Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis*

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Abstract

Background: Local allergic rhinitis (LAR) is a phenotype of chronic rhinitis exhibiting a local Th2-driven inflammation without positive clinical markers of atopy. Immunomodulatory effects of allergen-specific immunotherapy (AIT) induce allergen-specific tolerance. However, AIT is not well-recognized as a treatment for LAR.

Methodology: Systematic search on six electronic databases and registries was performed. Experimental and observational studies of AIT for LAR patients were retrieved. The primary outcomes were symptom score, medication score, combined symptom medication score, and disease-specific quality of life. Secondary outcomes were serum specific(s) IgG4, sIgE, and adverse events.

Results: Four double-blind randomized controlled trials (156 patients) from two research units assessed the effects of subcutaneous immunotherapy (SCIT). Compared with placebo, SCIT showed significant reductions in symptom score, medication score, combined symptom medication score, disease-specific quality of life, and an increase in serum sIgG4. There was no significant change in serum sIgE. Likewise, two observational studies (one using SCIT and one using sublingual immunotherapy) improved post-therapeutic symptom score. No studies assessed the effects after discontinuation of treatment. AIT was safe without serious adverse events.

Conclusion: AIT has beneficial effects and safe for LAR. Its effects are restricted to studies with short-term follow-up. AIT may be considered in LAR patients.

Key words: allergen, local allergic rhinitis, immunotherapy, subcutaneous, sublingual

Introduction

Chronic rhinitis is an inflammatory condition of the nasal mucosa, which is classified into allergic rhinitis (AR) and non-allergic rhinitis (NAR)[1]. AR is associated with immunoglobulin E (IgE)-mediated response via the Th2 inflammatory pathway after exposure to inhalant allergens[2]. Clinical tests for atopy are used to confirm the diagnosis of AR, including skin prick test (SPT) and serum specific(s) IgE. At least one of these two markers of atopy are positive in AR patients[2]. Chronic rhinitis patients with negative for both markers are diagnosed with NAR. One-quarter of NAR patients have positive nasal allergen provocation test (NAPT)[3]. This condition indicates a localized allergic condition or entopy[3-6]. Although the concept of local allergy in the absence of systemic atopy was postulated for the first time in 1975[7], the term local allergic rhinitis (LAR) was recognized after better understanding of local mucosal allergic immune reaction without systemic response[5,8,9]. However, there are controversies regarding the inconsistency of local sIgE detection in patients with NAR[10]. In addition, some studies found the transformation from LAR to AR after years of follow-up. As a result, the concept

of LAR was challenged[11-13].

LAR, also known as entopic rhinitis[5], is a new distinct phenotype exhibiting the Th2-driven inflammatory response, a prominent local allergic response to aeroallergens, such as house dust mites, grass and olive pollens, and molds[8,9]. Clinical features of LAR include moderate-to-severe nasal symptoms, an association with asthma or conjunctivitis, and worsening severity over time[4,13]. Environmental control and symptomatic treatment, such as oral antihistamine and intranasal corticosteroids, are recommended in daily practice[4,6]. Nevertheless, neither allergen avoidance nor symptomatic treatment can ease the clinical worsening and alter the progression of comorbidities[13]. To avoid the negative impact of LAR, the treatment is established following putative immunological mechanisms.

Immunomodulatory effects of allergen-specific immunotherapy (AIT) induce allergen-specific tolerance. Therefore, AIT can be indicated for AR or asthma patients who had inadequate benefits from pharmacotherapy[2,14]. As AR and LAR share several immunologic similarities[7-9,15], researchers aim to assess the potential of AIT for treating LAR patients[4,6]. However, this management is still not well-recognized. In addition, there is a lack of systematic reviews and meta-analyses evaluating the efficacy of AIT with seasonal or perennial allergens on LAR. This systematic review aimed to assess the current evidence of clinical trials investigating the therapeutic role of AIT on LAR. The main objective of this study was to evaluate the efficacy and safety of AIT regarding clinical outcomes and immunological markers for treating LAR. The second objective was to investigate the impact of the type of allergens and the age of study participants on the immunomodulatory effects of AIT.

Materials and methods

The study protocol was registered on PROSPERO under the identification number of CRD42021233645. The study screening process and selection process were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16].

Search strategy

Electronic searches on PubMed, EMBASE, ClinicalTrials.gov, Web of Science, Scopus, HTA, and Cochrane Library were performed. ClinicalTrial.gov was searched to collect unpublished data. The last search was 22 July 2021. A manual reference search was performed to retrieve missed relevant studies. For more details of the search strategy, see Table S1 in the Supplement.

Eligibility criteria

Experimental (randomized-controlled trials (RCTs) or non RCTs) and observational (case-control, cohort) studies of AIT in LAR patients were included. The inclusion criteria of the study participants were 1) adult and children with any age, 2) clinical symptoms characteristic of perennial or seasonal rhinitis, 3) a positive NAPT, 4) negative SPT, and 5) negative serum sIgE [4]. The exclusion criteria were 1) allergic rhinitis, 2) chronic rhinosinusitis, 3) acute rhinosinusitis, 4) cystic fibrosis, 5) immunotherapy started within the prior year, and 6) aspirin-exacerbated respiratory disease. Protocols of AIT with any route, type of specific allergen, dosage, treatment duration, and follow-up period were accepted. Randomized controlled trials (RCTs) that assessed the effects of AIT compared with either placebo or standard pharmacotherapy (oral antihistamines or intranasal corticosteroids) for LAR were eligible for the assessment of AIT effectiveness. Quasi-randomized controlled trials and crossover RCTs were included. All clinical studies with any study design were eligible for the assessment of AIT safety. Reviews, meeting abstracts, and comments were excluded.

Study selection process and data extraction

Two review authors (MPH and JS) undertook the title and abstract screening based on the prespecified criteria. The full texts of screened studies were assessed for eligibility. Two authors (MPH and KSe) separately extracted the data from the included studies. When there was insufficient information for extraction or imputation, the corresponding author of that study was contacted for more information. Any conflicts during screening and extraction were resolved by discussion among the authors or with the final decision by the corresponding author (KSn). Data extraction was performed and followed the predefined information sheet. The extracted data included patient characteristics, AIT and control group interventions, treatment duration, follow-up period, and outcome measures. The effects of AIT were categorized as either short-term or long-term. The effects ≤ one year after discontinuation of AIT or during treatment were defined as short-term effects. The effects greater than one year after discontinuation of AIT were regarded as long-term effects[17].

