AARD
Allergy Asthma Respir Dis 12(1):17-25, January 2024 https://doi.org/10.4168/aard.2024.12.1.17
pISSN: 2288-0402
eISSN: 2288-0410
ORIGINAL ARTICLE

Head-to-head comparison between subcutaneous and sublingual immunotherapy in perennial allergic rhinitis: A systematic review and meta-analysis

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Purpose: Few meta-analyses of head-to-head comparisons between subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for perennial allergic rhinitis (AR) have been performed so far. This study aimed to compare the efficacy, safety, and adherence of SCIT and SLIT in patients with house dust mite (HDM)-sensitized AR through a meta-analysis of head-to-head comparative studies.

Methods: A meta-analysis based on direct comparisons of SCIT and SLIT in HDM-sensitized AR was performed, using randomized controlled trials (RCTs) and nonrandomized studies (NRSs), on efficacy, safety, and adherence, which had been published until April 30, 2021. Treatment efficacy was calculated as the standardized mean difference in symptoms and medication scores after treatment between SCIT and SLIT. Safety and adherence to treatment were compared with the relative risk (RR) of SCIT and SLIT.

Results: Six RCTs and 3 NRS scores were analyzed. No statistically significant difference was noticed in improvement in symptoms and medication scores between SCIT and SLIT groups. Systemic adverse events occurred more frequently in SCIT than in SLIT in both RCT (RR, 3.97; 95% confidence interval [CI], 0.50–31.57) and NRS (RR, 5.48; 95% CI, 1.94–15.50). SCIT showed significantly higher adherence than did SLIT (RR, 1.16; 95% CI, 0.92–1.47).

Conclusion: No significant difference in efficacy was noticed between the 2 modalities for HDM-sensitized AR. However, SLIT had significantly lower number of systemic adverse reactions, and SCIT had more preferable adherence. (*Allergy Asthma Respir Dis 2024;12:17-25*)

Keywords: Allergens, Immunotherapy, Allergic rhinitis, Meta-analysis, House dust mites

INTRODUCTION

Allergic rhinitis (AR) is an allergic reaction mediated by immunoglobulin E (IgE) and chronic inflammation of the nasal mucosa, resulting in a clear runny nose, stuffy nose, sneezing, itchy nose, and itchy eyes.[1] The prevalence of AR is continuously globally increasing, and it is a clinically important disease that reduces the quality of life of patients and imposes medical and social burden.[2] Although pharmacotherapy using oral H1-antihistamines, topical nasal antihistamines, and intranasal corticosteroids is the basic treatment, allergen-specific immunotherapy (AIT) is considered if AR is refractory to these treatments.[3] AIT is the only treatment that changes the disease course, such as relieving allergic symptoms for a long time, reducing the risk of progression from rhinitis to asthma, and reducing sensitization to new allergens.[4]

AIT may be administered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), both of which have demonstrated clinical efficacies in randomized controlled trials (RCTs) and meta-analyses.[5-7] However, the comparative efficacy of SCIT and SLIT is not yet conclusive. Only a few RCTs have directly compared the two; however, the number of study subjects was small and showed conflicting results.[8-12] To overcome this limitation, meta-analysis-based indirect comparisons, which compared the differences between SCIT-placebo and SLIT-placebo, or network meta-analyses were recently performed to compare the efficacy of SCIT and SLIT. Some meta-analyses by indirect compari-

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Received: May 26, 2023 **Revised:** August 8, 2023 **Accepted:** August 23, 2023

sons reported that SCIT was more effective in symptom control than SLIT in patients with AR sensitized to grass pollen[13] and house dust mite (HDM).[14] However, other meta-analyses showed that SCIT and SLIT had comparable efficacy in controlling symptoms of AR,[15] specifically in grass pollen AR.[16] Therefore, the results of indirect comparisons of SCIT and SLIT are conflicting. However, a meta-analysis of direct comparative studies of SCIT and SLIT has not yet been performed.

