APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

House dust mite allergen immunotherapy for monosensitized versus polysensitized patients with allergic rhinitis: A systematic review and meta-analysis

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Abstract

Background: Most patients with allergic rhinitis are polysensitized. The efficacy of house dust mite (HDM) allergen immunotherapy (AIT) compared between monosensitized and polysensitized patients remains limited.

Objective: To systematically review the efficacy and safety of HDM AIT compared between monosensitized and polysensitized patients with allergic rhinitis.

Methods: We searched PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) until June 2022. The primary outcome was the changes from baseline in total nasal symptom score (TNSS). Secondary outcomes were changes from baseline in total medication score (TMS), combined symptom medication score (CSMS), visual analog scale (VAS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, immunological parameters, and adverse events (AEs).

Results: Of 13 eligible studies, 10 prospective cohorts, 2 retrospective cohorts, and 1 matched cohort, we identified 10 studies for quantitative synthesis. There were 1,113 patients with allergic rhinitis, 566 with HDM monosensitization and 547 with polysensitization to HDM and other allergens. There was no significant difference in the pooled mean changes of the 2 groups in TNSS (SMD -0.05, 95%CI: -0.22 to 0.11, p = 0.532) and VAS (SMD -0.20, 95%CI: -0.42 to 0.01, p = 0.060) with moderate certainty of evidence. The changes in TMS, CSMS, and RQLQ were similar between the 2 groups with very low certainty of evidence. The AEs were mild and comparable between the 2 groups. The immunological indices remained inconsistent and were not predictive of clinical responses.

Conclusion: A single HDM AIT similarly improved clinical outcomes in monosensitized and polysensitized patients with allergic rhinitis.

Key words: allergen immunotherapy, allergic rhinitis, effectiveness, efficacy, house dust mite, monosensitized, polysensitized, subcutaneous immunotherapy, sublingual immunotherapy

Citation:
Phinyo, P., Krikeerati, T., Wongyikul, P., Lao-Araya, M., Thongngarm, T. (2022). House dust mite allergen immunotherapy for monosensitized versus polysensitized patients with allergic rhinitis: A systematic review and meta-analysis. *Asian Pac J Allergy Immunol*, 40(4), 337-352. https://doi.org/10.12932/ap-190822-1440

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Abbreviations:

AEs	Adverse events
AIT	Allergen immunotherapy
AR	Allergic rhinitis
CSMS	Combined symptom medication score
Der p	Dermatophagoides pteronyssinus
Der f	Dermatophagoides farinae
HDM	House dust mite
RCT	Randomized controlled trial
RQLQ	Rhinitis Quality of Life Questionnaire
SCIT	Subcutaneous immunotherapy
sIgE	Specific immunoglobulin E
sIgG4	Specific immunoglobulin G4
SLIT	Sublingual immunotherapy
TMS	Total medication score
TNSS	Total nasal symptom score
VAS	Visual analog scale

Introduction

Patients with allergic rhinitis can be sensitized to a single (monosensitized) or multiple (polysensitized) allergens. Polysensitization accounts for 27.5-74.3% of patients in the United States and European populations.[1-4] Of importance, the more significant number of allergens being sensitized, the more severe the allergic diseases.[5] Strategies for treating polysensitized patients with allergen immunotherapy (AIT) vary among clinicians. In the United States, polysensitized patients are generally treated with multi-allergen AIT, whereas in Europe, with a single or 2 most clinically relevant allergens.[6,7] The disparity of both concepts remains debated.

Ortiz et al[8] found that the efficacy of single-, pauci- and multi-allergens sublingual immunotherapy (SLIT) was comparable in improving nasal symptoms and quality of life in polysensitized patients. If the majority of sensitization had been pollens, the cross-reactivity of allergenic proteins would have explained the efficacy of a single allergen AIT. However, the study did not report the sensitization pattern of enrolled patients. Kim et al[9] showed that multi-allergen AIT treating polysensitized asthmatic children was less effective than a single house dust mite (HDM) AIT for monosensitized ones. In contrast, Zhang et al[10] have recently reported that a single HDM SLIT was as clinically effective as multi-allergen AIT for treating polysensitized patients with asthma.

The results from the randomized controlled trials (RCTs), of which 66-90% of the recruited patients with allergic rhinitis were polysensitized, have demonstrated the efficacy of HDM SLIT tablets in improving clinical symptoms.[11-15] The pooled analysis from 2 of those RCTs showed that HDM SLIT tablets effectively improved total combined rhinitis score of -1.20 (95%CI; -2.0 to -0.5) in the monosensitized group and -0.9 (95%CI; -1.3 to -0.4) in polysensitized group, compared with placebo.[16] Although those RCTs excluded patients with clinically relevant allergens other than HDM to avoid their polysensitization being a confounder, HDM-induced perennial symptoms may still conceal clinical symptoms caused by other allergens. Taking the findings of those studies into account, the issue of whether a single HDM AIT may be beneficial for polysensitized patients is of interest.

Herein, we conducted a systematic review and meta-analysis to assess the efficacy of HDM AIT in monosensitized versus polysensitized patients with allergic rhinitis on total nasal symptom score (TNSS), total medication score (TMS), combined symptom and medication score (CSMS), visual analog scale (VAS), rhinitis quality of life questionnaire (RQLQ) score, immunologic parameters, and adverse events (AEs).

Methods

This systematic review and meta-analysis was conducted following the Cochrane Handbook for Systematic Reviews of Intervention[17] and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020.[18] The review protocol was registered on PROSPERO (CRD42022332703).

Data sources and search strategy

A pre-specified search strategy was used to search for relevant literature from its inception to the end of June 2022. Electronic medical databases included PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). A search for grey literature was conducted through Google scholar and Clinical Trial Registry.[19] The authors also reviewed the previous list of references from previously reported systematic reviews and/or meta-analyses on the same topic.