Outcome measures

In accordance with the European Academy of Allergy and Clinical Immunology and the Food and Drug Administration recommendations, the primary outcomes of AIT were combined symptom and medication score (CSMS), symptom score (SS), medication score (MS), and disease-specific quality of life (QoL) [18]. Secondary outcomes were serum sIgG4, serum sIgE, and adverse events. Adverse events were classified as local reaction, systemic reaction, anaphylaxis, and death.

Risk of bias in individual studies

Two review authors (MPH and JS) independently assessed risk of bias of the included RCTs following the Cochrane Collaboration's tool[19]. There were seven domains in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete

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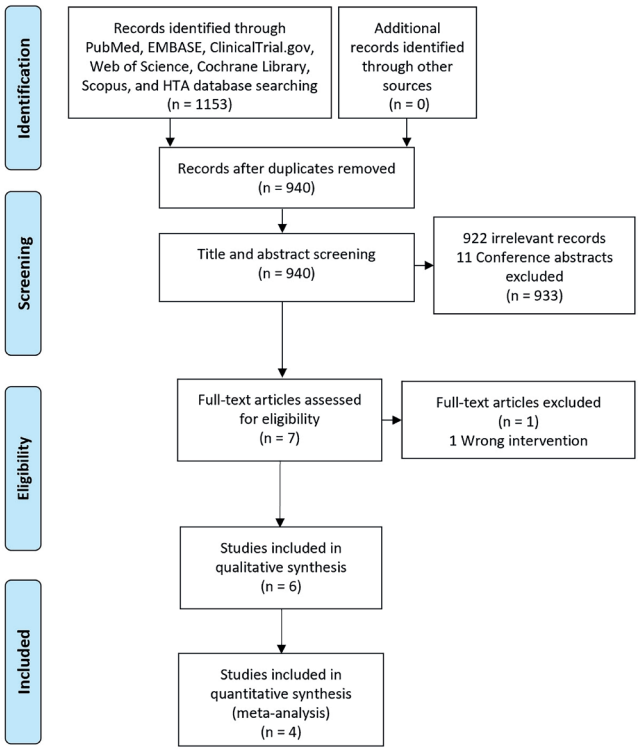

Figure 1. Flow diagram of study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

outcome data, selective outcome reporting, and other bias. Each domain was assessed and expressed as "low risk" when the domain had a clear explanation of the method, "high risk" when the respective domain had not been mentioned, or "unclear risk" when the domain was mentioned but inadequately described. Quality assessment of the non-randomized controlled trials used the methodological index for non-randomized studies (MINORS) with eight domains for non-comparative studies or 12 domains for comparative studies(20). Individual domains were scored from 0 to 2. A total score of the non-comparative studies below 11 and the comparative studies below 16 represented high risk of bias.

Data synthesis and statistical analysis

Data were pooled for meta-analysis. The risk of adverse events was presented as risk ratio (RR) and 95% confidence interval (CI). Mean difference (MD) or standardized mean difference (SMD) with standard deviation (SD) and 95% CI were calculated to assess continuous outcomes. If the change from baseline to endpoint was not available, the final score was extracted. The standard error, interquartile range, and 95% CI were interpreted if the SD was not reported[21]. Discrepancies in treatment effects among different trials were assessed using heterogeneity (I^2) statistic. An I^2 of <40%, 40-60% and >60% represented low, moderate and substantial heterogeneity, respectively. When the heterogeneity was low, a fixed-effect model was used. A random-effects model was used if the heterogeneity was high for a more conservative estimate of the differences. Subgroup analyses by characteristic of rhinitis symptoms, age of the participants, and study quality were conducted. Studies with any high risks of bias were grouped as "Low-quality study". Funnel plot was used to assess publication bias. Egger's test was used to measure small-study effects for quantitative syntheses of at least ten studies. All statistical assessments were performed using Review Manager (RevMan) version 5.4.1[22].

Results

Study selection

A total of 1153 studies were retrieved after the initial search. After removing duplicate studies, the remaining 940 articles underwent title and abstract screening. Full texts of 7 articles were assessed for eligibility. Finally, six studies were selected for qualitative synthesis (4 RCTs[23-26] and two observational studies[27,28]), of which four RCTs were included in the meta-analysis. Neither quasi-randomized controlled trial nor crossover RCT was found. Figure 1 displays the study selection process according to PRISMA.

Participants

There were 236 participants with the mean age ranging from 23.8 to 39.9 years. One hundred and thirty-nine participants (58.9%) were female. One study recruited patients under 15 years of age[28]. Three RCTs[24-26] and one comparative observational study[27] assessed LAR with seasonal rhinitis symptoms. One RCT[23] and one non-comparative observational study[28] assessed LAR with perennial rhinitis symptoms. Asthma and conjunctivitis were the common comorbidities with the proportion of 36.73%[23,25-27] and 70.27%[23,25,27], respectively. Table 1 shows characteristics of the included studies.

Intervention

Sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) were used in one[28] and five[23-27] studies, respectively. Allergen extracts administrated in the included studies consisted of pollen extracts[24-27], *Dermatophagoides pteronyssinus*[27], and *Dermatophagoides farinae*[28]. Aluminum-containing adjuvants were used in all five SCIT studies[23-27]. No study assessed the effects after discontinuation of treatment.

Comparisons

Four RCTs compared SCIT with placebo[23-26]. One observation study compared SCIT with rescue medication (oral antihistamine, intranasal and oral corticosteroid)[27]. One non-comparative observational study assessed the efficacy and safety of SLIT[28].

Short-term outcomes

Combined symptom and medication score (CSMS)

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Table 1. Characteristics of the included studies.

First Author, Year	Study Design	Patient (n)	Female (%)	Mean Age (years)	Allergy	AIT	Control	Outcomes	Duration (months)
Rondon [27], 2011	Cohort	20	75.0	31.1	Grass mix pollen	SCIT	Medication only	SS, MS, MFD, sIgG4, sIgE, NAPT	6
Rondon [23], 2016	DBRCT	36	75.0	39.9	DP	SCIT	Placebo	CSMS, SS, MS, MFD, sIgG4, sIgE, NAPT	24
Bozek [24], 2018	DBRCT	29	48.3	23.8	Betula verrucosa	SCIT	Placebo	CSMS, SS, MS, RQLQ, sIgG4, sIgE, nsIgE	24
Rondon [25], 2018	DBRCT	55	63.6	38.3	Phleum pratense	SCIT	Placebo	CSMS, SS, MS, MFD, NS, OS, BS, RQLQ, sIgG4, sIgE	24
Yin [28], 2019	Cohort	60	41.6	39.5	DF	SLIT	None	SS, VAS of severity symptoms, NAPT, nsIgE	36
Bozek [26], 2020	DBRCT	36	63.9	26.4	Betula verrucosa	SCIT	Placebo	CSMS, SS, MS, RQLQ, sIgG4, sIgE, BAPT	36

DBRCT, double-blind randomized controlled trial; AIT, allergen-specific immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SS, symptom score; MS, medication score; CSMS, combined symptom medication score; MFD, medication free days; NS, nasal score; OS ocular score; BS, bronchial score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; NAPT, nasal allergen provocation test; BAPT, bronchial allergen provocation test; sIgG4, serum specific immunoglobulin G4; sIgE, serum specific immunoglobulin E; nsIgE, nasal specific immunoglobulin E; DP, *Dermatophagoides pteronyssinus*; DF, *Dermatophagoides farinae*.

Four RCTs compared the improvement in CSMS between SCIT and placebo[23-26]. The effect on CSMS reduction favored SCIT over placebo (SMD -2.88; 95% CI -4.55, -1.21; p<0.01). An I^2 of 92% represented substantial heterogeneity. The comparisons of CSMS and forest plot are shown in Figure 2.

Symptom score (SS)

Four RCTs compared the improvement in SS between SCIT and placebo using different scales (4-point scale[23,25] and visual analogue scale[24,26]). The effect on SS reduction favored SCIT over placebo (SMD -2.59; 95% CI -3.88, -1.29; p<0.01). An I^2 of 88% represented substantial heterogeneity. The comparisons of SS and forest plot are shown in Figure 3. One observational study showed a greater improvement of SS in SCIT group than the rescue medication group[27]. The other observational study showed a significant reduction of the post-therapeutic SS, after 3-year treatment with SLIT[28].

Medication score (MS)

Four RCTs compared the improvement in MS between SCIT and placebo using different scales (maximum score of 3.4[23,25] and 6[24,26]). The effect on MS reduction favored SCIT over placebo (SMD -1.84; 95% CI -3.10, -0.57; p<0.01). An I^2 of 92% represented substantial heterogeneity. The comparisons of MS and forest plot are shown in Figure 4.

Disease-specific quality of life

Three RCTs assessed improvement in disease-specific QoL between SCIT and placebo in LAR with seasonal rhinitis symptoms[24-26]. All of them used the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The effect on improvement of RQLQ favored SCIT over placebo (SMD -1.14; 95% CI -1.54, -0.74; p<0.01). An I^2 of 10% represented low heterogeneity. The comparison of RQLQ and forest plot are shown in Figure 5.

Subgroup analysis by characteristic of rhinitis symptoms

When subgroup analysis by characteristic of rhinitis was conducted (perennial vs. seasonal symptoms), SCIT significantly reduced the CSMS and SS better than placebo in both subgroups (Figure 2-3). There was a significant difference between subgroups in SS improvement (p<0.01), the effect was greater in the seasonal rhinitis subgroup (SMD -3.17; 95% CI -4.62, -1.72) compared with the perennial rhinitis subgroup (SMD -1.01; 95% CI -1.71, -0.31) (Figure 3). Likewise, the effect on MS improvement favored SCIT over placebo was demonstrated only in the seasonal rhinitis symptoms subgroup (SMD -2.31; 95% CI -4.13, -0.49), not the perennial symptoms group (SMD -0.60; 95% CI -1.27, 0.07). However, there was no significant difference between the subgroups (p=0.08) (Figure 4).

Subgroup analysis by the age of participants

Subgroup analysis by the age of participants was not conducted because none of the included RCTs assessed pediatric subjects. There was only one non-comparative observational study assessing pediatric subjects[28].

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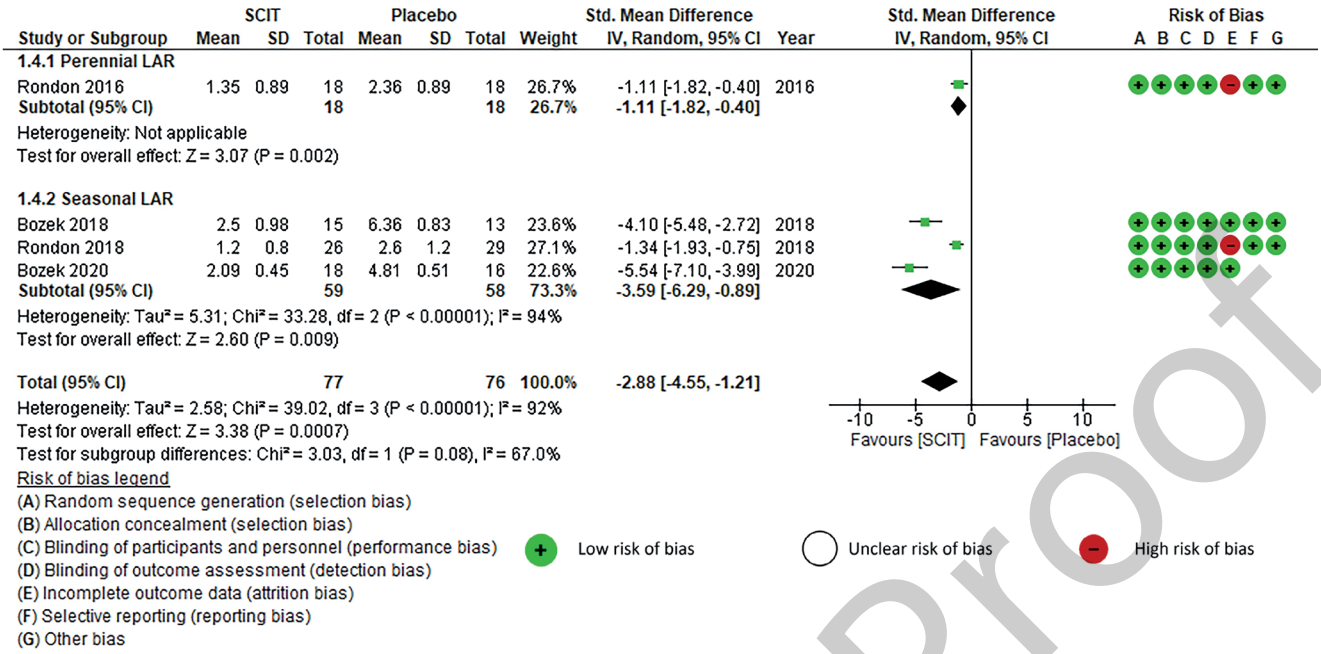

Figure 2. Short-term improvement in combined symptom and medication score and subgroup analysis by characteristic of rhinitis symptoms: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

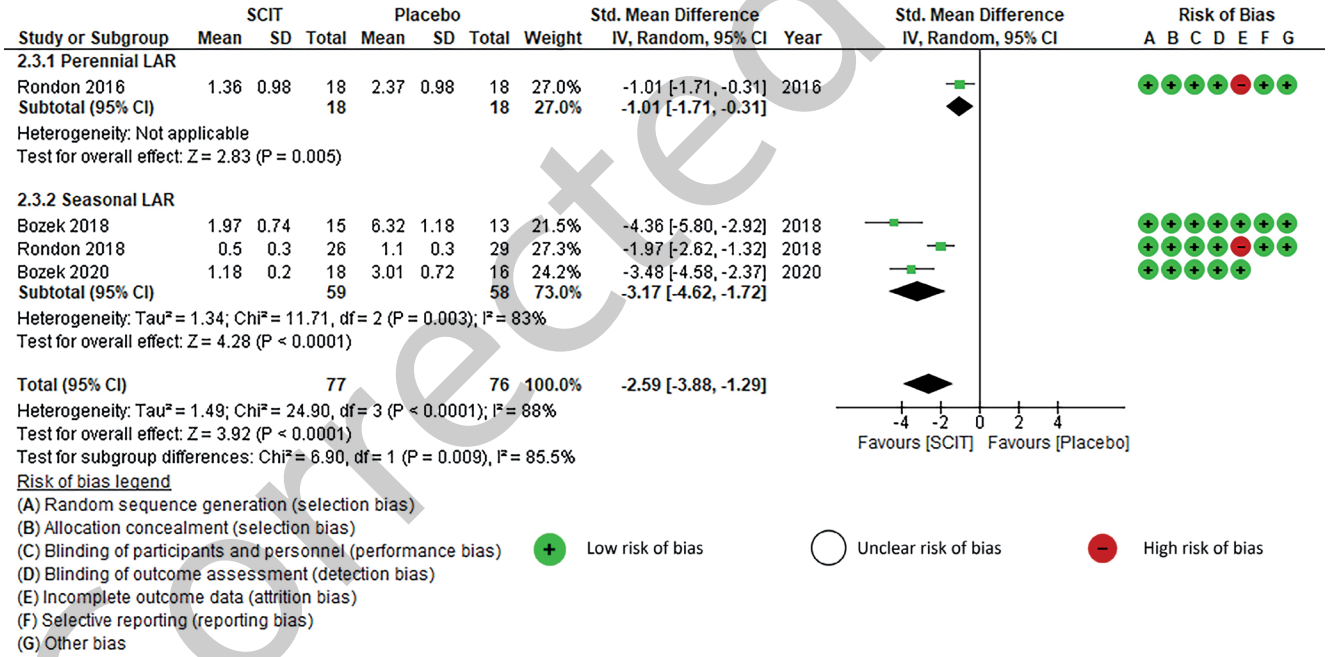

Figure 3. Short-term improvement in symptom score and subgroup analysis by characteristic of rhinitis symptoms: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

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Subgroup analysis by study quality

When subgroup analysis by study quality was performed (high-quality vs. low-quality), SCIT significantly reduced CSMS, SS, and MS better than placebo in both subgroups. SCIT showed a greater magnitude of benefit regarding CSMS, SS, and MS in high-quality studies than low-quality studies significantly ($p<0.01$) in all outcomes (Figures S1-S3).

Serum specific IgG4 level

Four RCTs assessed serum sIgG4 levels between SCIT and placebo[23-26]. Data from one RCT were not extracted because the mean and SD were not reported[26]. There was no difference

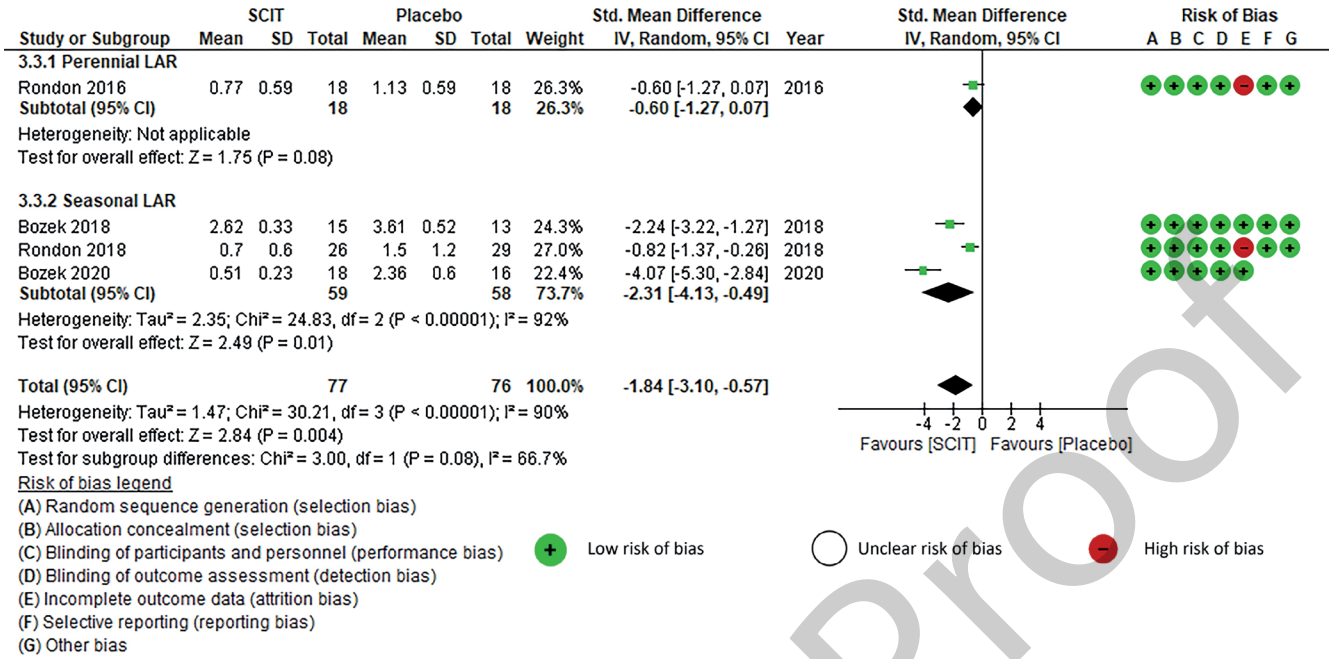

Figure 4. Short-term improvement in medication score and subgroup analysis by characteristic of rhinitis symptoms: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

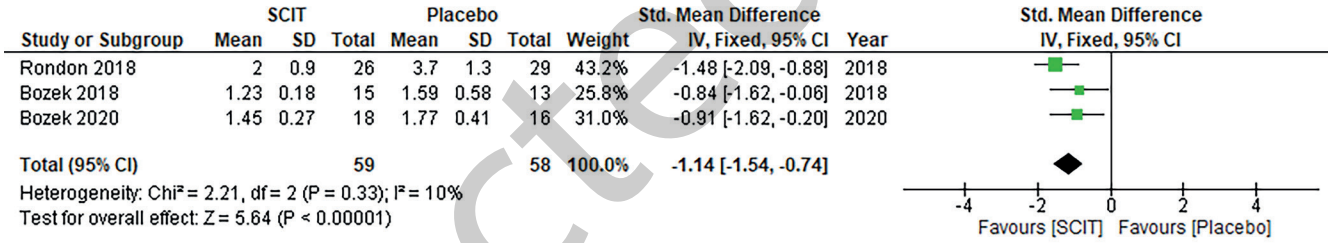

Figure 5. Short-term improvement in Rhinoconjunctivitis Quality of Life Questionnaire: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

in the 1-year effect on increasing sIgG4 level (SMD 0.98; 95% CI -0.49, 2.45; p=0.19) but the 2-year effect favored SCIT over placebo (SMD 2.84; 95% CI 0.43, 5.26; p=0.02). I^2 of 92% and 96% represented substantial heterogeneity, respectively. The comparisons of sIgG4 and forest plots are shown in Figure 6. In an observational study[27], a significant increase in sIgG4 level after 1-year SCIT was observed.

Serum specific IgE level

Four RCTs assessed serum sIgE levels between SCIT and placebo[23-26], in which sIgE levels were not detected in the placebo arm of two RCTs[24,26]. Therefore, the data from these two studies could not be pooled for meta-analysis[23,25]. There were no differences in the 1-year effect (SMD 0.31; 95% CI -0.19, 0.80; p=0.23) and the 2-year effect (SMD 0.05; 95% CI -0.36, 0.46; p=0.81). An I^2 of 0% represented low heterogeneity. No significant change of serum sIgE level after 1-year SCIT was observed in one observational study[27].

Long-term outcomes

None of the studies assessed the effects after discontinuation of treatment.

Adverse events

All included studies assessed the safety of AIT. There were no significant differences in the risk of local reaction between SCIT and placebo in total participants (RR 2.39; 95% CI 0.57, 10.04; p=0.23; I^2=0%)[23,25] nor in total injections (RR 1.10; 95% CI 0.65, 1.87; p=0.72)[24]. However, one RCT reported a higher risk of local reaction in SCIT compared with placebo[26]. There was no signifi-

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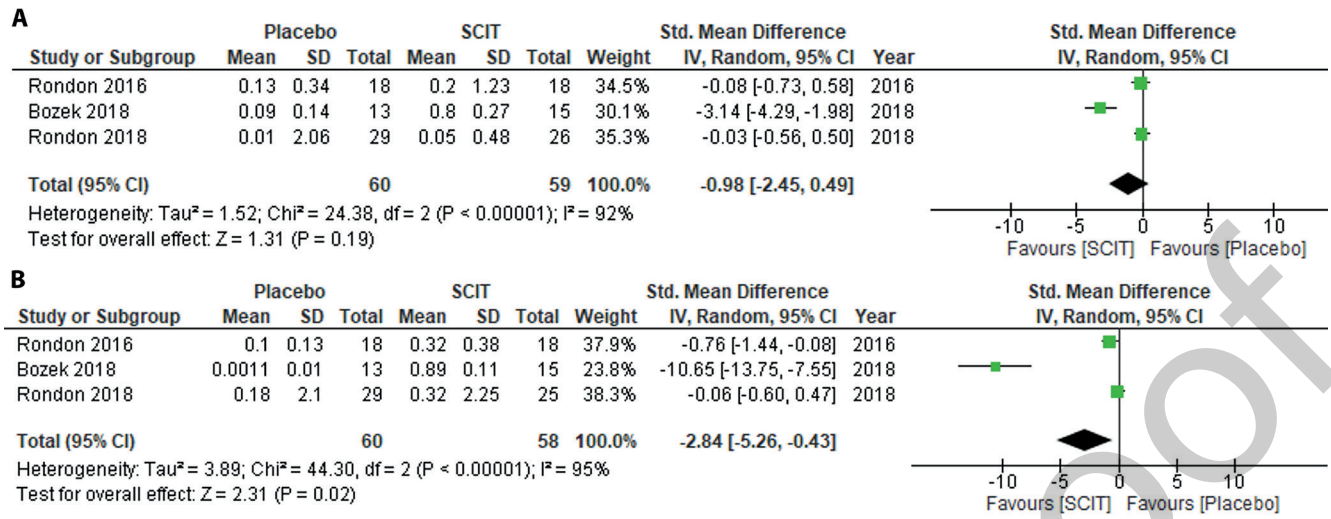

Figure 6. Change on specific IgG4 level: subcutaneous immunotherapy versus placebo (higher = better). (A) 1 year. (B) 2 years. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

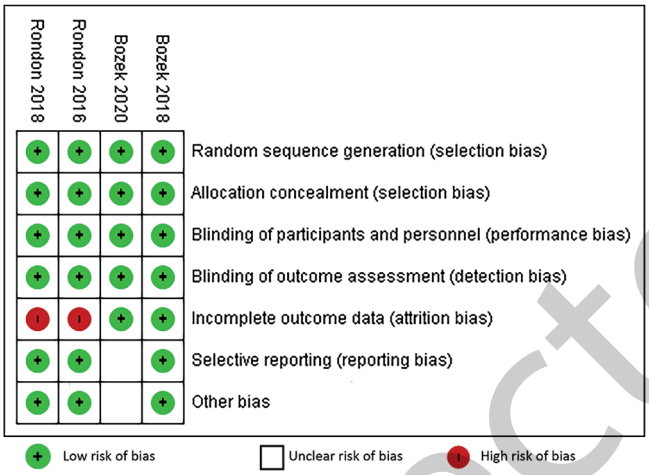

Figure 7. Risk of bias assessment of included RCTs.

cant difference in the risk of systemic reaction between SCIT and placebo (RR 0.87; 95% CI 0.06, 12.52; p=0.92)[24]. In two observational studies, one local reaction was reported in one of the 20 patients who used SCIT(27), while 60 participants received 3-year SLIT without adverse events[28].

Quality of the included studies

Four RCTs had low risks of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Two studies by Rondon et al.[24,26] had high risk of bias in incomplete outcome data due to high dropout rate. Bozek et al.[26] reported different outcomes with insufficient data from NCT trial registration. Therefore, we rated them as unclear risks of reporting bias and other bias (Figure 7). One comparative observational study had low risk of bias and one non-comparative study had high risk of bias with total MINORS scores of 21[27] and 10[28] points, respectively (Table S2). Neither Funnel plot nor Egger's test was performed due to the limited number of the included studies.

Discussion

LAR is acknowledged as a distinct non-allergic rhinitis subtype associated with Th2 patterns which is characterized by nasal production of sIgE antibodies[6], increased eosinophils, $CD3^+$ T cells, and $CD4^+$ T cells in the nasal fluid after exposure to allergens[9]. The expression of the direct class switch recombination to IgE markers in the nasal B cells indicates the existence of local IgE synthesis and regulation of heavy chain switching to IgE in the nasal mucosa[15]. Rondon et al.[8] used flow cytometry and found a similar nasal leukocyte-lymphocyte phenotype between AR and LAR. There is indirect evidence of Th2 IgE-mediated inflammatory response showing that LAR patients have a positive basophil activation test response[29,30]. With its immunomodulatory effect, AIT can target the immunological mechanism of LAR and change the course of the disease despite the negative SPT and serum sIgE tests.

This is the first systematic review and meta-analysis that assessed the efficacy and safety of AIT as a treatment for LAR. Our meta-analysis showed significant short-term beneficial effects of AIT on improving CSMS, SS, MS, RQLQ, and serum sIgG4. Subgroup analysis suggests that patients with seasonal LAR have a greater benefit in terms of SS compared to those with perennial, though there was only one study (n=18) in the latter group. The difference in symptoms improvement between the patients with seasonal and perennial LAR may result from discrepancies in symptom severity scales. Bozek et al.[24,26] used a visual analogue scale for assessing seasonal symptoms while perennial symptoms were evaluated by a 4-point scale[23]. Noticeably, Th2 inflammation is not the only causative mechanism in all AR. Innate immune, representing as the group 2 innate lymphoid cells

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(ILC2s), is also involved in the development of AR, e.g. in house dust mite-induced AR[31]. In contrast to the dominant role of AIT in Th2-acquired immunity, remarkably in pollen-induced AR, AIT has modest effects on ILC2s-influenced AR[31]. Therefore, this indirect evidence may elicit the lesser degree of benefit of AIT for LAR with house-dust-mite allergens.

The immunologic outcomes were steadily changed in the AIT group with a significant increase in sIgG4 after two years of treatment, which was not seen in the placebo group. This is in line with a report on immunologic changes after using AIT for AR[32]. There were no differences in serum sIgE at any time point between AIT and placebo with low heterogeneity. This finding indicates a retained local allergic response without altering systemic sIgE. However, two RCTs by Rondon et al.[23,25] reported increased serum sIgE levels with positive SPT at the end of the study in some patients of both active and placebo groups. Although still debated, this may be initial evidence that supports the possible transformation from LAR to AR[11].

Interestingly, a gradual decrease in nasal sIgE level was seen in the active intervention but not in the placebo group of one study[24]. This result demonstrates the suppression of nasal sIgE production and the effectiveness of AIT for LAR. In agreement with this finding, Yin et al.[28] also showed a significant decrease in nasal sIgE after 3-year treatment with SLIT. However, the finding on nasal sIgE is still controversial due to inconsistency among studies[10]. The discrepancy of results might be a consequence of environmental and racial diversity.

A significant proportion of patients with LAR had comorbidities such as conjunctivitis and asthma[13,23,25-27]. However, it is sometimes difficult to find a relationship between asthma and LAR whether asthma is an independent disease or correlates with LAR as local allergic asthma[26,33]. One study demonstrated that the markers of direct class switch recombination to IgE were found in the bronchial mucosa of patients with asthma regardless of atopic condition[33]. These markers suggested the local IgE production in lower airways[33]. Bozek et al.[26] demonstrated the effect of AIT on improving bronchial responsiveness in five of seven LAR patients who were positive for the bronchial challenge to birch allergen test. This finding suggests that AIT can decrease the comorbidities progression and improve quality of life in LAR patients.

All 4 RCTs and 2 observational studies displayed the safety of AIT, in which no significant risk of systemic reaction of AIT was shown. All but one RCTs showed no difference between the risk of local reaction between AIT and placebo[23-25]. Although a higher risk of local reaction in active intervention than placebo was observed in one RCT[26], this trial used a different product from the others.

Our systematic review and meta-analysis had limitations in several aspects. First, four RCTs were only conducted by two teams in two regions. Thus, they might not represent the effectiveness of AIT in general since the severity of LAR is very heterogeneous in terms of race and environment. Second, the meta-analyses had substantial heterogeneity. Although analyzed by subgroups, a subgroup of patients with seasonal symptoms still had substantial heterogeneity. There is a possibility that a broad inclusion of any type of AIT might have led to the substantial heterogeneity of the results, particularly when there was no heterogeneity among studies performed by the same study group. The other possibility was the scoring systems for CSMS, symptom score and medication score used by Rondon et al. and Bozec et al. were different. Lastly, the included studies had risks of bias. They had high dropout rates and reporting bias. The number of participants in four RCTs was small which might also affect the accuracy of outcomes in this review. It is worthwhile to mention that no study evaluated the effect of AIT after discontinuation of treatment and only SCIT was studied in RCTs. Future studies with long-term follow-up and/or different forms of AIT (e.g. SLIT) are warranted in this respect.

Conclusion

Evidence from four RCTs and two observational studies supported the short-term effectiveness and safety of AIT for treating LAR. These short-term benefits included the improvements of combined symptom and medication score, symptom score, medication score, disease-specific quality of life, and sIgG4. The sustained effects were inconclusive due to a lack of studies. There is a need for further studies of immunotherapy in LAR with measurement of long-term outcomes. The evidence of AIT in pediatric population is lacking. The effects of SLIT investigated by high-quality studies are required.

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Authorship contribution

MPH: study design, search, study selection, data collection, data analysis, drafting the article, and final approval. JS: search, study selection, data collection, revising the article, and final approval. KSe: search, study selection, data collection, revising the article, and final approval. WC: revising the article, and final approval. KSn: conception, study design, data analysis, drafting the article, and final approval.

Conflict of interest

Kornkiat Snidvongs received honoraria for speaking at symposia from Merck Sharp & Dohme, Mylan, and Menarini. Minh P. Hoang, Jompol Samuthpongtorn, Kachorn Seresirikachorn, Wirach Chitsuthipakorn declare that they have no conflict of interest.

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Corrected Proof

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Search strategy.

PubMed MEDLINE (625)	EMBASE (58)
#1 "desensitization, immunologic" [Mesh] #2 "immunotherapy" [Mesh] #3 "desensitization" [All Fields] #4 "oral immunotherapy" [All Fields] #5 "oral desensitization" [All Fields] #6 "sublingual immunotherapy" [Mesh] #7 "subcutaneous immunotherapy" [All Fields] #8 "allergen-specific immunotherapy" [All Fields] #9 "epicutaneous immunotherapy" [All Fields] #10 "intradermal immunotherapy" [All Fields] #11 "intralymphatic immunotherapy" [All Fields] #12 "intranasal immunotherapy" [All Fields] #13 "specific immunotherapy" [All Fields] #14 "grazax" [All Fields] #15 "ACARIZAX" [All Fields] #16 "ALK-Abello" [All Fields] #17 "odactra" [All Fields] #18 "grastek" [All Fields] #19 "ragwitek" [All Fields] #20 "pangramin plus" [[All Fields] #21 "Depigoid" [All Fields] #22 "ALK SQ Depot" [All Fields] #23 "Purethal" [All Fields] #24 "Chanllergen-Df" [All Fields] #25 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	#1 exp desensitization, immunologic/ #2 exp immunotherapy/ #3 desensitization.mp. #4 oral immunotherapy.mp. #5 oral desensitization.mp. #6 sublingual immunotherapy.mp. #7 subcutaneous immunotherapy.mp. #8 allergen-specific immunotherapy.mp. #9 epicutaneous immunotherapy.mp. #10 Intradermal Immunotherapy.mp. #11 intralymphatic immunotherapy.mp. #12 intranasal immunotherapy.mp. #13 specific immunotherapy.mp. #14 grazax.mp. #15 ACARIZAX.mp. #16 ALK-Abello.mp. #17 odactra.mp. #18 grastek.mp. #19 ragwitek.mp. #20 pangramin plus.mp. #21 Depigoid.mp. #22 ALK SQ Depot.mp. #23 Purethal.mp. #24 Chanllergen-Df.mp. #25 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26 "local allergic rhinitis" [All Fields] #27 "entopy" [All Fields] #28 "entopic rhinitis" [All Fields] #29 #26 OR #27 OR #28	#26 local allergic rhinitis.mp. #27 entopy.mp. #28 entopic rhinitis.mp. #29 #26 OR #27 OR #28
#30 #25 AND #29	#30 #25 AND #29
Cochrane Library (21), Web of Science (53), ClinicalTrial.gov (4), Scopus (373), HTA (19)	
#1 ("immunologic, desensiti*" OR "immunotherapy" OR "oral immunotherapy" OR "oral desensitization" OR "sublingual immunotherapy" OR "subcutaneous immunotherapy" OR "epicutaneous immunotherapy" OR "intradermal immunotherapy" OR "intralymphatic immunotherapy" OR "intranasal immunotherapy" OR "grazax" OR "ACARIZAX" OR "ALK-Abello" OR "odactra" OR "grastek" OR "ragwitek" OR "pangramin plus" OR "Depigoid" OR "ALK SQ Depot" OR "Purethal" OR "Chanllergen-Df")	
#2 ("local allergic rhinitis" OR "entopy" OR "entopic rhinitis")	
#3 #1 AND # 2	

Table S2. Risk of bias assessment of non-randomized studies using MINOR.

	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Rondon, 2011	2	2	2	2	0	2	2	2	1	2	2	2	21/24
Yin, 2019	2	0	2	2	0	2	2	0					10/16

MINOR, methodological index for non-randomized studies

Corrected Proof

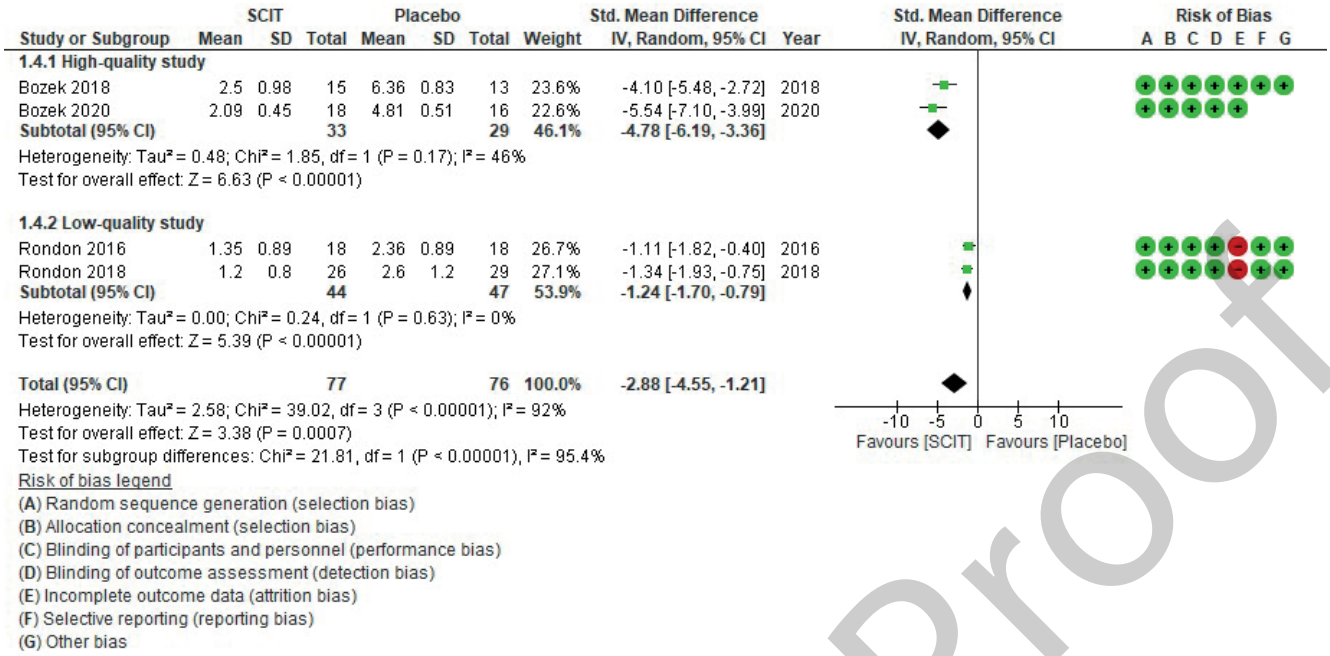

Figure S1. Short-term improvement in combined symptom and medication score and subgroup analysis by quality of study: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

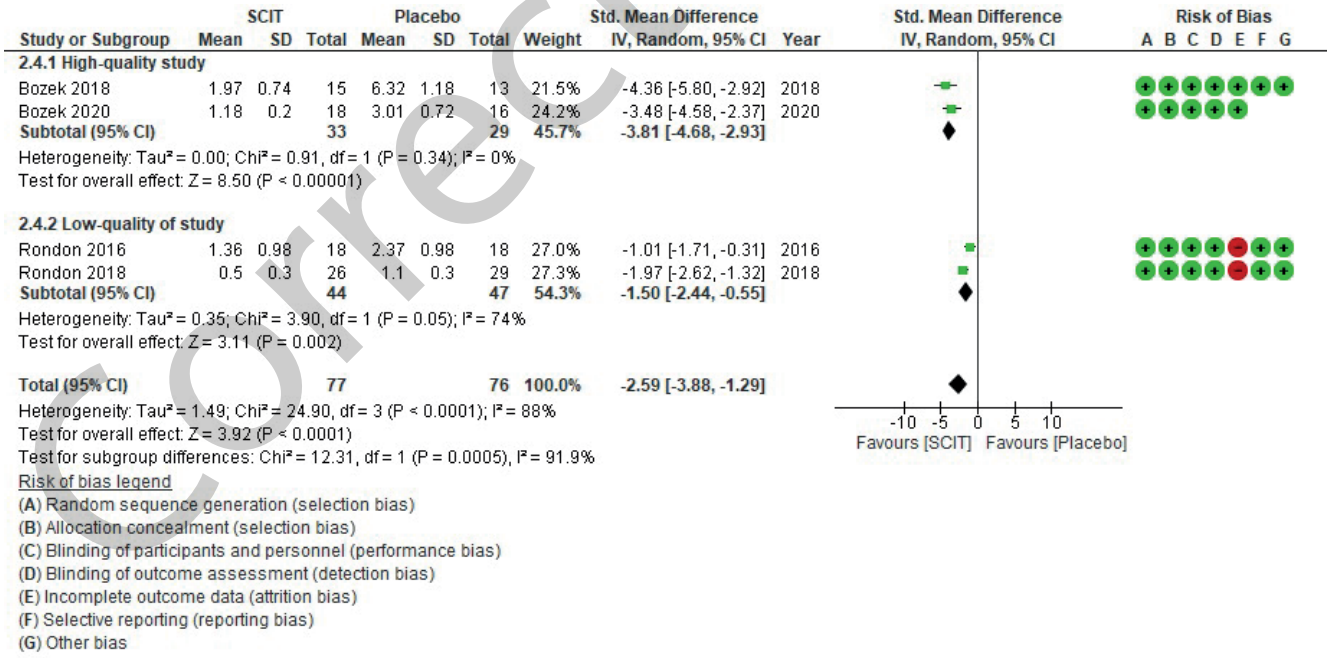

Figure S2. Short-term improvement in symptom score and subgroup analysis by quality of study: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

Corrected Proof

Study or Subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
3.4.1 High-quality study									
Bozek 2018	2.62	0.33	15	3.61	0.52	13	24.3%	-2.24 [-3.22, -1.27]	2018
Bozek 2020	0.51	0.23	18	2.36	0.6	16	22.4%	-4.07 [-5.30, -2.84]	2020
Subtotal (95% CI)			**33**			**29**	**46.7%**	**-3.12 [-4.91, -1.33]**	
Heterogeneity: Tau² = 1.35; Chi² = 5.20, df = 1 (P = 0.02); I² = 81%									
Test for overall effect: Z = 3.42 (P = 0.0006)									
3.4.2 Low-quality of study									
Rondon 2016	0.77	0.59	18	1.13	0.59	18	26.3%	-0.60 [-1.27, 0.07]	2016
Rondon 2018	0.7	0.6	26	1.5	1.2	29	27.0%	-0.82 [-1.37, -0.26]	2018
Subtotal (95% CI)			**44**			**47**	**53.3%**	**-0.73 [-1.15, -0.30]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%									
Test for overall effect: Z = 3.35 (P = 0.0008)									
Total (95% CI)			**77**			**76**	**100.0%**	**-1.84 [-3.10, -0.57]**	
Heterogeneity: Tau² = 1.47; Chi² = 30.21, df = 3 (P < 0.00001); I² = 90%									
Test for overall effect: Z = 2.84 (P = 0.004)									
Test for subgroup differences: Chi² = 6.49, df = 1 (P = 0.01), I² = 84.6%									

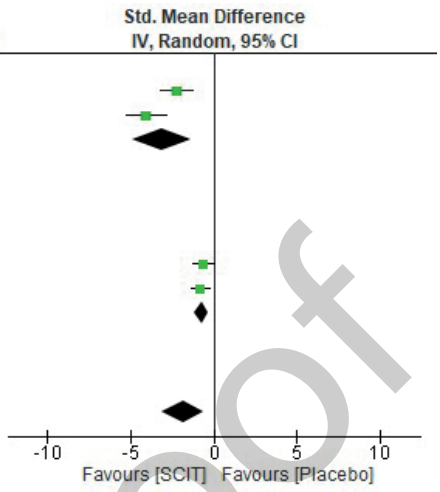

Figure S3. Short-term improvement in medication score and subgroup analysis by characteristic of rhinitis symptoms: subcutaneous immunotherapy versus placebo. SCIT = subcutaneous immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

Corrected Proof