Furthermore, SLIT possesses less systemic side effects than does SCIT.[13] SLIT is expected to have high adherence because it is relatively safe and can be administered at home; however, a problem of poor adherence compared to that in SCIT has been suggested.[17]

Therefore, the objective of this study is to conduct a systematic review and meta-analysis with direct comparative studies between SCIT and SLIT to answer the following question: Among SCIT and SLIT, which is better in terms of clinical efficacy, safety, and adherence in patients with HDMs-sensitized AR?

MATERIALS AND METHODS

1. Study selection and evaluation

Electronic databases (PubMed/MEDLINE, Embase, Cochrane Library, and KoreaMed) were systematically searched for RCTs and nonrandomized studies (NRSs) according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[18] A computerized search was performed to identify the literature on the comparison between SCIT and SLIT in terms of efficacy, systemic side effects, and adherence in patients with AR with the following medical subject headings: "rhinitis, allergic," and "immunotherapy" OR "desensitization," OR "hyposensitization." Our search strategy is shown on the Supplementary Table 1. Electronic databases were searched for studies published up to April 30, 2021, without any language restrictions.

Inclusion criteria for the review were defined using the PICOS (population, intervention, control, outcomes, and study) approach. Studies were chosen, in which comparisons of efficacy between SCIT and SLIT using symptom and medication scores, safety, and adherence in patients with perennial AR sensitized to HDM were performed. RCTs were searched for efficacy, whereas NRSs were searched for safety and adherence. According to the established retrieval strategy, data from 10% of the studies were evaluated and extracted. Differences were resolved through discussion. After the concordance rate was confirmed as 95% or higher, the data from the remaining 90% of all studies were evaluated and extracted. Subsequently, a full-text review was performed by 2 researchers. Potentially relevant articles that were identified as references during the screening process were manually searched.

2. Data extraction

A standard data extraction guide was used for each study. The data collected included the number of subjects, inclusion criteria, study details (country and duration), immunotherapy details (allergen, frequency, dosage, and duration), symptom scores, medication scores, systemic side effects, and adherence. Studies were excluded if they lacked adequate outcome measures or data to contribute to analyses involving means and standard deviations (SDs) (e.g., a study that only reported median data). Rhinitis symptoms scores were assessed for rhinorrhea, sneezing, nasal itching, and nasal obstruction, most commonly using a 4-point severity scale from 0–3 for each symptom: 0, no symptoms; 1, mild; 2, moderate; and 3, severe. Medication scores were primarily based on the type of medicines taken by patients each day during the study, most commonly using a four-point severity scale from 0–3 for each medicine: 0, no use; 1, antihistamines or low-dose intranasal steroids; 2, intranasal steroids; and 3, oral or high-dose intranasal steroids. One study calculated medication scores as follows: 2 points, steroids, budesonide nasal spray (64 μg/puff); 1.6 points, corticosteroid (prednisolone, 5 mg/tablet); and 6 points: antihistamine (loratadine, 10 mg/tablet).

The quality of the included RCTs was evaluated by assessing the risk of bias as guided by the Cochrane Collaboration.[18] The risk of bias was clearly described in the methods used for each domain, including the randomization process, deviations from intended interventions, measurement of the outcome, missing outcome data, and selection bias in the reported results. The quality of NRSs was assessed using ROBINS-I (Risk Of Bias In Non-randomized Studies-of Interventions), a tool for assessing the risk of bias in NRSs of interventions,[19] and seven domains analyzed including biases owing to confounding, in selection of participants into the study, in classification of interventions, owing to deviations from intended interventions, owing to missing data, in measurement of outcomes, and in selection of the reported result. Adverse events, defined as AIT-related systemic allergic reactions, were collected from RCTs and NRSs. Adherence was expressed as the proportion (%) of patients who completed AIT at the end of the study period.

3. Statistical analysis

A meta-analysis was performed on studies reporting differences in changes in symptom and medication scores between SCIT and SLIT. Different scoring systems and scales for symptoms and medications were used. Therefore, to compare the results, analyses were performed using the standardized mean difference (SMD) method, which expresses the differences in means between SLIT and SCIT in terms of units of pooled SD. SMD with a 95% confidence interval (CI) was calculated if the results were captured using the same symptom scales with continuous variables. In addition, the relative risk (RR) and 95% CI were used for dichotomous data to compare systemic adverse events and adherence between the 2 modalities.

The I^2 statistic was used to evaluate statistical heterogeneity. I^2 $<$25%, 25%–75%, and $>$75% represented low, moderate, and substantial heterogeneity, respectively. As a result of the review by 2 researchers, a random effect model was applied instead of the fixed effect model when heterogeneity between studies was judged to be high considering the characteristics of the study, subjects, treatment method, and research environment. Statistical assessments were performed using Review Manager (RevMan) ver. 5.3 (Cochrane Group, London, UK). Risk of bias table was generated by Risk-of-bias VISualization (robvis).[20]

RESULTS

1. Study selection and evaluation

The initial search identified 4,468 articles, and 2 additional articles were identified during full-text review. After removing duplicates, 3,974 articles were screened for titles and abstracts, and 26 full articles were assessed for eligibility. Finally, 6 RCTs and 3 NRSs were included in the meta-analysis (Fig. 1).

The details of the study characteristics are presented in Table 1. The 5 RCTs included 364 patients treated with immunotherapy

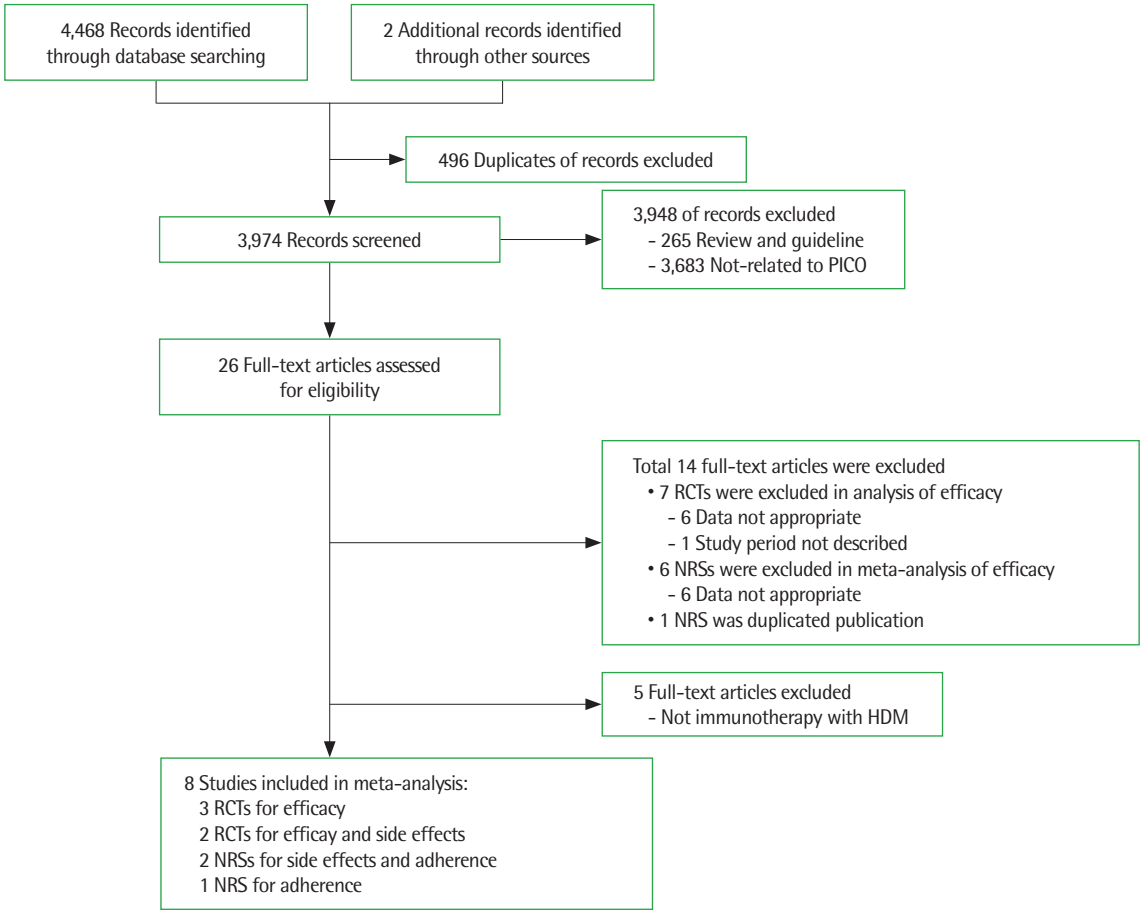

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) diagram of literature search and study selection process. PICO, patient/population, intervention, comparison and outcomes; RCT, randomized controlled trial; NRS, nonrandomized study; HDM, house dust mite.

Table 1. Study characteristics and summary of data

Study, country	Study design	No. of subjects			Age (yr)	Asthma (%)	Sensitization status	Type of allergen		Cumulative dose		Duration (mo)	Outcome
		SCIT	SLIT	Placebo				SCIT	SLIT	SCIT	SLIT		
Tahamiler et al. (2008), Turkey[21]	RCT	96	97	None	SLIT: 26.5±5.7 (12–51) SCIT: 24.9±4.9 (13–49)	None	Monosensitized	Dp+Df, ALK-Abello, Denmark	Dp+Df drop, ALK-Abello, Denmark	NR	NR	36	SS, MS
Eifan et al. (2010), Turkey[22]	RCT, open label	14	15	14	SLIT: 6.5±1.6 (5–10) SCIT: 7.0±1.8 (5–10) Placebo: 7.6± 2.0 (5–10)	SLIT: 87.5 SCIT: 87.5 Placebo: 87.5	Monosensitized	Dp+Df, ALK-Abello, Denmark	Dp+Df drop, ALK-Abello, Denmark	73,876.8 STU	1,131,540 SQ-U	12	SS, MS, SSE
Karakoc-Aydine et al. (2015), Turkey[23]	RCT	12	9	10	SLIT: median 10.1 SCIT: 10.5 Placebo: 10.4	SLIT: 83.3 SCIT: 72.7 Placebo: 85.7	Monosensitized	Dp+Df, ALK-Abello, Denmark	Dp+Df drop, ALK-Abello	NR	NR	36	SS, MS, SSE
Wang and Shi (2017), China[24]	RCT	34	34	None	SLIT: 9.6±2.5 SCIT: 9.4±2.4	NR	Polysensitized	Multiple-allergen extracts (HDM in combination with other clinically relevant allergen extracts), New-Hualian Union Pharmaceutical Company, China	Df drop, chenllergen, Wolwopharma Biotechnology Company, China	NR	NR	12	SS, MS
Xian et al. (2020), China[9]	RCT, double-blind, double dummy	26	27	14	SLIT: 24.2±14.3 SCIT: 21.1±12.0 Placebo: 24.9±6.1	SLIT: 87.8 SCIT: 80.8 Placebo: 78.6	Monosensitized	Dp+Df, Alutard, ALK-Abello, Denmark	Dp+Df drop, Pangramin, ALK-Abello, Denmark	81.2 μg	118.2 μg	12	SS, MS
Zhu et al. (2010), China[27]	NRS, observational study	81	79	None	SLIT: 17.7±3.2 SCIT: 19.0±2.7	NR	Monosensitized	Alutard, ALK-Abello, Denmark	Df drop, Chanllergen, WolwoPharma	NR	NR	24	SSE, Ad
You et al. (2016), China[25]	NRS	51	64	None	Could not be translated	NR	Monosensitized	Could not be translated	Could not be translated	NR	NR	24	Ad
Liu et al. (2021), China[26]	NRS, prospective open-label	200 (84 Alutard, 116 NHD)	125	None	SLIT: 8.5±3.1 Alutard: 9.4±4.2 NHD: 10.2±2.7	NR	Monosensitized	Dp (Alutard, ALK-Abello, Denmark) or Dp+Df (NovoHelisen Depot; Allergopharma, Germany)	Df drop, Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd, China	NR	NR	24	SSE, Ad

SCIT, subcutaenous immunotherapy; SLIT, sublingual immunotherpay; RCT, randomized controlled trial; NR, not reported; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*; NRS, nonrandomized controlled study; IR, index of reactivity; SS, symptom score; MS, medication score; STU, standard therapeutic units; SQ-U, standardized quality units; SSE, systemic side effects; HDM, house dust mites; NHD, NovoHelisen Depot; Ad, adherence.

(182 patients with SCIT and 182 patient with SLIT) and 38 placebo controls. Four RCTs were performed in Turkey, and 2 in China. The subjects were from different age groups in 3 studies and children only in other 3 studies.[9,21-24] The 3 NRSs included totally 600 patients treated with immunotherapy (332 patients for SCIT and 268 patients for SLIT), without any placebo control. In 2 study, subjects were of different age groups, 1 study included adults.[25-27] Immunotherapy with HDM extract only was performed in all except for 1 study where HDM extract in combination with other clinically relevant allergen extracts was used.[24] SLIT was administered by sublingual drops in all studies. The variable doses and administration methods were observed for both SLIT and SCIT (Table 1). The duration of AIT ranged from 1 to 3 years. The risk of bias is shown in Supplementary Table 2 for the 6 RCTs and Supplementary Table 3 for the 3 NRSs. Among RCTs, 1 study had low risk of bias but 4 studies showed some concerns of risk of bias and 1 study showed a high risk of bias. Among NRSs, 1 study had a moderate risk of bias but risk of bias of 2 studies was too high to estimable.

2. Rhinitis symptom score

Five RCTs were meta-analyzed for the AR symptom score, as shown in Fig. 2.[9,21-24] After 1 year of treatment, SCIT improved symptom scores more than SLIT did, but the difference was not statistically significant (SMD, -0.06; 95% CI, -0.38 to 0.26). After treatment for 3 years, SCIT improved scores more than SLIT did, and the difference was bigger than that after 1 year, even though it was not statistically significant (SMD, - 0.17; 95% CI, -0.38 to 0.03)[22] (Supplementary Fig. 1). Although the I^2 statistic revealed no heterogeneity for rhinitis symptom score (I^2 = 0%), the random effect model was selected because the heterogeneity of each study was high when the 2 researchers reviewed it.

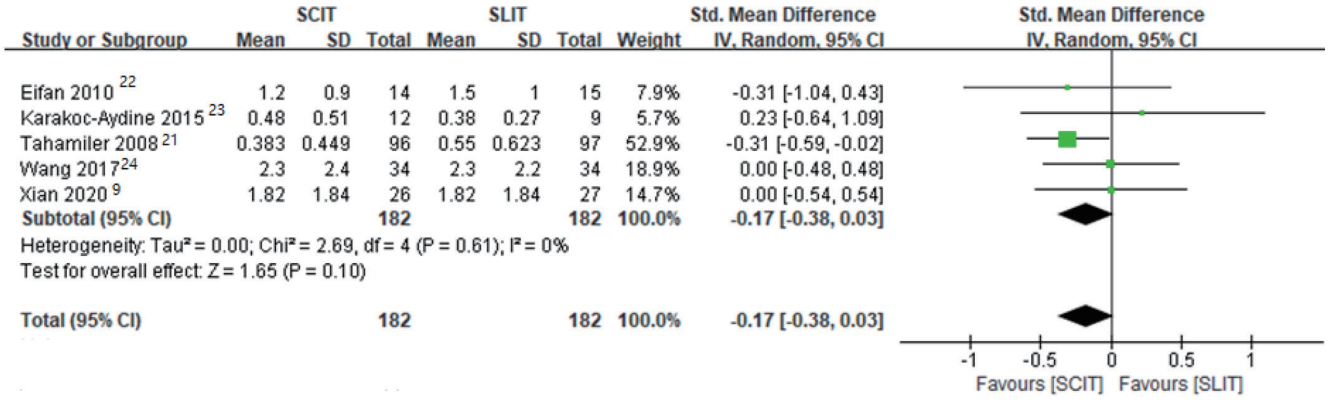

Fig. 2. Forest plot comparing SCIT with SLIT for symptom scores of rhinitis. SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SD, standard deviation; CI, confidence interval; *df*, degrees of freedom.

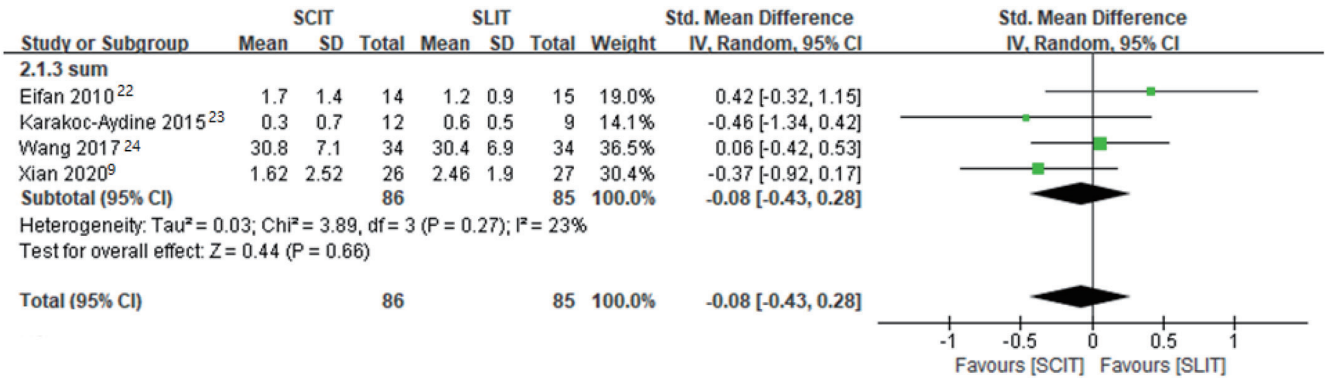

Fig. 3. Forest plot comparing SCIT with SLIT for medication scores. SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SD, standard deviation; CI, confidence interval; *df*, degrees of freedom.

3. Medication score

Four RCTs were meta-analyzed for the medication score, as shown in Fig. 3.[9,22-24] After treating for one year, SCIT improved the medication score more than did SLIT; however, the different was not statistically significant (SMD, -0.03; 95% CI, -0.35 to 0.30). After treatment of 3 years, SCIT improved scores more than did SLIT, and the difference was greater than that after 1 year, even though it was not statistically significant (SMD, -0.08; 95% CI, -0.43 to 0.28) (Supplementary Fig. 2). Although the I^2 statistic revealed low heterogeneity for the medication score (I^2 = 23%), the random effect model was selected because the heterogeneity of each study was high when the 2 researchers reviewed it.

4. Safety

Four RCTs and 2 NRSs were meta-analyzed for systemic side effects, as shown in Fig. 4. Systemic side effects of SCIT occurred more frequently than that of SLIT in RCTs (RR, 3.95; 95% CI, 0.49–31.70)[21-23,28] and NRSs (RR, 5.76; 95% CI, 0.98–33.80).[26,27] For RCTs, although the I^2 statistic revealed no heterogeneity for safety (I^2 = 0%), the random effect model was selected because the heterogeneity of each study was high when the 2 researchers reviewed it. For NRS, the I^2 statistic revealed moderate heterogeneity for safety (I^2 = 39%), the random effect model was selected because the heterogeneity of each study was high when the 2 researchers reviewed it. In 2 of the RCTs, no systemic side effects were observed in SCIT and SLIT.[21,28] In one study, 2 immunotherapy cases were discontinued owing to

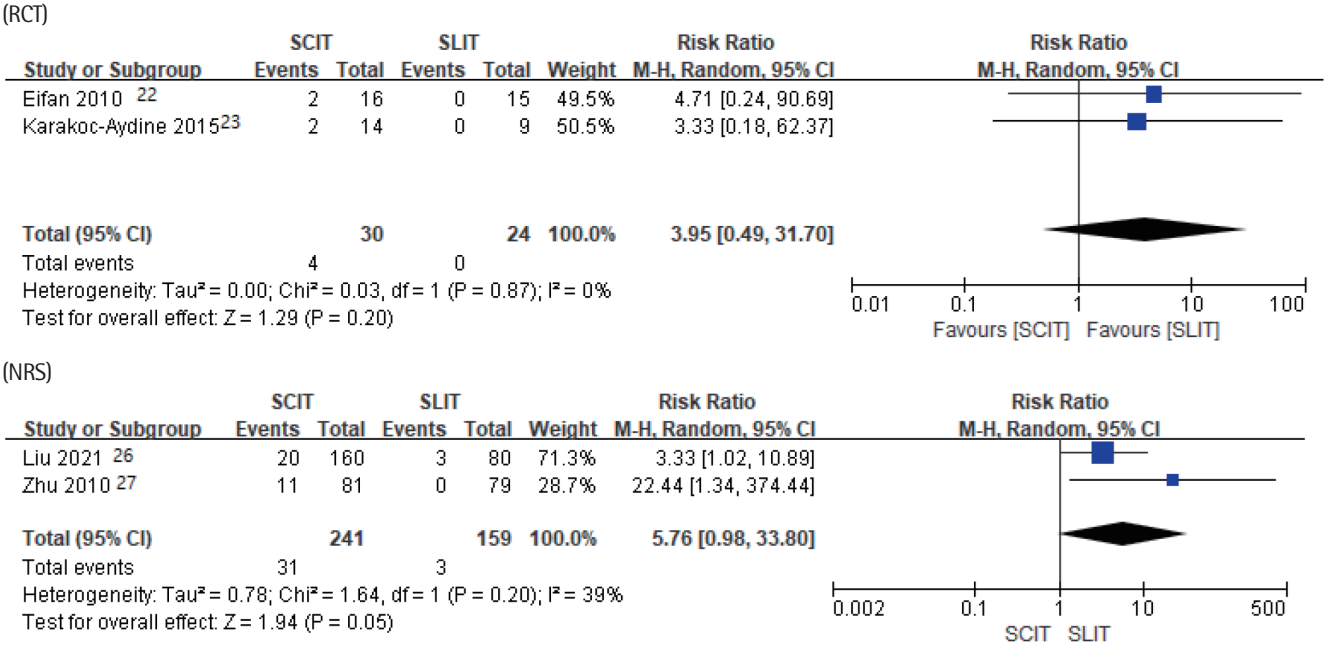

Fig. 4. Forest plot comparing SCIT with SLIT for systemic side effects. RCT, randomized controlled trial; NRS, nonrandomized study; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SD, standard deviation; CI, confidence interval; *df*, degrees of freedom.

Fig. 5. Forest plot comparing SCIT with SLIT for adherence. SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SD, standard deviation; CI, confidence interval; *df*, degrees of freedom.

anaphylaxis for one and severe asthma attack for the other during SCIT.[22] Similarly, in another study, 2 cases of anaphylaxis occurred during SCIT, resulting in the discontinuation of immunotherapy.[23] In one of the NRSs, 3 severe asthma attacks in SCIT but no anaphylaxis were observed.[27]

5. Adherence

Three NRSs were meta-analyzed for adherence, as shown in Fig. 5.[25-27] SCIT showed higher adherence than did SLIT (RR, 1.16; 95% CI, 0.92–1.47). In the second year of treatment, adherence was 1.35 times higher in SCIT than in SLIT in one study; however, in the third year of treatment, SCIT showed a lower difference in adherence than did SLIT by 1.09 times (Supplementary Fig. 3). I^2 statistic revealed a high heterogeneity for adherence ($I^2 = 85\%$) and the random effect model was selected because the heterogeneity of each study was high when the 2 researchers reviewed it.

DISCUSSION

This meta-analysis of direct comparative studies showed that both SCIT and SLIT had comparable effects in controlling the symptoms of rhinitis and reduction of using medication in patients with HDM-sensitized perennial AR. Furthermore, systemic side effects were less common with SLIT than with SCIT, whereas SCIT had the advantage of higher adherence to treatment than did SLIT. To our knowledge, this study is the first meta-analysis of head-to-head comparisons between SCIT and SLIT in HDM-sensitized AR.

SCIT and SLIT are effective in controlling the symptoms of AR in RCTs. However, only a few RCTs performed head-to-head comparisons between SCIT and SLIT, and the results were inconsistent.[8-12] A meta-analysis on indirect comparison by Tie et al.[15] showed no significant differences in symptom and medication scores between SCIT and SLIT in AR without limiting the sensitized allergens. When limited to grass pollen AR, Nelson et al.[16] reported that drops or tablets for SLIT and SCIT did not show any differences in efficacy by network meta-analysis. In contrast, Di Bona et al.[13] reported that SCIT showed better efficacy than those for SLIT drops or tablets in a meta-analysis on indirect comparison in grass pollen AR. In HDM-sensitized perennial AR, a recent network meta-analysis by Kim et al.[14] indicated that SCIT were more effective than those of SLIT drops or tablets in symptom control. Therefore, the results of meta-analysis on indirect comparison of SCIT and SLIT are still conflicting. However, our meta-analysis on direct comparison showed that SCIT and SLIT were equally effective in improving symptoms and medication scores in HDM-sensitized perennial AR. Although no significant difference in efficacy was observed between SCIT and SLIT, SCIT showed better symptom scores than did SLIT after 3 years of immunotherapy compared to those after one year. Further head-to-head comparative RCTs with a larger study population for a longer duration (>3 years) are needed to address this issue.

SLIT is a safer treatment than SCIT in terms of systemic side effects.[29] Life threatening side effects, including anaphylaxis requiring epinephrine administration, were reported in SCIT.[30] On the other hand, SLIT reported a significantly lower rate of major adverse events than did SCIT, and anaphylaxis requiring the use of epinephrine was rarely observed.[13,31] Similarly, in this meta-analysis, SLIT had fewer systemic side effects than SCIT. However, most of the systemic side effects are manageable and no deaths have been reported in SCIT.[31] In one study, overall adverse events, including local side effects, were reported to be higher for SLIT than for SCIT.[13] Therefore, systemic side effects may not be a significant concern for choosing AIT modality if health care providers are well-trained for these issues. AIT needs long-term treatment for at least 3–5 years, and nonadherence acts as a major obstacle in AIT, which can be influenced by various factors including patients, disease, treatment modality, and physicians.[32] One report mentioned that the initial adherence of SLIT is more than 96%; however, the long-term compliance after 3 years is only 18%. Therefore, maintaining the adherence of SLIT to patients may be critical.[17] SCIT was reported to have better compliance than SLIT, which is further supported by the results of our meta-analysis.[26] To overcome noncompliance with SLIT, patient education, regular follow-up every 3 months, and monitoring using an online platform have been tried.[17]

Our analysis had several limitations. First, the number of studies, particularly the number of NRSs was low. Second, even within the RCTs, differences in study design were present, including an open label,[22] patients' age, sex, the type of HDM extract and concentration, drug schedule, duration, and follow-up schedule. For these reasons, the heterogeneity of studies and risk of bias were evaluated as high. Third, the studies were limited to only 2 nations, and generalizing the results to all races was difficult. Finally, all SLITs in our study were of the drop type. However, in a recent network analysis of HDM-sensitized AR, no significant difference between SLIT drops and tablets were observed in terms of symp-

tom score.[14] The head-to-head comparison of SCIT and SLIT tablet is also necessary.

In conclusion, this meta-analysis compared the symptom scores, medication scores, side effects, and adherence between SCIT and SLIT in HDM-sensitized perennial AR using direct comparative studies. No significant differences in clinical efficacy were observed between the 2 modalities; however, systemic side effects were lower in SLIT, and adherence was higher in SCIT. Therefore, with a full consideration of those systemic side effects and adherence, clinicians should carefully select either SCIT or SLIT.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1-3 and Figs. 1-3 can be found via http://www.aard.or.kr/src/sm/aard-12-17-s001.pdf.

ACKNOWLEDGMENTS

We specially give thanks to all members of Korean Academy of Asthma, Allergy, and Clinical Immunology (KAAACI), the Working Group on Allergic Rhinitis.

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