Study selection and outcomes

The study inclusion was based on the following criteria: 1) a longitudinal study (e.g., cohort or case-control); 2) patients with allergic rhinitis of all ages prescribed with HDM AIT for maintenance treatment for at least 3 months; and 3) patients were categorized into monosensitized and polysensitized groups according to their sensitization status using standard tests, and the outcomes of interest were reported for each group. Exclusion criteria were non-English studies, studies with no abstract or available full text, duplicated studies, and studies that excluded polysensitized patients.

The primary outcome of interest was the changes from baseline in TNSS. The secondary outcomes were the changes from baseline in TMS, CSMS, VAS, RQLQ score, immunologic parameters, and AEs.

Screening

Two screening procedures were employed in this review. Firstly, two investigators (TK and PW) screened records using Rayyan.[20] Secondly, one investigator (PP) screened through the rearranged records using ASReview, an open-source machine learning for prioritized screening.[21] The screening was stopped after the investigator had screened 50% of the records. The results of the two procedures were combined. Disagreements during the screening process were resolved through discussion with a clinical expert in allergy (TT).

Data extraction

Two authors (TK and PW) independently extract the following data from each study: study characteristics, country/location including environmental factors, study design, inclusion and exclusion criteria, population type (i.e., children, or adults), patient demographics, including age and gender, and potential effect modifiers. Any discrepancy was resolved through discussion with a clinical expert (TT).

For continuous outcomes, we extracted the mean change values and their standard deviation (SD) for each treatment arm. For studies that did not directly report the mean values of the outcomes, the methods proposed by Luo et al[22] and Wan et al[23] were employed to estimate the mean values. If the SDs were not reported, we followed the methods suggested by the Cochrane Handbook to impute these values.[17] Digitizelt was used to extract data from graphs if needed. The total number of patients and events within each treatment arm were collected for the categorical endpoint. We contacted the corresponding authors for studies with incomplete outcome data.

Risk-of-bias assessment

Two authors (TK and PW) independently evaluated the quality of each included study using the Newcastle-Ottawa Scale (NOS).[24] NOS assessed the study quality based on three domains: subject selection, comparability, and outcome assessment. Studies were rated as good, fair, or poor quality according to the number of stars received within each domain. Any disagreement was resolved by consulting with a clinical expert in allergy (TT) and a clinical methodologist (PP).

Data synthesis and analysis

All analyses were performed using Stata 17 (StataCorp). *P*-values < 0.05 were considered statistically significant. Tabulation methods were used to assess the similarity across studies in terms of clinical questions prior to meta-analysis. A pairwise meta-analysis was performed using DerSimonian and Laird random-effects model. Heterogeneity was evaluated using the Cochrane Q test and the I-squared statistics. For continuous outcomes, we pooled the estimates as standardized mean difference (SMD). A treatment effect with an SMD of 0.2, 0.5, and 0.8 was considered a small, medium, and large effect.[25]

For the efficacy outcomes, we focused on the changes in TNSS, TMS, CSMS, VAS, and RQLQ after being treated with HDM AIT for at least 3 months. Only studies reporting score change from 12 months onwards after treatment initiation were included. For studies that provide the data on only TNSS and TMS but did not report CSMS, we calculated the CSMS according to the standard formula: TNSS/4 + TMS.[26]

Subgroup analyses were performed using the quality of study according to the NOS. Sensitivity analyses were conducted by excluding studies with baseline imbalance. A leave-one-out sensitivity analysis was performed to examine the robustness of the main results. Publication bias was not evaluated as the number of included studies was less than 10.

Quality and certainty of evidence

Two authors (PW and PP) rated the certainty and quality of synthesized evidence following the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach.[27] The quality of evidence depends on study design, risk of bias, consistency, directness, and precision of the findings. Each outcome was graded as having very low, low, moderate, or high quality of evidence. A team discussion with all other authors was used to resolve any disagreements.

Results

Search results

A total of 2929 records were identified from a systematic search. Thirty studies were identified from manual screening, and another was identified from ASReview. However, we could not retrieve full-text articles for 6 studies. Thus, only 28 full-text articles were assessed. Fifteen studies were excluded, 13 were conference abstracts, and the other two studies[28,29] were published in Chinese. Finally, 13 studies were included in this systematic review, but only 10 of them had sufficient outcome data for meta-analysis. The PRISMA 2020 flow diagram is shown in **Figure 1**.

Characteristics of the included studies

A total of 13 studies were included in this systematic review, 9 prospective cohorts,[30-38] 3 retrospective cohorts,[39-41] and 1 matched cohort.[42] Eight studies were from China, 3 from Korea, 1 from Turkey, and 1 from Italy. The summary of characteristics and the main findings of each study are presented in **Table 1**. This systematic review included a total of 1,113 patients, 566 with HDM monosensitization and 547 with polysensitization (HDM and other allergens sensitized). One study[34] included polysensitized patients who were not polyallergic, 1 study[40] included those who were polyallergic, and the remaining 11 studies did not report the status of their polysensitized patients. Nine studies[30,31,35,37-42] treated patients with HDM SLIT, while 4[32-34,36] used HDM subcutaneous immunotherapy (SCIT). All studies had 1 year or greater duration except for the one[34] from Turkey. Both monosensitized and polysensitized patients in all included studies experienced a similar improvement in clinical symptoms during the treatment period, with no significant differences between the 2 groups. However, 1 study followed patients 5 more years after cessation of a 2-year HDM SLIT and found a more sustained clinical benefit, favoring the monosensitized group only at year 5 of the total 7-year study duration.[31] Three studies compared the degree of responses to HDM AIT between monosensitized and polysensitized patients and found no significant difference between the 2 groups.[30,35,41]

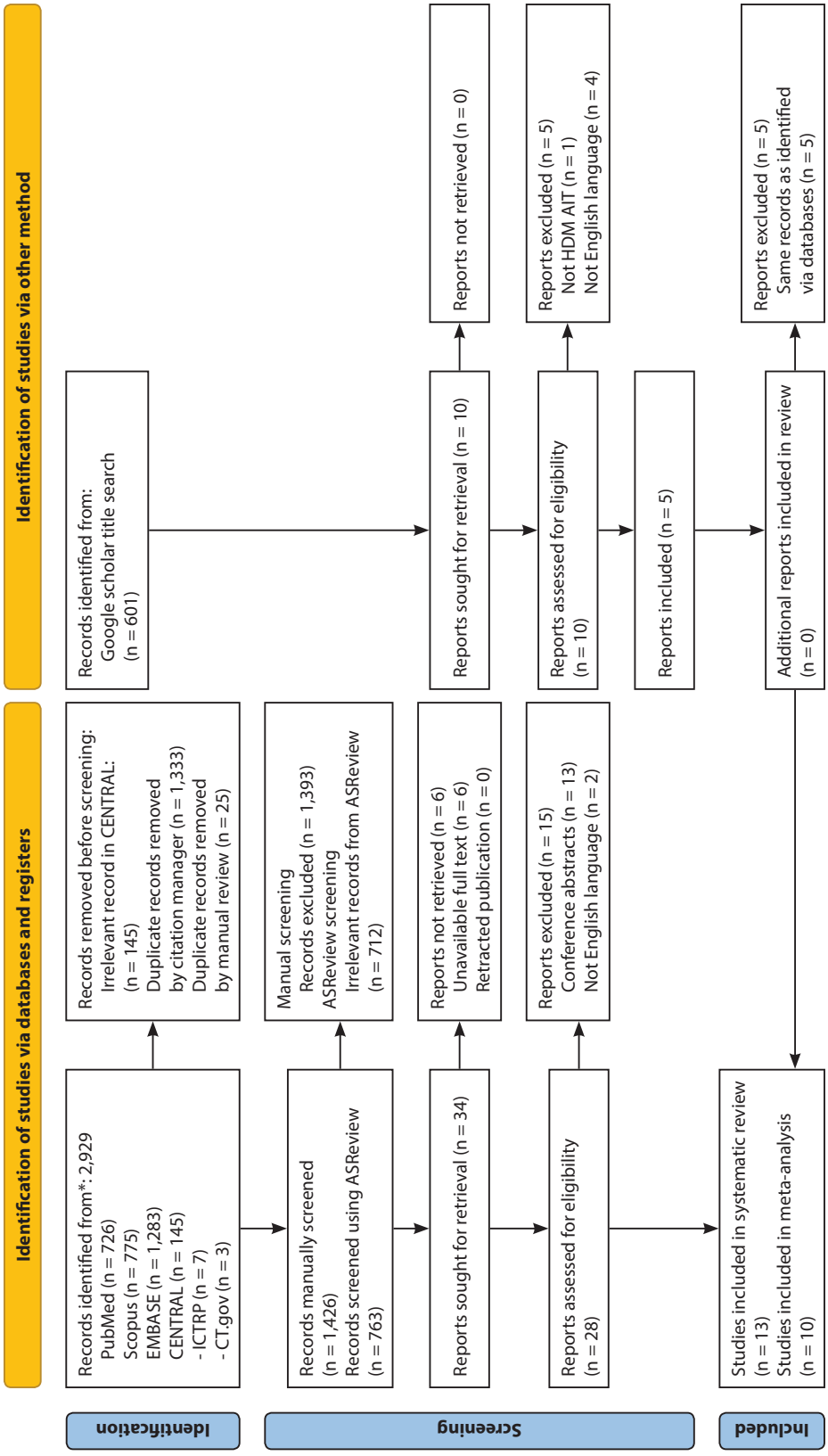

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of included and excluded studies.

Table 1. Characteristics of included studies of house dust mite allergen immunotherapy in monosensitized versus polysensitized patients with allergic rhinitis

Studies	Site of studies	Type/duration of studies	Study size (n)	Route of HDM AIT	Dose of HDM AIT[c]	Patients, n	Age (y)	Pre-TNSS	Post-TNSS	Pre-TMS	Post-TMS	Pre-CSMS	Post-CSMS
Ma 2021[39]	China	Retrospective cohort/12 mo	68	SLIT-D daily	Der f[d] 100 μg/d (Adult) 50 μg/d (< 14 y)	Monosensitized AR, 36	21.7 ± 15.1	6.70 ± 2.44	2.63 ± 2.22	2.32 ± 1.07	0.51 ± 0.95	4.00 ± 1.68[f]	1.17 ± 1.51[f]
						Polysensitized AR, 32	16.5 ± 9.9	6.94 ± 2.22	2.28 ± 2.41	2.44 ± 1.14	0.21 ± 0.58	4.18 ± 1.70[f]	0.78 ± 1.18[f]
Gao 2020[30]	China	Prospective cohort/36 mo	110	SLIT-D daily	Der f[d] 100 μg/d (Adult) 50 μg/d (< 14 y)	Monosensitized AR, 68	16.89 ± 13.33	NR	NR	NR	NR	6.33 ± 0.55	1.12 ± 0.73
						Polysensitized AR, 42 (≤ 3 allergens)		NR	NR	NR	NR	6.48 ± 0.54	1.01 ± 0.71
Cui 2019[31]	China	Prospective cohort/24 mo	80	SLIT-D daily	Der f[d] 50 μg/d	Monosensitized AR, 40	7.10 ± 2.09	NR	NR	NR	NR	4.31 ± 0.51	1.22 ± 0.3
						Polysensitized AR, 40 (≤ 3 allergens)	6.62 ± 1.63	NR	NR	NR	NR	4.30 ± 0.51	1.20 ± 0.36
Tu 2019[32]	China	Prospective cohort/24 mo	58	SCIT q 6 wk	9.8 μg Der p1	Monosensitized AR, 35	11[a] (5-53)	7.00[b] (6.00, 9.75)	2.00[b] (0.00, 4.00)	3.7 (median)	1.4 (median)	NR	NR
						Polysensitized AR, 23		10.00[b] (7.75, 11.00)	2.00[b] (1.50, 4.00)			NR	NR
Zhang 2019[40]	China	Retrospective cohort/24 mo	183	SLIT-D daily	HDM[d] (unspecified species) 50 μg/d	Monosensitized AR, 65	7.5 ± 1.3	11.27 ± 1.50	3.48 ± 1.5	1.67 ± 0.43	0.52 ± 0.4	4.49 ± 0.81[f]	1.39 ± 0.78[f]
						Polysensitized AR, 118	7.1 ± 1.4	11.54 ± 1.42	3.56 ± 1.56	1.64 ± 0.44	0.55 ± 0.41	4.53 ± 0.80[f]	1.44 ± 0.80[f]
Kim 2019[41]	Korea	Retrospective cohort/24 mo	80	SLIT-D daily	200 STU/d	Monosensitized AR, 22	10.6 ± 6.2	8.6 ± 2.1	4.06 ± 2.43	NR	NR	NR	NR
						Polysensitized AR, 58	13.1 ± 8.8	8.0 ± 2.9	2.78 ± 2.03	NR	NR	NR	NR
Song 2018[33]	China	Prospective cohort/60 mo	106	SCIT q 6 wk	4.5 μg Der p1	Monosensitized AR, 89	9.1 ± 4.3	NR	NR	0.49 ± 0.09	0.23 ± 0.08	NR	NR
						Polysensitized AR, 17		NR	NR			NR	NR

Asian Pac J Allergy Immunol 2022;40:337-352 DOI 10.12932/AP-190822-1440

Table 1. (Continued)

Studies	Site of studies	Type/duration of studies	Study size (n)	Route of HDM AIT	Dose of HDM AIT[c]	Patients, n	Age (y)	Pre-TNSS	Post-TNSS	Pre-TMS	Post-TMS	Pre-CSMS	Post-CSMS
Soyyigit 2016[34]	Turkey	Prospective cohort/20 wk	43	SCIT q 4 wk	9.8 µg Der p1	Monosensitized AR, 19	33.57 ± 10.19	NR	NR	0.19	0.22	NR	NR
						Polysensitized AR, 24	31.4 ± 8.88	NR	NR	0.19	0.20	NR	NR
Xu 2015[35]	China	Prospective cohort/12 mo	50	SLIT-D daily	Der f[d] 150 µg/d (Adult)[e] 50 µg/d (< 14 y)[e]	Monosensitized AR, 20	42 ± 11	NR	NR	NR	NR	NR	NR
						Polysensitized AR, 30	43 ± 12	NR	NR	NR	NR	NR	NR
Kim 2014[36]	Korea	Prospective cohort/24 mo	60	SCIT q 1-3 mo	HDM (unspecified dose and species)	Monosensitized AR, 30	23 (17-39)	11.3 ± 1.2	3.2 ± 1.2	11.6 ± 0.9	2.91 ± 1.02	14.43 ± 1.20[f]	3.71 ± 1.34[f]
						Polysensitized AR, 30	26 (15-42)	11.8 ± 1.1	3.8 ± 1.31	13.7 ± 0.5	4.10 ± 1.15	16.65 ± 0.78[f]	5.05 ± 1.52[f]
Li 2014[37]	China	Prospective cohort/12 mo	112	SLIT-D daily	Der f[d] 150 µg/d (Adult) 50 µg/d (< 14 y)	Monosensitized AR, 56	6.80 ± 2.77	4.85 ± 2.08	0.95 ± 0.19	2.01 ± 1.18	0.05 ± 0.09	3.22 ± 1.70[f]	0.29 ± 0.14[f]
						Polysensitized AR, 56	7.06 ± 2.22	4.31 ± 2.63	0.95 ± 0.19	2.36 ± 1.51	0.34 ± 0.09	3.44 ± 2.17[f]	0.58 ± 0.14[f]
De Castro 2013[42]	Italy	Matched prospective cohort/36 mo	29	SLIT-T (allergoid) daily	Combined 50% Der p 1 + 50% Der f 1 of 5.4-13.5 µg/d	Monosensitized, 16	10.46 ± 3	NR	NR	NR	NR	NR	NR
						Polysensitized, 13		NR	NR	NR	NR	NR	NR
Lee 2011[38]	Korea	Prospective cohort/12 mo	134	SLIT-D 3 times weekly	250 STU/dose	Monosensitized AR, 70	14.3 ± 9.9	11.4 ± 4.1	5.7 ± 3.31	96.9 ± 27.4	47.5 ± 17	NR	NR
						Polysensitized AR, 64	15.3 ± 10.4	10.2 ± 4.6	4.6 ± 3.55	93.6 + 28.4	42.8 ± 17.1	NR	NR

Numbers are mean ± SD unless stated otherwise; [a]Median (range); [b]Median (interquartile 25,75)
[c]The dose recommended by the manufacturer
[d]Dose calculated by estimating 1 drop = 0.05 mL
[e]No manufacturer name or recommended dose mentioned
[f]The CSMS presented in this systematic review was calculated from the reported TNSS and TMS based on following the equation: CSMS = TNSS/4 + TMS.
Abbreviations: AR, allergic rhinitis; CSMS, combined symptom and medication score; HDM, house dust mite; mo, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT-D, sublingual immunotherapy drop; STU, standard therapeutic unit; TMS, total medication score; TNSS, total nasal symptom score; wk, week

Quality of included studies

According to the NOS, 7 studies were rated high quality, and 6 were rated low quality. All included studies did not show any serious concern regarding the selection of population and ascertainment of exposure. The lack of comparability was the most common reason that affected the quality of studies, followed by outcome assessment and adequacy of follow-up.

Changes from baseline in TNSS following HDM AIT

Seven studies reported the changes in TNSS from baseline to post-treatment in monosensitized and polysensitized patients.[32,36-41] Both groups showed a decreasing trend in TNSS from baseline to post-treatment. There was no significant difference in the pooled effect size of the 2 groups in TNSS changes (SMD -0.05, 95% Confidence interval (CI): -0.22 to 0.11, p = 0.532) with non-significant level of heterogeneity (I^2 = 15.23%, P-value = 0.314) (**Figure 2A**).

A subgroup analysis by the quality of the study was conducted for TNSS changes, and no significant difference was revealed (P = 0.230). A sensitivity analysis was performed by removing Tu et al[32] study due to the imbalance in pre-treatment TNSS. The result after removal remained unchanged (SMD -0.01, 95%CI: -0.17 to 0.15, P = 0.937). The results of the leave-one-out sensitivity analysis for TNSS changes did not differ from the main results.

Changes from baseline in TMS following HDM AIT

Five studies, including 300 polysensitized and 257 monosensitized patients, were assessed for the difference in TMS changes from baseline to post-treatment.[36-40] Following AIT, both groups showed a decrease in TMS. The overall effect of sensitization status on the TMS changes was insignificant (SMD -0.05, 95%CI: -0.36 to 0.27, p = 0.767) with moderate level of heterogeneity (I^2 = 69.15%, P-value = 0.011) (**Figure 2B**).

A subgroup analysis by the study quality did not reveal a significant difference (P = 0.986). A leave-one-out sensitivity analysis result did not differ from the main result.

Changes from baseline in CSMS following HDM AIT

The overall difference in CSMS changes was pooled from six studies involving 593 patients with AR.[30,31,36,37,39,40] Like TNSS and TMS, the CSMS showed a decremental trend following treatment in both groups, and there was no significant difference in the mean changes of CSMS from baseline between the 2 groups (SMD -0.12, 95%CI: -0.38 to 0.15, p = 0.384) (**Figure 2C**). The pooled result was, however, affected by significant heterogeneity (I^2 = 58.20%, P-value = 0.035). All studies for CSMS changes were rated as high-quality; hence, subgroup analysis was not performed.

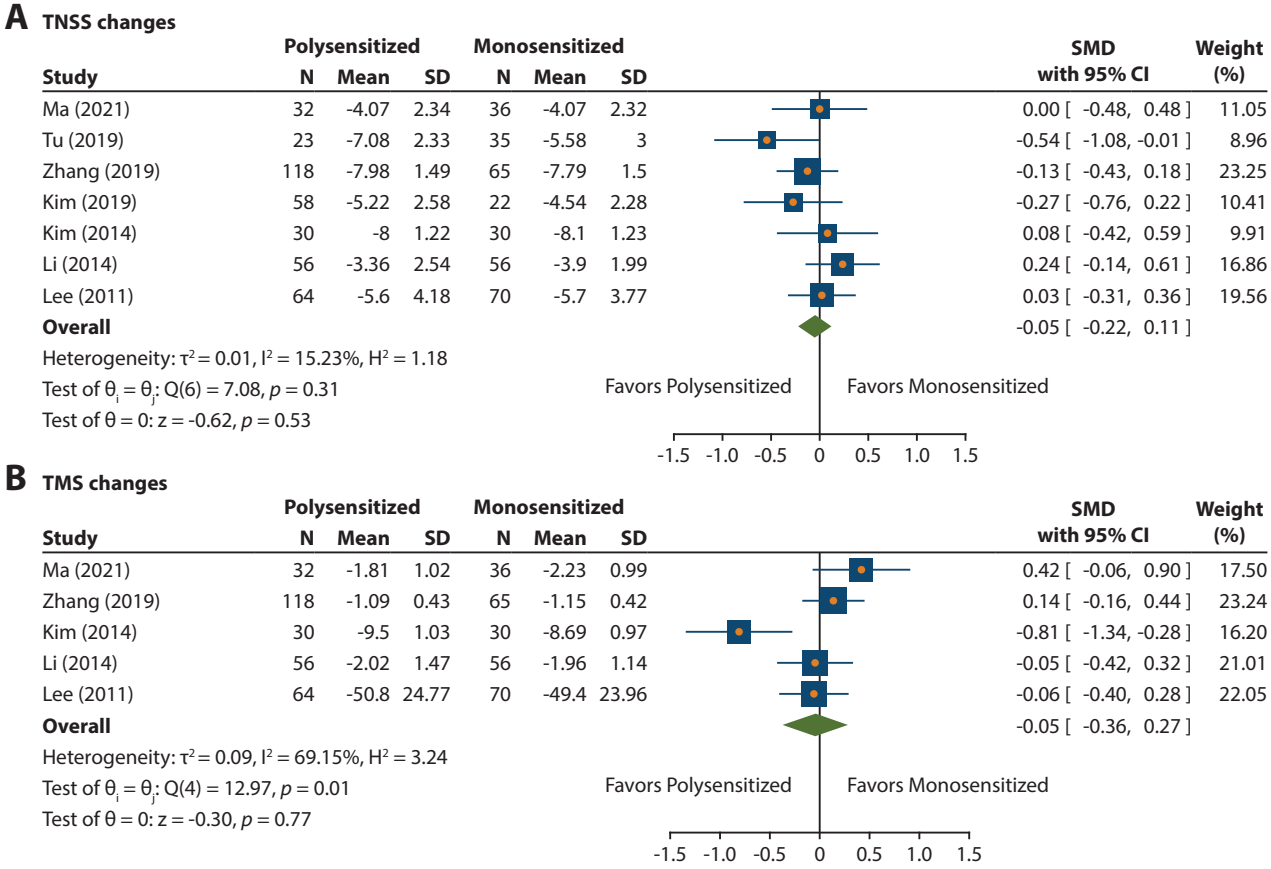

Figure 2. Changes from baseline in each clinical outcome following house dust mite allergen immunotherapy between monosensitized and polysensitized patients. (A) total nasal symptom score. (B) total medication score. (C) combined symptom and medication score. (D) visual analog scale.

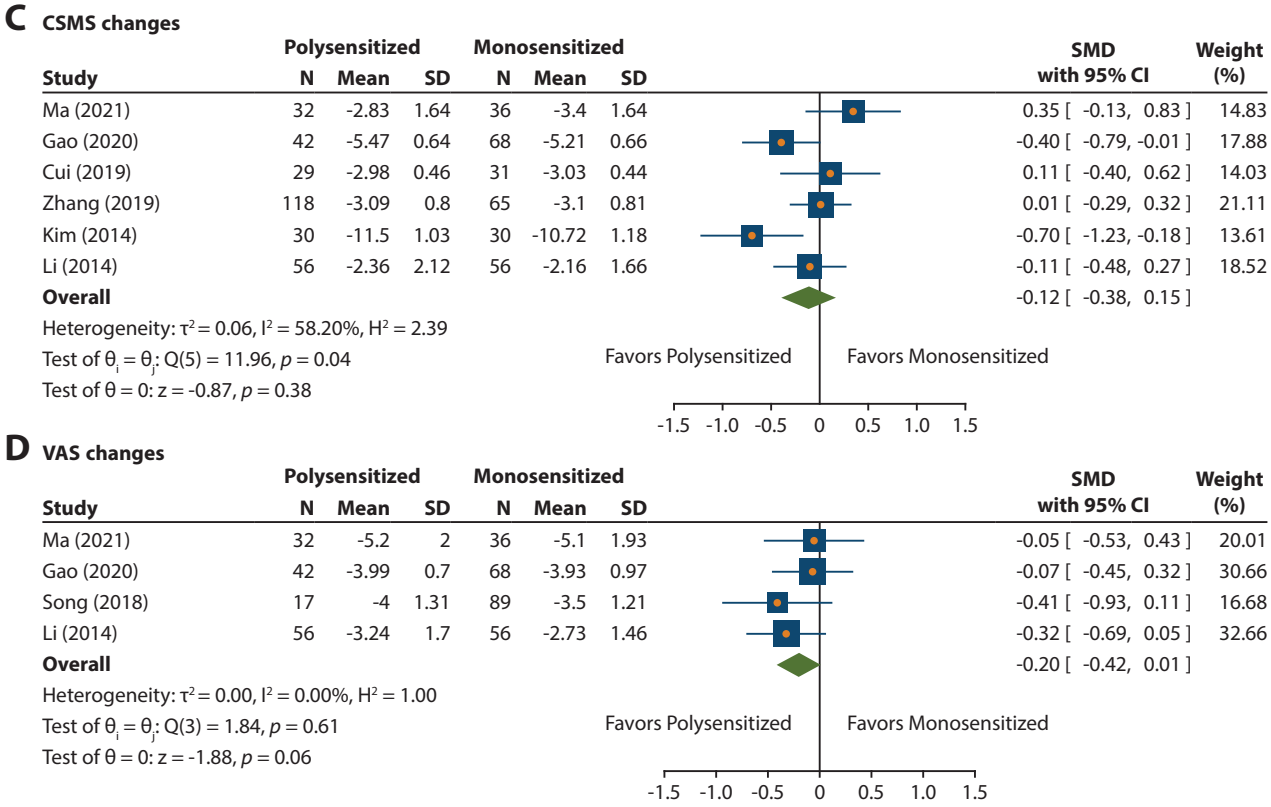

Figure 2. (Continued)

Changes from baseline in VAS following HDM AIT

Four studies compared the changes in VAS after HDM AIT.[30,33,37,39] The pooled mean changes from baseline in VAS were not significantly different between polysensitized and monosensitized groups (SMD -0.20, 95%CI: -0.42 to 0.01, p = 0.060) with no statistical evidence of heterogeneity (I^2 = 0.00%, P = 0.605) (**Figure 2D**).

A subgroup analysis by the quality of the study was conducted for VAS changes, and no significant group difference was revealed (P = 0.402). When we excluded Song et al[33] and Li et al[37] studies due to an imbalance in the baseline VAS, the main result was unaffected (SMD -0.06, 95%CI: -0.36 to 0.24, p = 0.687). The results were consistent in the leave-one-out sensitivity analysis when Ma et al[39] and Gao et al[30] studies were excluded.

Changes from baseline in RQLQ following HDM AIT

The data on RQLQ changes were reported in two studies.[33,36] Both studies had balanced RQLQ at baseline. No statistically significant changes from baseline in RQLQ following treatment were identified (SMD 0.24, 95%CI: -0.13 to 0.60, p = 0.201). The test of heterogeneity revealed non-significant results (I^2 = 0.00%, P-value = 0.641).

GRADE Quality of the pooled evidence

Table 2 shows the overall quality rating according to GRADE. The primary outcome was rated as moderate certainty. Thus, the conclusion can be made that the difference in sensitization status probably results in little to no difference in TNSS changes. For secondary outcomes, VAS was rated as moderate certainty, while others were rated as very low certainty.

Immunologic indices and their changes from baseline following HDM AIT

Total IgE, sIgE, and sIgG4 and their alteration following HDM AIT were summarized in **Table 3**. At baseline, sIgE and IgG4 levels were similar between monosensitized and polysensitized groups except for Zhang et al[40] and Kim et al 2019[41] studies. Polysensitized patients in Zhang et al[40] study had more significant levels of total IgE, sIgE, and sIgG4, while those in Kim et al 2019[41] had a higher *Der p* sIgE level than the monosensitized one. Following HDM AIT, both groups showed an increase in sIgE and sIgG4 in most studies. Of note, Soyyigit et al[34] found that the sIgE/total IgE ratio was significantly higher in polysensitized patients, while Kim et al 2019[41] found more significant changes in *Der p* sIgG4 and *Der f* sIgG4 in the monosensitized groups; however, neither of those findings correlated with clinical response.

Soyyigit et al[34] also found that at baseline, the polysensitized group had higher CD203c expression on basophils than the monosensitized one. The more CD203c expression in the polysensitized group remained persistent after receiving a 14-week HDM SCIT. Zhang et al[40] demonstrated that IL-2 and TGF-β1 significantly increased, whereas IL4 and IL17α significantly decreased in both groups following a 2-year HDM SLIT.

Table 2. GRADE (Grading of Recommended Assessment, Development, and Evaluation) quality rating of the pooled evidence.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polysensitized	Monosensitized	Relative (95% CI)	Absolute (95% CI)		
TNSS changes (follow-up: 12+ months; assessed with: TNSS)												
7	observational studies	not serious[a]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed[b]	381	314	-	SMD **0.05 SD lower** (0.22 lower to 0.11 higher)	⊕⊕⊕◯ Moderate	CRITICAL
TMS changes (follow-up: 12+ months; assessed with: TMS)												
5	observational studies	not serious	serious[c]	not serious	not serious	none	300	257	-	SMD **0.05 SD lower** (0.36 lower to 0.27 higher)	⊕◯◯◯ Very low	IMPORTANT
CSMS changes (follow-up: 12+ months; assessed with: CSMS)												
6	observational studies	not serious	serious[c]	not serious	not serious	none	307	286	-	SMD **0.12 SD lower** (0.38 lower to 0.15 higher)	⊕◯◯◯ Very low	IMPORTANT
VAS changes (follow-up: 12+ months; assessed with: VAS)												
4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed[b]	147	249	-	SMD **0.2 SD lower** (0.42 lower to 0.01 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
RQLQ changes (follow-up: 12+ months; assessed with: RQLQ)												
2	observational studies	serious[d]	not serious	not serious	serious[e]	none	47	119	-	SMD **0.24 SD higher** (0.13 lower to 0.6 higher)	⊕◯◯◯ Very low	IMPORTANT

Abbreviations: CI, confidence interval; CSMS, combined symptom and medication score; RQLQ, rhinoconjunctivitis quality of life questionnaire; TMS, total medication score; TNSS, total nasal symptoms score; SMD, standardized mean difference; VAS, visual analog scale.

Explanations:

[a]Three out of seven studies were rated as low quality. Both subgroup analysis and sensitivity analysis confirmed that the primary result was robust.

[b]Subgroup analysis by study quality showed that studies with a high risk of bias (low-quality study) reported spurious treatment effects.

[c]There was a moderate to a high level of heterogeneity across studies.

[d]One of the studies was rated as low quality

[e]Only two studies were included. Widened confidence intervals.

Asian Pac J Allergy Immunol 2022;40:337-352 DOI 10.12932/AP-190822-1440

Table 3. Specific IgE, total IgE, and specific IgG4 changes from baseline following house dust mite allergen immunotherapy.

Immunological indices	Groups	Baseline	6 mo	12 mo	24 mo	Changes from baseline	*P*-values within the group
sIgG4							
Zhang 2019[40]	Polysensitized (n = 118)	713.6 (22.7)	NR	NR	1208.1(31.3)	+494.5 (28.0)	***P* < 0.01**
	Monosensitized (n = 65)	681.5 (19.4)	NR	NR	1175.4 (34.9)	+439.9 (30.3)	***P* < 0.01**
	P-values between the groups	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	
Soyyigit 2016[34]	Polysensitized (n = 24)	0.07 (0.01, 0.41)[a]	0.68 (0.04, 6.21)[a]	NR	NR	NR	***P* < 0.025**
	Monosensitized (n = 19)	0.08 (0.01, 2.63)[a]	0.18 (0.03, 18.4)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				
***Der p* sIgG4**							
Kim 2019[41]	Polysensitized (n = 58)	0.21 (0.02, 0.80)[b]	NR	NR	0.33 (0.04, 1.20)b	0.11 (-0.46, 0.89)[b]	NR
	Monosensitized (n = 22)	0.22 (0.04, 0.80)[b]	NR	NR	0.42 (0.10, 1.78)b	0.22 (-0.24, 1.41)[b]	NR
	P-values between the groups	*P* = 0.510			*P* = 0.140	***P* = 0.020**	
***Der f* sIgG4**							
Kim 2019[41]	Polysensitized (n = 58)	0.26 (0.06, 1.61)[b]	NR	NR	0.36 (0.04, 2.52)[b]	0.07 (-0.80, 2.13)[b]	NR
	Monosensitized (n = 22)	0.23 (0.04, 1.18)[b]	NR	NR	0.43 (0.11, 2.67)[b]	0.19 (-0.12, 1.57)[b]	NR
	P-values between the groups	*P* = 0.327			*P* = 0.308	***P* = 0.005**	
sIgE							
Zhang 2019[40]	Polysensitized (n = 118)	72.9 (4.5)	NR	NR	74.7 (6.9)	+1.8 (6.1)	***P* < 0.05**
	Monosensitized (n = 65)	68.3 (3.8)	NR	NR	71.9 (4.1)	+3.6 (4.0)	***P* < 0.01**
	P-values between the groups	***P* < 0.001**			***P* = 0.003**	***P* = 0.034**	
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* = 0.826	
Soyyigit 2016[34]	Polysensitized (n = 24)	1.65 (0.01, 52.6)[a]	5.47 (0.4, 90.3)[a]	NR	NR	NR	***P* < 0.05**
	Monosensitized (n = 19)	0.75 (0.01, 39.1)[a]	1.47 (0.01, 49.2)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				

Table 3. (Continued)

Immunological indices	Groups	Baseline	6 mo	12 mo	24 mo	Changes from baseline	*P*-values within the group
***Der p* sIgE**							
Kim 2019[41]	Polysensitized (n = 58)	28.9 (0.2, 160.0)[b]	NR	NR	45.2 (0.2, 365.0)[b]	12.2 (-8.2, 271.1)[b]	NR
	Monosensitized (n = 22)	13.3 (1.9, 68.9)[b]	NR	NR	40.0 (6.1, 98.8)[b]	22.0 (-14.6, 81.7)[b]	NR
	P-values between the groups	**P = 0.010**			*P* = 0.442	*P* = 0.614	
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	222.4 (75.2)	NR	NR	252.8 (65.8)	+30.4 (71.0)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* =0.826	
***Der f* sIgE**							
Kim 2019[41]	Polysensitized (n = 58)	53.1 (0.3, 363.0)[b]	NR	NR	68.8 (0.16, 913.0)[b]	8.5 (-29.9, 550.0)[b]	NR
	Monosensitized (n = 22)	31.6 (3.2, 180.0)[b]	NR	NR	71.2 (8.1, 354.0)[b]	28.1 (-9.3, 271.9)[b]	NR
	P-values between the groups	*P* = 0.437			*P* = 0.692	*P* = 0.095	
Kim 2014[36]	Polysensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	Monosensitized (n = 30)	214.7 (62.3)	NR	NR	237.3 (58.9)	+22.6 (60.7)	NR
	P-values between the groups	*P* = 0.591			*P* = 0.580	*P* = 0.959	
Total IgE							
Zhang 2019[40]	Polysensitized (n = 118)	72.9 (4.5)	NR	NR	74.7 (6.9)	+1.8 (6.1)	**P < 0.05**
	Monosensitized (n = 65)	68.3 (3.8)	NR	NR	71.9 (4.1)	+3.6 (4.0)	**P < 0.01**
	P-values between the groups	**P < 0.001**			**P = 0.003**	**P = 0.034**	
Soyyigit 2016[34]	Polysensitized (n = 24)	90.1 (26.1, 702.0)[a]	161 (18.8, 816.0)[a]	NR	NR	NR	**P < 0.025**
	Monosensitized (n = 19)	84.6 (23.2, 1250.0)[a]	107.0 (21.0, 1764.0)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* = 0.826	

Numbers are mean ± SD unless stated otherwise; [a]Median (range); [b]Median (IQR)
Der f, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; IQR, interquartile range; mo, months; NR, not reported; sIgE, specific immunoglobulin E, sIgG4, specific immunoglobulin G4

Table 4. Summary of adverse events reported from included studies.

Study	Ma 2021[a]		Gao 2020[a]		Cui 2019[a]		Tu 2019[b]		Zhang 2019[a]		Kim 2019[a]		Song 2018[b]		Soyyigit 2016[b]		Xu 2015[a]		Kim 2014[b]		Li 2014[a]		De Castro 2013[a,c]		Lee 2011[a]	
AEs	Mono (36)	Poly (32)	Mono (68)	Poly (42)	Mono (39)	Poly (21)	Mono (35)	Poly (23)	Mono (65)	Poly (118)	Mono (22)	Poly (58)	Mono (89)	Poly (17)	Mono (19)	Poly (24)	Mono (20)	Poly (30)	Mono (30)	Poly (30)	Mono (41)	Poly (35)	Mono (16)	Poly (13)	Mono (70)	Poly (64)
Local AEs	36 (52.9%)	64 (50%)	28 (8.5%)[¶]		6 (1.4%)	5 (1.2%)	NR	NR	21 (5.7%)	45 (12.3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10 (13.2%)[¶]	7 (9.2%)[¶]	8 (4.2%) **		11 (8.2%)	
Systemic AEs not requiring epinephrine treatment			5 (1.5%)[¶]		0	0	25/1740 (1.4%)[†] (gr 1, 20; gr 2, 5)		0	1* (0.3%)	NR	NR	264/5406 (1.6%)[¥] (gr1, 253; gr3, 11)		NR	NR	NR	NR	NR	NR			6 (3.1%) **		26 (19.4%)	
Severe systemic AEs requiring epinephrine treatment	0	0	0	0	0	0	0	0	NR	NR	NR	NR	0	0	NR	NR	NR	NR	NR	NR	0	0	0	0	0	0

AEs, adverse events; Mono, monosensitized group; NR, not reported; Poly, polysensitized group
The reported numbers are the number of adverse events unless stated otherwise. The percentage is the incidence rate of adverse events per 100 person-years.
[a]Sublingual immunotherapy; [b]Subcutaneous immunotherapy; [c]Monomeric allergoid tablet
[¶]The numbers indicate the number of subjects with reported adverse events. The percentage is the incidence rate of subjects with AEs per 100 person-years.
[†]The number of adverse events per total injection; Percentage is an incidence rate of adverse events per administrations-year; grade 1, localized urticaria, rhinitis or mild asthma (PEF < 20% decrease from baseline); grade 2, slow onset (> 15 min) of generalized urticaria, moderate asthma (PF < 40% decrease from baseline).
[¥]The number of adverse events per total injection: grade 1, one organ system such as cutaneous, upper respiratory or conjunctival; grade 2, either lower respiratory (< 40% PEF or FEV1 drop), gastrointestinal or uterine cramps; grade 3, lower respiratory (asthma with 40% PEF or FEV1 drop, not responding to inhaled bronchodilator) or upper respiratory (laryngeal, uvula, or tongue edema); grade 4, respiratory failure or cardiovascular (hypotension) with or without loss of consciousness; grade 5, death.
*This patient developed wheezing, which recovered after symptomatic treatment. The wheezing reoccurred with subsequent immunotherapy and led to the discontinuation of treatment.
**The numbers indicate the reported AEs that were not classified by type of SLIT received (either grass or HDM).

Adverse events

HDM AIT was generally well-tolerated in both monosensitized and polysensitized groups, irrespective of the route of administration. Overall reported AEs were comparable between the two groups, ranging from 0.3% to 52.9% of the subjects (**Table 4**). