evidence for prevention is less robust, and a current double-blind, placebo-controlled trial of grass pollen sublingual tablet immunotherapy on asthma prevention in 812 children with SAR will be reported in 2016.[33]

An important question is whether the balance of effectiveness and side effects is in favor of either the subcutaneous or sublingual route. Two well-powered randomized controlled trials (RCTs) by Frew et al[34] using subcutaneous grass pollen immunotherapy and Dahl et al[11] using sublingual grass pollen tablet immunotherapy had very similar study designs and were conducted with similar methodology. Participants had moderate-to-severe grass pollen SAR for at least 2 years. The studies used the same standardized single-allergen *Phleum pratense* extract. The SCIT was administered in a cluster updosing regimen followed by monthly maintenance injections of alum-adsorbed extract that contained

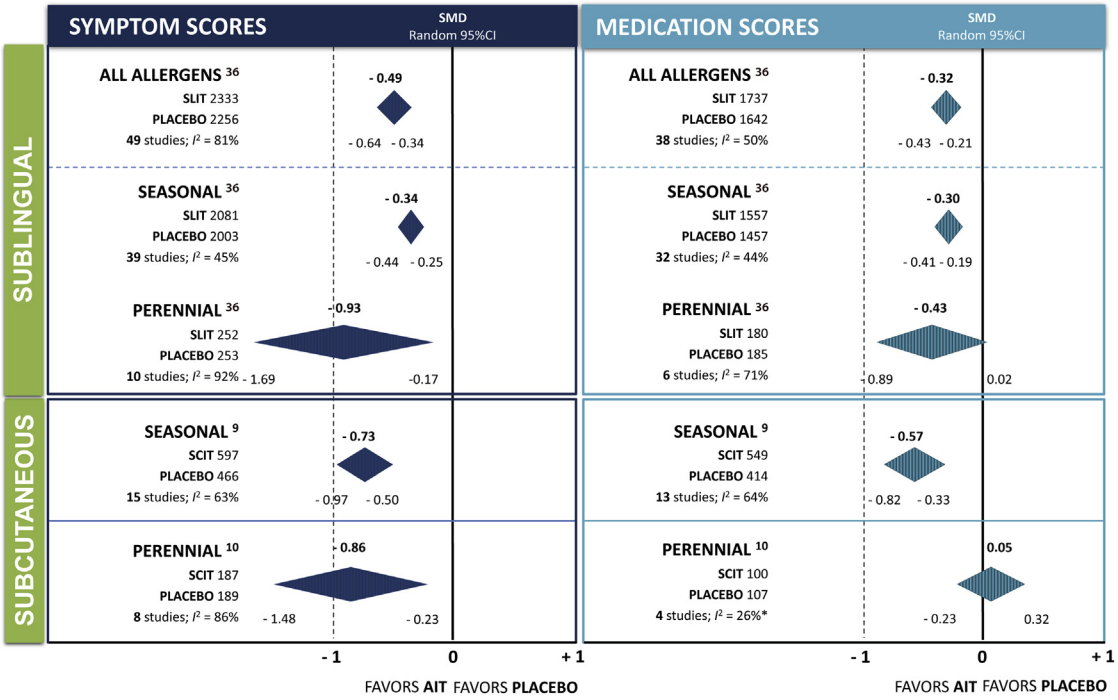

FIG 2. Overview of Cochrane meta-analyses on SCIT and SLIT for AR. *AIT*, Allergen immunotherapy.

20 μg of the major allergen Phl p 5. SLIT was administered daily as a lyophilized fast-dissolving tablet that contained 15 μg of Phl p 5. The mean effect sizes for improvement in nasal and ocular symptoms were very similar (26% to 36% reduction compared with placebo), and there was considerable overlap in CIs (Fig 1).[11,34] Sublingual tablet immunotherapy was associated with local side effects (oral pruritis in 46% and mouth edema in 18%) and resulted in withdrawal in 4% of 634 participants, whereas subcutaneous treatment was accompanied by the expected level of immediate systemic adverse events after injections (mild grade 2 reactions in 17.2% and non–life-threatening grade 3 reactions in 4.4% of participants treated with the currently recommended therapeutic dose).[35]

These 2 studies were pivotal in the registration of these vaccines in Europe, and the data might imply equivalent effect sizes for the 2 routes of administration. However, this remains speculative, and the present review aims to compare the efficacy and safety of SCIT and SLIT by using indirect evidence from Cochrane meta-analyses and more recent systematic reviews (SRs) and well-powered RCTs and by evaluating direct evidence from the few available double-blind, placebo-controlled head-to-head studies of SCIT versus SLIT.

COMPARISON OF SLIT AND SCIT

Indirect evidence from Cochrane reviews and meta-analyses

Three Cochrane SRs have compared the efficacy of allergen immunotherapy versus placebo in patients with AR: 2 for SCIT for seasonal allergic rhinitis (SAR)[9] and perennial allergic rhinitis (PAR)[10] and 1 for SLIT for both SAR and PAR (Fig 2).[9,10,36,37]

For SCIT for seasonal rhinitis,[9] 1111 publications were identified, of which 51 met the inclusion criteria for SR, and 15 RCTs (comprising 1063 participants) were included in the meta-analysis of symptom scores. A significant reduction in symptom scores was found in the SCIT group compared with the placebo group (standardized mean difference [SMD], −0.73; 95% CI, −0.97 to −0.50; I^2 = 63%). Medication scores from 13 trials (comprising 963 participants) also showed a reduction for the actively treated group (SMD, −0.57; 95% CI, −0.82 to −0.33; I^2 = 64%). None of these studies were conducted exclusively in children. Concerning adverse events, 30 studies documented the presence of local reactions, and 33 trials reported systemic adverse reactions. In most cases symptoms were mild and reversible with appropriate treatment. Four events were classified as early grade 4 systemic reactions (<30 minutes, n = 3 SCIT [2 cases of anaphylaxis and 1 asthma exacerbation] and n = 1 placebo [anaphylaxis]). A more comprehensive description of the occurrence of these adverse reactions has been included in Table E3 in this article's Online Repository at www.jacionline.org.[9] Thirteen studies reported the use of adrenaline: 19 events in the actively treated group (0.13% [14,085 injections given]) and 1 event in participants receiving placebo (0.01% [8,278 injections given]). There were no fatalities.[9]

A Cochrane SR and meta-analysis of RCTs is currently in progress to evaluate the efficacy of SCIT in patients with PAR.[10] Sixteen double-blind studies that randomized a total of 667 participants were included. Only 8 reported symptom scores and only 4 reported medication scores were suitable for meta-analysis. Participants receiving SCIT presented a significant reduction in nasal symptom scores (SMD, −0.86; 95% CI, −1.48 to −0.23; I^2 = 86%; RCTs, n = 8), allergic rhinoconjunctivitis (ARC) symptom scores (SMD, −1.24; 95% CI, −2.10 to −0.38; I^2 = 81%; RCTs, n = 4), and combined symptom medication ARC scores (SMD, −0.89; 95% CI, −1.66 to −0.11; I^2 = 54%; RCTs, n = 2). No effects were observed on medication scores (SMD, 0.05; 95% CI, −0.23 to 0.32; I^2 = 26%; RCTs, n = 4). Only 1 of the 16 RCTs was performed in children in whom SCIT

reduced symptom ($P = .03$) and medication ($P = .05$) scores.[38] Local or systemic reactions were reported in all 16 studies: local reactions, 92 (n = 65 for SCIT and n = 27 for placebo); grade I systemic reactions, 86 (n = 59 for SCIT and n = 27 for placebo); grade II systemic reactions, 15 (n = 13 for SCIT and n = 2 for placebo); grade III systemic reactions, 2 (SCIT); and grade IV systemic reactions, 8 (all SCIT). No fatalities were reported. Despite considerable heterogeneity (I^2), overall, the meta-analysis supported efficacy for SCIT for perennial AR.[10]

Radulovic et al[36] evaluated the efficacy and safety of SLIT. Sixty studies met the inclusion criteria, and 49 (that included a total of 4589 participants) were suitable for pooled analysis. Thirty-nine assessed seasonal and 10 assessed perennial rhinitis. A significant reduction in symptom scores (SMD, −0.49; 95% CI, −0.64 to −0.34; I^2 = 81%; RCTs, n = 49) and medication requirements (SMD, −0.32; 95% CI, −0.43 to −0.21; I^2 = 50%; RCTs, n = 38) was found in participants receiving active SLIT compared with those receiving placebo. A subanalysis found significant reductions in symptom scores for both seasonal (SMD, −0.34; 95% CI, −0.44 to −0.25; RCTs, n = 39) and perennial (SMD, −0.93; 95% CI, −1.69 to −0.17; RCTs, n = 10) allergens. However, heterogeneity was substantial for perennial but not for seasonal allergens (I^2 = 92% vs 45%, respectively). SLIT with seasonal allergens reduced rescue medication requirements (SMD, −0.30; 95% CI, −0.41 to −0.19; I^2 = 44%; RCTs, n = 32), whereas no significant effect was observed for perennial allergens (SMD, −0.43; 95% CI, −0.89 to 0.02; I^2 = 71%; RCTs, n = 6; Fig 2). This meta-analysis included a subanalysis of 15 RCTs of SLIT performed in children (n = 1392) who showed a significant reduction in symptom scores (SMD, −0.52; 95% CI, −0.94 to −0.10; $P = .02$), although with considerable heterogeneity (I^2 = 92%). Twelve also reported medication scores. A reduction in medication requirements in children was observed (SMD, −0.16; 95% CI, −0.32 to 0.00; I^2 = 36%) that just failed to achieve significance ($P = .056$).[36]

Adverse events were reported in 54 of the 60 RCTs. The majority were local and classified as mild. The most common were pruritus in the mouth (2290 events [SLIT = 1798; placebo = 492], 21 studies), throat irritation (272 events [SLIT = 243; placebo = 29], 10 trials), oral nonspecified (167 events [SLIT = 143; placebo = 24], 3 studies), and buccal-lingual edema (145 events [SLIT = 143; placebo = 2], 8 studies). Systemic reactions were observed in 18 of the 54 studies that reported adverse events. The most frequently reported were rhinitis (2437 events [SLIT = 1403; placebo = 1034], 16 trials), conjunctivitis (1560 events [SLIT = 774; placebo = 786], 8 studies), cough (524 episodes [SLIT = 313; placebo = 211], 8 studies), and headache (138 episodes [SLIT = 70; placebo = 68], 6 trials). There were 93 documented episodes of asthma/wheezing in 15 RCTs (SLIT = 51; placebo = 42). A description of the frequency and characteristics of these adverse reactions have been included in Table E4 in this article's Online Repository at www.jacionline.org.[36,37] None of the reactions required the use of adrenaline, and no studies reported anaphylaxis.[36] In clinical practice and postmarketing drug surveillance, sporadic and isolated cases of anaphylaxis associated with SLIT have been reported rarely.[18]

An overview of these Cochrane meta-analyses is summarized in Fig 2 to allow comparison of the effects of SCIT versus placebo with SLIT versus placebo for both seasonal and perennial allergens. Overall, these indirect comparisons suggest that SCIT might be more effective than SLIT, although this conclusion is unreliable for several reasons. The analyses involve multiple small studies with considerable heterogeneity, particularly for immunotherapy in patients with perennial disease, in whom there is not such a clear-cut history of symptoms on exposure and nonallergic factors might contribute to perennial symptoms. Another limitation is that geographic variation in allergen exposure can compromise efficacy of currently available commercial vaccines: grass allergy vaccines contain temperate grass pollens that have only limited cross-reactivity with tropical grasses, such as Bermuda.[39] Similarly, house dust mite vaccines contain *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* that might not be optimal in regions where *Blomia tropicalis* is dominant.[40] The reviews also contain older studies that might have been performed with less rigor compared with modern standards. There are far fewer studies of SCIT and fewer involving perennial allergens. Finally, there are incomplete data on adverse event reporting and few studies performed in children. However, if data for seasonal rhinitis alone are reviewed, there are more studies and acceptable levels of heterogeneity. The effect sizes for SCIT for both symptoms and rescue medication are approximately 2-fold higher than for SLIT, with no overlap in 95% CIs for symptom evaluations and very little overlap for use of rescue medication (Fig 2). Thus if one focuses on seasonal disease, these indirect comparisons are in favor of greater efficacy for SCIT. However, the overall balance of clinical benefit of SCIT versus SLIT must include a robust comparison of acceptability, tolerability, and adverse events. This is not possible for adverse events for which there is incomplete reporting hampered not least by the absence of international standardization of reporting for adverse events at the time of these meta-analyses.

Indirect evidence from more recent SRs and meta-analyses

For more information on indirect evidence from more recent SRs and meta-analyses, see Table I.[41-45]

Dretzke et al[41] conducted a SR of RCTs on SCIT and SLIT for SAR (grass, trees, and weeds) to update the Cochrane meta-analyses by Calderon et al[9] on SCIT and the Cochrane subanalysis by Radulovic et al[36] on SLIT. At least 5 bibliographic databases were searched up to April 2011. Twenty-eight new studies published after these reviews' search dates were identified. Some RCTs included in the previous meta-analyses were excluded on the basis of criteria used for this update. Incorporation of the new data did not change the overall effects for these comparisons. When evaluating SCIT versus placebo, there was a significant reduction in both symptom (SMD, −0.65; 95% CI, −0.85 to −0.45; I^2 = 57%; RCTs, n = 17) and medication (SMD, −0.55; 95% CI, −0.75 to −0.34; I^2 = 57%; RCTs, n = 16) scores. Similar findings were reported regarding SLIT: significant reductions in both symptom (SMD, −0.33; 95% CI, −0.42 to −0.25; I^2 = 42%; RCTs, n = 42) and medication (SMD, −0.27; 95% CI, −0.37 to −0.17; I^2 = 49%; RCTs, n = 35) scores were found. An indirect comparison between SCIT and SLIT was conducted by estimating the standardized score difference and 95% credible intervals; the standardized score difference was 0.351 (95% credible interval, 0.127-0.586), which is a statistically significant result in favor of SCIT.[41]

In a comprehensive SR of the efficacy of SCIT and SLIT for respiratory allergies, Lin et al[42] identified 142 RCTs published up to May 2012. For SLIT, only studies using subcutaneous aqueous allergens for sublingual administration (SLIT drops) were

TABLE I. Indirect evidence for efficacy of SCIT versus SLIT from more recent SRs and meta-analyses

First author, year, country	RCTs for SCIT (no.)	RCTs for SLIT (no.)	AIT (no.)	Placebo (no.)	Age group	Allergen	Symptom scores (comparison against placebo)	Medication scores (comparison against placebo)
Nelson et al,[45] 2015, United States	9	14 D 14 T	4016	3743	Adults and children	Grass pollen	SLIT D: SMD, −0.17; 95% CI, −0.37 to 0.04; I^2 = 65% SLIT T: SMD, −0.32; (95% CI, −0.41 to −0.23; I^2 = 52% SCIT: SMD, −0.32; 95% CI, −0.45 to −0.18; I^2 = 27%	SLIT D: SMD, −0.44; 95% CI, −0.83 to −0.06; I^2 = 88% SLIT T: SMD, −0.23; 95% CI, −0.29 to −0.17; I^2 = 0% SCIT: SMD, −0.33; 95%CI, −0.52 to −0.13; I^2 = 61%
Di Bona et al,[44] 2015, Italy	0	13	2281	2378	Adults and children	Grass pollen	SLIT T: SMD, −0.28; 95% CI, −0.37 to −0.19; I^2 = 54%	SLIT T: SMD, −0.24; 95% CI, −0.31 to −0.17; I^2 = 22%
Di Bona et al,[43] 2012, Italy	14	10 D 12 T	3014	2768	Adults and children	Grass pollen	SLIT D: SMD, −0.25; 95% CI, −0.45 to −0.05; I^2 = 48% SLIT T: SMD, −0.40; 95% CI, −0.54 to −0.27; I^2 = 66% SCIT: SMD, −0.92; 95% CI, −1.26 to −0.58; I^2 = 88%	SLIT D: SMD, −0.37; 95% CI, −0.74 to −0.00; I^2 = 86.9% SLIT T: SMD, −0.30; 95% CI, −0.44 to −0.16; I^2 = 64.3% SCIT: SMD, −0.58; 95% CI, −0.86 to −0.30; I^2 = 81.1%
Dretzke et al,[41] 2013, United Kingdom	17	42	2899	2904	Adults and children	Seasonal allergens	SLIT: SMD, −0.33; 95% CI, −0.42 to −0.25; I^2 = 42% SCIT: SMD, −0.65; 95% CI, −0.85 to −0.45; I^2 = 57%	SLIT: SMD, −0.27; 95% CI, −0.37 to −0.17; I^2 = 49% SCIT: SMD, −0.55; 95% CI, −0.75 to −0.34; I^2 = 57%
Lin et al,[42] 2013, United States	55*	52*	SCIT: 3487† SLIT: 4384† SCIT vs SLIT: 412†		Adults and children	Any allergen	No pooled analysis was performed.	No pooled analysis was performed.

AIT, Allergen immunotherapy; *D*, drops; *T*, tablets.
*Studies including participants with AR or ARC with or without asthma.
†Diverse comparators apart of placebo were included.

included (sublingual tablet studies were not included). The authors concluded that the strength of evidence was high that SCIT reduced AR symptoms, conjunctivitis symptoms, asthma plus ARC medication use, and ARC quality of life. The strength of evidence was moderate that SCIT reduced ARC medication scores. The strength of evidence was moderate that SLIT reduced AR/ARC symptoms, conjunctivitis symptoms, and medication scores and improved quality of life. In studies comparing SCIT with SLIT, the authors concluded that the strength of evidence was low. Regarding safety, local reactions were common with both SCIT and SLIT: there were rare cases of anaphylaxis in the SCIT RCTs and no anaphylaxis in the SLIT trials.[42]

Di Bona et al[43] conducted a meta-analysis–based comparison of SCIT versus placebo and SLIT versus placebo that was confined to published studies of SAR up to March 2012. Thirty-six RCTs were included (SLIT drops, n = 10; SLIT tablets, n = 12; and SCIT, n = 14). Reductions in symptom scores were observed compared with placebo for SLIT drops (SMD, −0.25; 95% CI, −0.45 to −0.05; I^2 = 48%), SLIT tablets (SMD, −0.40; 95% CI, −0.54 to−0.27; I^2 = 66%), and SCIT (SMD, −0.92; 95% CI, −1.26 to −0.58; I^2 = 88%). Reductions in medication scores were observed for SLIT drops (SMD, −0.37; 95% CI, −0.74 to −0.00; I^2 = 87%; RCTs, n = 10), SLIT tablets (SMD, −0.30; 95% CI, −0.44 to −0.16; I^2 = 64%; RCTs, n = 10), and SCIT (SMD, −0.58; 95% CI, −0.86 to −0.30; I^2 = 81%; RCTs, n = 11). The authors concluded that for SAR, SCIT might be more effective than SLIT, although in view of the heterogeneity and indirect methods used, further direct comparisons were needed.[43] The same group recently reported a more confined meta-analysis that focused on

TABLE II. Recent well-powered RCTs of SLIT for AR

First author, year, country	Allergen	Route	No. (R)	Groups (no., R)	Age (y)	Asthma (%)	Polysensitization (%)	Updosing	Frequency maintenance
Bergmann et al,[68] 2014, Germany	*D pteronyssinus and D farinae*	SLIT-T	509	500 IR = 169 300 IR = 170 Placebo = 170	18-50	29-32	48-55	Yes	Daily
Mosbech et al,[69] 2015, Denmark	*D pteronyssinus and D farinae*	SLIT-T	489	6 SQ = 134 3 SQ = 131 1 SQ = 117 Placebo = 107	≥14	100	83	No	Daily
Demoly et al,[70] 2015, France	*D pteronyssinus and D farinae*	SLIT-T	992	12 SQ = 318 6 SQ = 336 Placebo = 338	18-65	45-48	66-71	No	Daily
Okamoto et al,[71] 2015, Japan	Japanese cedar	SLIT-D	531	Active = 266 Placebo = 265	12-64	NA	NA	Yes	Daily
Maloney et al,[72] 2014, United States	*Phleum pratense*	SLIT-T	1501	MK-7243 = 752 Placebo = 749	5-65	25	85	No	Daily

AAdSS, Average adjusted symptom score; *AIT*, allergen immunotherapy; *DSS*, rhinoconjunctivitis daily symptom score; *HDM*, house dust mite; *JAU*, Japanese allergy units; *R*, randomized; *SLIT-D*, SLIT drops; *SLIT-T*, SLIT tablets; *SU*, standardized units; *TCRS*, total combined rhinitis score; *TCS*, total combined score; *TNSMS*, total nasal symptom and medication score; *TOSMS*, total ocular symptom and medication score.

efficacy and adverse events of sublingual grass pollen tablet immunotherapy in patients with SAR.[44] The search included double-blind, placebo-controlled, randomized clinical trials up to April 2014. There was a significant reduction in symptom scores in the participants treated with SLIT tablets compared with placebo by using the SMD (−0.28; 95% CI, −0.37 to −0.19; I^2 = 54%; RCTs, n = 13). Medication scores were also reduced in the actively treated group compared with the placebo group (SMD, −0.24; 95% CI, −0.31 to −0.17; I^2 = 22%; RCTs, n = 12). Seventy percent of the participants receiving SLIT reported adverse events compared with 44.5% in the placebo group. These data confirmed the results of previous meta-analyses that grass pollen tablet immunotherapy was effective, whereas the authors considered the effect size modest.[44]

Nelson et al[45] used the technique of network meta-analysis to determine the relative efficacy of SLIT tablets compared with SCIT and SLIT drops for grass pollen–induced SAR or seasonal asthma. This methodology facilitates the interpretation of the relative effect of multiple interventions used for the same disease that might or might not have been previously contrasted directly against each other.[46] The bibliographic search for double-blind, placebo-controlled, randomized clinical trials conducted in May 2013 found 37 trials that were included in the meta-analysis for symptom scores (SCIT, 9; SLIT tablets, 14; and SLIT drops, 14) and 33 for medication scores (SCIT, 7; SLIT tablets, 13; and SLIT drops, 13). Direct paired comparisons found statistically significant results favoring SCIT and SLIT tablets for symptom scores compared with placebo but not for SLIT drops. Network meta-analysis found no significant differences for both symptom and medication scores between SLIT tablets and SCIT or between SLIT tablets and SLIT drops.[45]

These more recent SRs include a larger proportion of more robust studies and overall support the Cochrane reviews that both subcutaneous and sublingual treatment are effective. Depending

TABLE II. *Continued*

AIT duration	Treatment-free observation	Allergen contents per dose (μg)	Cumulative dose	Units	Main outcome, mean difference (95% CI); *P* value	Reduction vs placebo (%)	Dropout rate
12 mo	12 mo	500 IR: 28/120 μg of Der p 1/Der f 1 300 IR: 16/68 μg of Der p 1/Der f 1	500 IR: ~10.2/43.8 mg of Der p 1/Der f 1 a year 300 IR: ~5.8/24.8 mg of Der p 1/Der f 1 a year	IR	AAdSS: 500 IR vs placebo, −0.78 (−1.34 to −0.22); *P* = .0066 AAdSS: 300 IR vs placebo, −0.69 (−1.25 to −0.14); *P* = .0150 AAdSS: 500 IR vs 300 IR, −0.09 (−0.66 to 0.49); *P* = .7638	500 IR: -20.2 300 IR: -17.9	Y1: 16% Y2: 22%
~12 mo	0	6 SQ-HDM: 7.5 μg of Der 1 (Der p 1 and Der f 1) and 7.5 μg of Der 2 (Der p 2 and Der f 2)	6 SQ = ~2190 SQ-HDM 3 SQ = ~1095 SQ-HDM 1 SQ = ~365 SQ-HDM	SQ-HDM	TCRS: 6 SQ-HDM, −0.78 (−1.52 to −0.04); *P* = .036 TCRS: 3 SQ-HDM, −0.70 (−1.45 to 0.04); *P* = .063 TCRS: 1 SQ-HDM, −0.47 (−1.24 to 0.30); *P* = .23	6 SQ: −28.8 3 SQ: −26 1 SQ: −17.4	17%
~12 mo	0	12 SQ-HDM: 15 μg of Der 1 (Der p 1 and Der f 1) and 15 μg of Der 2 (Der p 2 and Der f 2) 6 SQ-HDM: 7.5 μg of Der 1 (Der p 1 and Der f 1) and 7.5 μg of Der 2 (Der p 2 and Der f 2)	12 SQ = ~4380 SQ-HDM 6 SQ = ~2190 SQ-HDM	SQ-HDM	TCRS: Difference from placebo 12 SQ-HDM, 1.22 (0.49-1.96); *P* = .001 6 SQ-HDM, 1.18 (0.45-1.91); *P* = .002	12 SQ: −18.2 6 SQ: −17.5	12%
18 mo	0	2000 JAU/mL (10,000 JAU/mL = 7.3-21 μg of Cry j 1)	90-150 μg of Cry j 1 and Cry j 2 a month	JAU	TNSMS, entire season (second season): −1.14 (−1.63 to −0.65); *P* < .0001 TOSMS, entire season (second season): −0.46 (−0.73 to −0.18); *P* = .001	TNSMS: −26 TOSMS: −28	S1: 3% S2: 9%
~20 wk	0	15 μg of Phl p 5	2 mg of Phl p 5	SQ-U and BAU	TCS, entire season: −0.98 (−1.2 to −0.4); *P* < .001 DSS, entire season: −0.64 (−0.7 to −0.2); *P* = .001	TCS: −23% DSS: −20%	13%

on the criteria for selection of studies and the methodology of indirect comparison used, there remains controversy about whether the data support the superiority of SCIT over SLIT for seasonal rhinitis[41,43] or not.[45] All reviews acknowledge the need for further head-to-head studies of SLIT versus SCIT and the relative paucity (until very recently, see below) of data in patients with perennial disease for both SCIT and SLIT.

Direct evidence from head-to-head double-blind placebo-controlled trials

For more information on direct evidence from head-to-head double-blind, placebo-controlled trials, see Table E5 in this article's Online Repository at www.jacionline.org.[38,47-49]

A comprehensive literature search (November 2015) for studies comparing head-to-head SCIT versus SLIT for respiratory allergy found 19 publications. Of these studies, 13 were open comparisons,[50-62] 1 was a chart review,[63] and 1 was a survey questionnaire.[64] Nelson[65] reviewed 11 of these head-to-head randomized controlled studies, of which 7 were open and 4 were double-blind. Because these 4 represent the only blind head-to-head comparisons,[38,47-49] they are considered here in more detail (see Table E5).

Khinchi et al[47] conducted a double-blind, double-dummy, placebo-controlled study of high-dose SLIT and SCIT compared with placebo in patients with birch pollen–associated ARC. Reductions in symptom and medication scores were significant for SLIT ($P < .002$ and $P < .02$) and SCIT ($P < .002$ and $P < .002$) compared with placebo. Differences were numerically greater for SCIT but not significantly so compared with SLIT, although the study was inadequately powered to detect such differences. Five grade 3 systemic reactions and 1 grade 4 systemic reaction were observed in the SCIT group, 1 grade 3 systemic reaction was observed in the placebo group, and no grade

3 or 4 reactions were seen in the SLIT group. Thus both were effective, and serious systemic reactions only occurred after SCIT.[47]

Quirino et al[48] studied a 5-grass-pollen extract during 2 seasons in participants with seasonal rhinoconjunctivitis before and after 1 year of treatment. Twenty participants were allocated to receive active SLIT and placebo SCIT or active SCIT and placebo SLIT. No double placebo was included (see Table E5). After 12 months, the mean percentage reduction in total combined symptom and medication scores compared with the baseline year was 50% for SCIT and 51% for SLIT. Minor local reactions were confined to SCIT, and no systemic adverse events occurred in either group.[48] SCIT and SLIT appeared equivalent in efficacy and were well tolerated.

Ventura et al[49] studied an extract of *Juniperus ashei* in 40 adults with cypress pollen–associated SAR. Ten received active SLIT drops, 10 received active SCIT, 10 received placebo SLIT drops, and 10 received placebo injections. An additional control group comprised 10 nonatopic subjects receiving no treatment (see Table E5). After 12 months, both groups receiving active treatment, but not placebo-treated subjects, showed a reduction in symptoms. Decreases in eosinophil cationic protein levels and eosinophil chemotactic activity in nasal lavage fluid correlated with the decreases in symptoms. No numeric comparison is possible from the data, and there was no record of adverse events.[49]

Yukselen et al[38] carried out a 12-month randomized, double-blind, double-dummy trial of SLIT, SCIT, and placebo in 31 children with mite allergy and AR, mild asthma, and positive skin test responses and specific IgE levels to *D pteronyssinus* and *D farinae*. Compared with baseline, similar reductions in rhinitis symptom and medication scores were observed in participants treated with SLIT and SCIT but not in placebo-treated subjects. Regarding asthma symptom and medication scores, these were significantly reduced only in the SCIT-treated group. No systemic adverse reactions were reported in any of the groups.[38]

In summary, in the only 4 double-blind head-to-head comparisons, there were no differences for SCIT versus SLIT in rhinitis symptom or medication scores. Limitations of these trials include small numbers, variable study design, inability to compare doses, and, in 3 of 4, elements that indicate a risk of bias. Whereas both SCIT and SLIT were effective for AR, as concluded by other recent reviews,[42,66,67] no firm conclusions can be drawn from the direct comparisons concerning the relative efficacy of the 2 treatment routes, whereas systemic adverse events were more common after SCIT.

RECENT WELL-POWERED STUDIES OF SLIT (2014-2015)

Five recent well-powered double-blind RCTs provide further evidence of the efficacy and safety of SLIT in patients with AR (Table II).[68-72] These 5 trials included 4022 subjects, which is almost equivalent to the 4589 participants included in the 49 trials evaluated in the Cochrane meta-analysis of SLIT.[36] Three trials of sublingual tablets were performed in patients with perennial rhinitis sensitized to house dust mite.[68-70] Tablets comprised a mixture of *D pteronyssinus* and *D farinae* and were administered daily for 12 months. Participants were adults and comprised a high proportion of subjects who were polysensitized (48% to 83%) and had comorbid mild asthma (29% to 100%). All 3 trials showed evidence of efficacy in rhinitis with a clear dose response and an 18% to 28% reduction in combined symptom-medication scores in the active compared with placebo-treated groups. The largest immunotherapy trial performed to date involved 1501 adults and children (age range, 5-65 years) with grass pollen ARC, of whom 85% were polysensitized and 25% had asthma.[72] Use of grass pollen tablets (containing 15 μg of Phl p 5) daily for 20 weeks resulted in a 20% decrease in rhinoconjunctivitis symptoms and a 23% decrease in total combined scores compared with placebo. Similarly, in patients with Japanese cedar allergy, SLIT drops (containing 3-5 μg of Cry j 1) daily for 18 months resulted in a 26% decrease in total combined nasal symptom medication scores.[71]

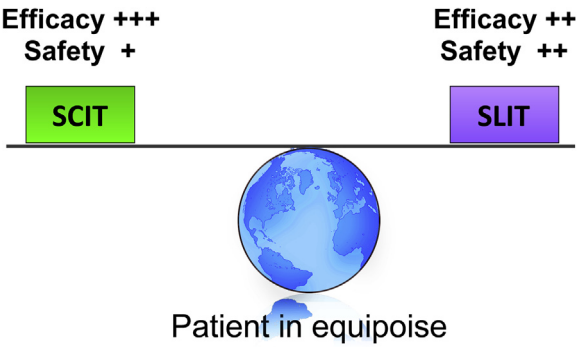

FIG 3. SCIT versus SLIT: a balance of efficacy and safety.

In these trials adverse events were reported in both the actively treated (59% to 86%) and placebo-treated (24% to 80%) groups. Local side effects (itching, swelling, and throat irritation) occurred in the active (41% to 89%) and placebo (12% to 21%) groups and were mild to moderate in intensity and generally well tolerated. Treatment-related adverse events resulted in withdrawal in both the active (0.6% to 6%) and placebo-treated (0.6% to 1%) groups. Although 51 serious adverse events were reported in 4 studies (0% to 4% of subjects receiving active SLIT and 0% to 3% receiving placebo),[68-71] only 6 were assessed as related to treatment. Adrenaline was administered in 5 participants (4 in the active SLIT groups and 1 in the placebo group); in 2 subjects symptoms were assessed as unrelated to the study interventions (1 in the active SLIT group and 1 in the placebo group),[72] whereas 3 participants receiving active treatment received adrenaline because of local reactions in the absence of clear respiratory compromise or hypotension. Two of these participants discontinued treatment,[72] and 1 completed the trial.[70] In the study by Maloney et al,[72] 1 participant receiving placebo treatment presented a moderate systemic reaction assessed as moderate anaphylaxis (wheezing, cough, and nasal congestion) on day 1. The patient was treated with β_2-agonists and antihistamines; symptoms resolved, and the participant discontinued.[72] In a recent phase I RCT conducted in 12- to 17-year-old children who received sublingual house dust mite tablets or placebo, treatment was generally well tolerated, there were no systemic reactions, and side effects were mild to moderate in intensity (55% received active SLIT and 43% received placebo). Throat irritation was the most common local side effect (19% received active SLIT and 6% received placebo).[73] No fatalities were reported in any of these studies.

SUMMARY AND CONCLUSIONS

Both SCIT and SLIT are effective in reducing symptoms and requirement for rescue medication in patients with AR. The evidence base is stronger for patients with seasonal than perennial

Box 1. Key points

SCIT	SLIT
● Effective in patients with seasonal rhinitis (high-quality evidence).	● Effective in patients with seasonal rhinitis (high-quality evidence).
● Induces long-term remission (moderate evidence).	● Induces long-term remission (high-quality evidence).
● Effective in patients with perennial rhinitis (moderate evidence).	● Effective in patients with perennial rhinitis (high-quality evidence).
● Indirect evidence suggests SCIT is more effective than SLIT in patients with SAR.	● Indirect evidence suggests SLIT is better tolerated and safer than SCIT in patients with SAR.
● Evidence base in children is less convincing; more studies are needed.	● Evidence base in children is less convincing; more studies are needed.
● Local side effects (pain and swelling) are common and well tolerated.	● Local side effects (itching and swelling) are common and well tolerated.
● SCIT requires administration in a specialist clinic.	● SLIT can be self-administered.
● Adherence is easily monitored.	● Adherence can be a problem.
● Direct comparative evidence versus SLIT is weak, and definitive trials are needed.	● Direct comparative evidence versus SCIT is weak, and definitive trials are needed.
● Some patients prefer SCIT (informed personal decision).	● Some patients prefer SLIT (informed personal decision).

disease and stronger in adults than in children. Three years of treatment with both SCIT and SLIT has been shown to provide long-term clinical benefits for at least 2 years after their discontinuation. Recent well-powered trials provide good evidence for the efficacy of SLIT tablet treatment also in patients with perennial rhinitis caused by house dust mites.[68-72]

Indirect comparisons of the relative efficacy of SCIT versus SLIT in the literature have been controversial, with 2 favoring SCIT[41,43] and a third showing no difference.[45] Our subgroup analysis of the Cochrane databases for seasonal disease implies that SCIT might be more effective than SLIT based on their relative effect sizes compared with placebo and the lack of overlap in 95% CIs. Direct comparisons add little to the debate because of evidence being limited to small studies and an overall low grade of evidence that does not allow firm conclusions.

In contrast, on the grounds of tolerability and safety, indirect comparisons favor SLIT over SCIT. SCIT can be associated with anaphylaxis, necessitating close supervision. For SLIT, the large database now available from clinical trials and postmarketing surveillance[68-72] indicates that systemic side effects are rare, anaphylaxis is extremely rare, and SLIT can be safely self-administered. Local side effects of itching and swelling in the mouth are common but generally mild and resolve without treatment, such that withdrawals on the grounds of local side effects are uncommon.

There remains an unmet need to perform an adequately powered direct comparative study of SCIT versus SLIT. This could be performed for patients with SAR, with patient selection being more straightforward. The study should use well-characterized products of proved value in previous placebo-controlled trials. The study should be randomized, double-blind, double-dummy, and placebo controlled and performed according to international guidelines,[74-76] with standardized methodology and use of recommended outcomes (a combined symptom and medication score as primary outcome).[77] There should be equal attention to comprehensive recording of safety and tolerability outcomes,[35,78] as well as efficacy end points. Action rather than yet another review is needed to address this question.

At present, where both SCIT and SLIT products of proved value are available, the overall balance of efficacy and side effects leaves the patient in equipoise, and choice of either SCIT or SLIT can be determined on the grounds of convenience, availability of resources, and personal preference (Fig 3; Box 1).

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What do we know?

- **Both SLIT and SCIT are effective for SAR.**
- **Both SLIT and SCIT induce long-term symptom remission.**
- **Recent studies support their use also in perennial mite allergy**

What is still unknown?

- **The evidence base for immunotherapy in children is less convincing.**
- **More rigorous documentation of the side effects of immunotherapy in clinical trials according to recent World Allergy Organization guidelines will better inform the risk/benefit ratio.**
- **An adequately powered randomized, placebo-controlled, head-to-head SCIT versus SLIT comparison using proved immunotherapies will better inform patient choice.**

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TABLE E1. Long-term efficacy of SLIT: Randomized, double-blind, placebo-controlled clinical trials

Author, year, country	SLIT	Placebo	Patients' characteristics	Allergen	Study methods and immunotherapy schedule	Units	Cumulative dose	Total study duration (y)	Immuno-therapy duration (y)	Years after cessation	Years blinded after cessation	Symptom scores		Medication scores		Dropout rate
Durham et al[6,15] and Dahl,[11] 2006, 2010, 2012, United Kingdom	316	318	Age: 18-65 y Diagnosis: 2-y history of grass pollen–induced ARC Tests: Positive sIgE level and SPT response to *Phleum pratense* Asthma: Patients with perennial asthma were excluded.	*P pratense*	Study description: Treatment started 16 weeks before the expected start of the grass pollen season. Treatment was continued during 3 years. Blind follow-up was continued 2 years after completion of the 3-year period of treatment. Build-up phase: No Maintenance phase: *Frequency*: Daily *Dose*: 75,000 SQ-T (15 μg of Phl p 5) Duration: 3 years	SQ-T	5.48 mg per 365-day period	5	3	2	2	Reduction relative to placebo: Season 1 −31% ($P < .0001$) Season 2 −36% ($P < .0001$) Season 3 −29% ($P < .001$) Follow-up season 4 −26% ($P < .001$) Follow-up season 5 −25% ($P = .004$)		Reduction relative to placebo: Season 1 −38% ($P < .0001$) Season 2 −45% ($P < .0001$) Season 3 −40% ($P < .001$) Follow-up season 4 −29% ($P = .022$) Follow-up season 5 −20% ($P = .114$)		Y1: 10.4% Y2: 50.2% Y3: 54.7% Y4: 59.5% Y5: 62%
Ott et al,[22] 2009, Germany	142	67	Age: 7-64 years Diagnosis: ARC associated with grass pollen Tests: Positive sIgE level and SPT response to grass pollen Asthma: 11% to 14%	Five-grass mix	Study description: Sublingual drops were administered during 3 consecutive pollen seasons (coseasonal). The fourth pollen season during which participants were not treated was the follow-up period.	IR	22,000 IR per season (1,500 μg of group 5 major allergen)	4	3	1	1	SLIT change: Season 1 −0.03 ± 4.19 $P = .036$	Placebo change: Season 1 +1.49 ± 4.57	SLIT change: Season 1 +0.86 ± 11.72 $P = .35$	Placebo change: Season 1 −0.39 ± 3.04	57.3% PP
					Build-up phase: *Frequency*: 20-minute intervals (0, 20, 40, and 60 minutes) *Dose*: 30, 90, 150, and 300 IR *Duration*: 1 day							Season 2 −0.89 ± 4.37 $P = .023$	Season 2 +0.91 ± 4.29	Season 2 −0.08 ± 11.69 $P = .51$	Season 2 −0.93 ± 2.69	
					Maintenance phase: *Frequency*: Daily *Dose*: 300 IR/mL (21 μg/mL Phl p 5) *Duration*: 3 years							Season 3 -1.02 ± 4.54 $P = .0004$	Season 3 + 1.32 ± 4.40	Season 3 −0.28 ± 11.55 $P = .29$	Season 3 −0.92 ± 2.47	

(Continued)

TABLE E1. *(Continued)*

Author, year, country	SLIT	Placebo	Patients' characteristics	Allergen	Study methods and immunotherapy schedule	Units	Cumulative dose	Total study duration (y)	Immuno-therapy duration (y)	Years after cessation	Years blinded after cessation	Symptom scores	Medication scores	Dropout rate
												Follow-up −1.94 ± 5.05 Follow-up −0.30 ± 4.40 $P = .015$	Follow-up 0.07 ± 11.69 Follow-up −0.98 ± 2.61 $P = .83$	
Didier et al,[16,23,24] 2011, 2013, 2015, France	207 (2M) 207 (4M)	219	Age: 18-50 years Diagnosis: 2-year history of grass pollen–induced ARC Tests: Positive sIgE level and SPT response to grass pollen Asthma: 11% to 16%	5-grass mix	Study description: Treatment was initiated 2 mo (2M) or 4 mo (4M) before the expected start of the pollen season. Treatment was continued once a day during the pollen season for 3 consecutive years. Follow-up was continued 2 years, treatment free, after completion of the 3-year period of treatment. Build-up phase: No Maintenance phase: *Frequency*: Daily *Dose*: 300 IR (25 μg of group 5 major allergen) *Duration*: 3 years	IR	9,000 IR a month (750 μg of group 5 major allergen a month)	5	3	2	2	Reduction relative to placebo [4M] Daily rhinoconjunctivitis total symptom score (DRTSS) Year 1: −11% Year 2: −31.4% ($P < .0001$) Year 3: −38.5% ($P < .0001$) Follow-up year 4: −23.4% ($P < .005$) Follow-up year 5: −23.5%	Reduction relative to placebo [4M] Daily rescue medication score (DRMS) Year 1: −22.5% ($P < .005$) Year 2: −46.6% ($P < .0001$) Year 3: −38% ($P < .0005$) Follow-up year 4: −27.9% ($P < .05$) Follow-up year 5: −33.8% ($P < .05$)	Y1: 9.6% Y2: 23.2% Y3: 27.8% Y4: 31.6% Y5: 41.2%

NR, Not reported; *PP*, per protocol; *SAR*, seasonal allergic rhinitis; *SPT*, Skin prick test.

TABLE E2. Long-term efficacy of SCIT: Randomized, double-blind, placebo-controlled clinical trials

Author, year, country	SCIT	Placebo	Patients' characteristics	Allergen	Study methods and immunotherapy schedule	Units	Cumulative dose	Total study duration (y)	Immuno-therapy duration (y)	Years after cessation	Years blinded after cessation	Symptom scores	Medication scores	Dropout rate
Naclerio et al,[25] 1997, United States	10	10	Age: 18-55 years Diagnosis: Ragweed-induced hay fever Tests: ID skin test with ragweed extract. Asthma: Patients with mild asthma were included.	Ragweed	Study description: Twenty subjects who had been receiving SCIT with a ragweed extract for at least 3 years were randomized either to continue active treatment or to switch to placebo. Build-up phase: *Frequency*: NA *Dose*: NA *Duration*: NA Maintenance phase: *Dose*: 12 μg of Amb a 1 (5000 AU) *Frequency*: Every 2 weeks *Duration*: 3 (open) + 1 (DB, PC) years	AU	480,000 AU ~1,150 μg of Amb a 1	4-5	3-4	1	1	Open phase: After 3 years of AIT, there was a reduction in the number of sneezes ($P = .005$) and reductions in TAME esterase ($P = .0004$), histamine ($P = .008$), and kinin ($P = .0004$) levels in NF after NAC. DB, PC phase: Those who continued on AIT maintained the treatment effects 1 year after randomization. Those receiving placebo had no significant changes in the number of sneezes after NAC ($P = .57$), but they had partial increase of local mediator release, TAME esterase ($P = .005$), histamine ($P = .04$), and kinin ($P = .07$) levels.	NA	0% (DB phase)

(Continued)

TABLE E2. *(Continued)*

Author, year, country	SCIT	Placebo	Patients' characteristics	Allergen	Study methods and immunotherapy schedule	Units	Cumulative dose	Total study duration (y)	Immuno-therapy duration (y)	Years after cessation	Years blinded after cessation	Symptom scores	Medication scores	Dropout rate
Durham et al,[21] Walker et al,[26] and Varney et al,[27] 1991, 1995, 1999, United Kingdom	21	19	Age: 19-52 years Diagnosis: Severe SAR associated with grass pollen Tests: Positive SPT response to *Phleum pratense* Asthma: Patients with chronic asthma were excluded.	*P pratense*	Study description: Forty patients with severe SAR were randomized to receive SCIT (n = 21) or placebo (n = 19). After 1 year, patients receiving placebo started active SCIT until completing 3 years. Thirty-two completed the third year. Then, they were randomized to continue receiving SCIT (n = 16) or receive placebo (n = 16) for 3 years. Fifteen matched patients with AR were included as control group (No AIT). Build-up phase: *Frequency*: Twice a week *Dose*: From 10 to 100,000 SQ-U *Duration*: 7-8 weeks Maintenance phase: *Frequency*: Monthly *Dose*: 100,000 SQ-U (20 μg of Phl p 5) *Duration*: (1st DBPC phase) 3 years + (2nd DBPC phase) 3 years.	SQ-U	~1,400 μg of Phl p 5	7	Up to 6	3	3	Total symptom scores *AUC*: Year 7 *Maintenance group*: 921 (0–2,299) *Discontinuation group*: 504 (45–4,567 [P = .60]) *No immunotherapy*: 2,863 (774–12,033)	Total medication scores *AUC*: Year 7 *Maintenance group*: 672 (0–1,827) *Discontinuation group*: 357 (0–7,637 [P = .88]) *No immunotherapy*: 4,729 (1,197–8,505)	Y1: 7.5% Y2: 17.5% Y3: 20%

(Continued)

TABLE E2. *(Continued)*

Author, year, country	SCIT	Placebo	Patients' characteristics	Allergen	Study methods and immunotherapy schedule	Units	Cumulative dose	Total study duration (y)	Immuno-therapy duration (y)	Years after cessation	Years blinded after cessation	Symptom scores	Medication scores	Dropout rate
Ariano et al,[28] 1999, Italy	13	12	Age: 13-62 years Diagnosis: ARC with single sensitization to *Parietaria* species Tests: Positive sIgE level and SPT response to *Parietaria* species Asthma: 20% mild asthma	*Parietaria judaica and Parietaria officinalis*	Study description: This was a DBPC trial during the first year. After completing 12 months of treatment, subjects previously treated with placebo were switched to active SCIT for 2 additional years, and then AIT was discontinued. A subjective evaluation was conducted 4 years after AIT cessation. Build-up phase: *Frequency*: Weekly *Dose*: 1,000, 2,000, 4,000, 6,000, 8,000, and 10,000 AU *Duration*: 6 weeks Maintenance phase: *Frequency*: Monthly *Dose*: 10,000 AUeq *Duration*: (DBPC phase) 1 year + (open phase) 2 years	AU	Year 1: 100,000–120,000 AUeq Subsequent years: 120,000 AUeq	7	3	4	0	The active group had significant reductions in SMS in year 1 compared with placebo ($P = .02$). After switching to the active treatment, participants previously receiving placebo also showed a significant reduction in SMS compared with baseline ($P = .004$). Patients receiving active SCIT reported a subjective improvement assessed by an analogue scale from year 1 ($P = .01$), and this remained unchanged up to 4 years after the discontinuation of AIT. Participants receiving initially placebo improved after switching to active SCIT, and this was maintained 4 years after AIT discontinuation.	Included in previous column	8%

AIT, Allergen immunotherapy; *AU*, allergy units; *AUC*, area under the curve; *DBPC*, double-blind, placebo-controlled; *ID*, intradermal; *NA*, not available; *NAC*, nasal allergen challenge; *NF*, nasal fluid; *SAR*, seasonal allergic rhinitis; *SMS*, symptoms and medication scores; *SPT*, skin prick test; *SQ-U*, standardized quality units; *TAME*, N-alpha-tosyl-L-arginine methyl ester.

TABLE E3. Local and systemic reactions and adrenaline use reported in RCTs included in a Cochrane SR on subcutaneous immunotherapy for AR[9]

		SCIT		Placebo	
Type of reaction	**RCTs**	**No.**	**Total events (% participants)**	**No.**	**Total events (% participants)**
Local					
Not requiring treatment	24	907	834 (92)	697	227 (33)
Requiring treatment	7	208	21 (10)	186	8 (4)
Systemic					
Early systemic reaction, grade 2 (<30 min)	17	706	154 (22)	566	44 (8)
Early systemic reaction, grade 3 (<30 min)	13	615	43 (7)	463	3 (0.65)
Early systemic reaction, grade 4 (<30 min)	9	417	3 (0.72)	303	1 (0.33)
Late systemic reaction (>30 min)	11	514	458 (89)	412	148 (36)
Adrenaline use	13	557	19 (3.41); injections, 14,085 (0.13%)	404	1 (0.25); injections, 8,278 (0.01%)

TABLE E4. Local and systemic reactions and adrenaline use reported in RCTs included in a Cochrane SR on SLIT for AR[36,37]

		SLIT		Placebo	
Type of reaction	**RCTs**	**No.**	**Total events (per participant)**	**No.**	**Total events (per participant)**
Local					
Labial edema	11	604	55 (0.09)	536	7 (0.01)
Buccal pruritus	21	1126	1798 (1.6)	1075	492 (0.46)
Buccolingual edema	8	648	143 (0.22)	606	2 (0.003)
Throat irritation	10	770	243 (0.3)	747	29 (0.04)
Oral (nonspecified)	3	68	143 (2.1)	71	24 (0.34)
Local nonspecified	3	119	7 (0.06)	116	3 (0.03)
Systemic					
Urticaria	8	204	7 (0.03)	199	9 (0.04)
Pruritis/rash	10	363	13 (0.04)	222	9 (0.04)
Conjunctivitis	8	262	774 (2.95)	238	786 (3.3)
Rhinitis	16	965	1403 (1.45)	912	1034 (1.13)
Rhinoconjunctivitis	6	184	60 (0.33)	176	58 (0.33)
Asthma/wheeze	15	488	51 (0.1)	450	42 (0.09)
Cough	8	337	313 (0.93)	304	211 (0.69)
Gastrointestinal	20	630	88 (0.14)	561	10 (0.02)
Headache	6	535	70 (0.2)	548	68 (0.12)
Anaphylaxis	6	291	0	288	0
Systemic nonspecified	5	330	4 (0.01)	36	0
Adrenaline use	0	0	0	0	0

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TABLE E5. Head-to-head double-blind, controlled trials of SLIT versus SCIT for allergic rhinitis

First author, year, country	Study design	Allergen	No. of groups	SLIT group (no.)	SCIT group (no.)	Placebo group (no.)	Age (y)	Inclusion criteria	Asthma	Sensitization status
Khinchi et al,[47] 2004, Denmark	Randomized, double-blind, double-dummy, placebo controlled study	Birch (Bet v 1)	3	23	24	24	30 (20-58)	1. 2 y of birch-associated ARC 2. Positive sIgE level, conjunctival provocation test result, and SPT response to birch pollen	SLIT: 39% SCIT: 29% Placebo: 37%	1. HDM sensitization: 11% to 14% 2. Grass pollen symptoms June-July: 38% to 56%
Quirino et al,[48] 1996, Italy	Double-blind, double-dummy controlled study	Grass mix	2	10	10	—	27 (13-39)	1. Clinical history of grass pollen sensitization 2. Positive sIgE level and SPT response to grass pollen	SLIT: 80% SCIT: 80%	1. Patients sensitized to other inhalant allergens were excluded.
Ventura et al,[49] 2009, Italy	Randomized, double-blind, placebo-controlled study	*Juniperus ashei*	4	10	10	SL: 10 SC: 10	39 ± 2.4 (18-55)	1. ARC correlated with the cypress pollen season. 2. Positive sIgE level and SPT response to grass pollen	SLIT: NA SCIT: NA	1. Participants in this study were monosensitized to cypress.
Yukselen et al,[38] 2012, Turkey	Randomized, double-blind, double-dummy, placebo-controlled study	*D pteronyssinus* and *D farinae*	3	11	10	10	SLIT: 9.2 ± 3.4 SCIT: 10.9 ± 3.2 Placebo: 10.1 ± 2.7	1. Clinical history of at least 1 year of rhinitis with asthma associated with HDM. 2. Positive sIgE level and SPT response for both *D pteronyssinus* and *D farinae*	SLIT: 100% SCIT: 100%	1. Participants included in this trial were monosensitized to HDM.

	SLIT									SCIT								
	Build-up phase			Maintenance phase						Build-up phase			Maintenance phase					
First author, year, country	Frequency	Dose	Duration	Frequency	Dose	Duration	Cumulative dose	Units	SLIT method	Frequency	Dose	Duration	Frequency	Dose	Duration	Cumulative dose	Units	Placebo
Khinchi et al,[47] 2004, Denmark	Every second day	Initial: 0.0164 μg Top: 49.2 μg of Bet v 1	30 days	Every second day	49.2 μg of Bet v 1	21-23 months	11.18 mg of Bet v 1	μg	SLIT: Swallow Drops	Weekly	Initial: 0.0164 μg Top: 3.28 μg of Bet v 1	12 weeks	Monthly	3.28 μg of Bet v 1	21 months	51 μg of Bet v 1	μg	Caramelized s ugar (drops) and histamine dihydrochloride (injection)
Quirino et al,[48] 1996, Italy	Daily	Initial: 0.002 BU Top: ~6.25 BU	~25 days	3 times a week	~6.25 BU or MTD	11 months	510 BU	BU	SLIT: Spit Drops	Weekly	Initial: 0.025 BU Top: ~20 BU	12 weeks	Every 3 weeks	~20 BU or MTD	8 months	210 BU	BU	Identical appearance, presentation, taste (SLIT), and color to the active therapy
Ventura et al,[49] 2009, Italy	NA	NA	30 days	3 times a week	228 μg of Jun a 1	11 months	~30 mg of Jun a 1	IR	SLIT: Swallow Drops	Weekly	NA	12 weeks	Monthly	NA	9 months	NA	IR	Sugar (drops) and histamine dihydrochloride plus aluminum hydroxide (injection)
Yukselen et al,[38] 2012, Turkey	Daily	Initial: 0.5 TU Top: 1400 TU	12 weeks	3 times a week	1400 TU	8 months	173,733 TU (*D pteronyssinus* 86,867 TU and *D farinae* 86,867 TU)	TU	SLIT: Swallow Drops	Weekly	Initial: 10 TU Top: 4,000 TU	12 weeks	Every 4 weeks	4,000 TU or MTD	8 months	43,770 TU (*D pteronyssinus* 21,885 of TU and *D farinae* 21,885 TU)	TU	Caramelized sugar (drops) and histamine dihydrochloride (injection)

(Continued)

TABLE E5. *Continued*

First author, year, country	Score	SLIT Before	SLIT After	SCIT Before	SCIT After	Placebo Before	Placebo After	Findings	Observations	Total study duration (Months)	Dropout rate	Cochrane risk of bias tool: Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Free of selective reporting	Other bias
Khinchi et al,[47] 2004, Denmark	Rhinoconjunc-tivitis (peak season week)	1.94 ± 1.27	1.83 ± 1.08	1.67 ± 0.91	1.42 ± 1.25	1.68 ± 1.28	2.74 ± 1.41	In 1st treatment season median ARC SS (scale, 0–3) decreased cf baseline in SLIT-treated (−0.36; 95% CI, − 0.18 to −0.86) and in SCIT-treated (−0.75; 95% CI, +0.02 to −1.31) patients, both significant ($P < .002$) compared with placebo (0.20; 95% CI, −0.22 to 1.05). Median medication scores increased (0.29; 95% CI, −0.82 to +2.57) in the SLIT group and were unchanged (0.0; 95% CI, −2.65 to +1.52) in the SCIT group, both significantly reduced ($P < .02$ and $P < .002$, respectively) compared with placebo (1.35; 95% CI, −0.12 to +4.04). No significant differences were observed between SLIT and SCIT groups.	Low weekly pollen counts in 2nd year resulted in no efficacy evaluation.	24	32%	L	L	L	L	L	L
	ARC rescue medications (peak season week)	4.49 ± 4.95	6.92 ± 6.00	3.24 ± 3.81	3.63 ± 4.50	3.10 ± 3.81	7.76 ± 7.44										
Quirino et al,[48] 1996, Italy	Symptom scores	501.5 ± 162.9	250.5 ± 81	574.6 ± 232	278.5 ± 129.6	—	—	Significant decreases in symptom and medication scores compared with baseline were observed in the SLIT group (both $P = .002$) and in the SCIT group ($P = .002$ and $P = .004$, respectively). No significant differences were observed between SLIT and SCIT groups.	Method of randomization not reported.	12	0	H	U	L	L	L	L
	Medication scores	245 ± 116.8	115.1 ± 50.2	239.6 ± 158	119.6 ± 65.5	—	—										

(Continued)

TABLE E5. *(Continued)*

First author, year, country	Score	SLIT Before	SLIT After	SCIT Before	SCIT After	Placebo Before	Placebo After	Findings	Observations	Total study duration (Months)	Dropout rate	Cochrane risk of bias tool: Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Free of selective reporting	Other bias
Ventura et al,[49] 2009, Italy	Clinical symptom score	NA	NA	NA	NA	NA	NA	After 12 months of treatment, participants receiving active SLIT and active SCIT showed a decrease in symptom scores (CSSs), whereas in subjects receiving placebo, these values remained unchanged. No numeric comparison of SLIT versus SCIT was possible from data.	Clinical scores and rescue medication reported only as individual data plots.	12	NA	L	U	L	H	L	L
	Rescue medication	NA	NA	NA	NA	NA	NA										
Yukselen et al,[38] 2012, Turkey	AR symptom scores	NR	3.74 ± 1.12	NR	2.85 ± 1.16	NR	4.03 ± 1.07	In the SCIT group symptom and medication scores for AR when compared with baseline decreased ($P = .03$ and $P = .05$) compared with placebo. In the SLIT group symptom and medication scores for AR also decreased, although not significantly compared with placebo. No statistical differences were observed between SLIT and SCIT groups in symptoms of rhinitis.	None	12	6%	L	U	L	L	L	L
	AR medication scores	NR	1.78 ± 0.97	NR	1.22 ± 1.09	NR	1.98 ± 0.88										

BU, Biological units; *CSS*, clinical symptom scores; *H*, high risk; *HDM*, house dust mite; *IR*, index of reactivity; *L*, low risk; *MTD*, maximum tolerated dose; *NA*, not available; *SC*, subcutaneous route; *SPT*, skin prick test; *TU*, therapeutic units; *U*, unclear risk.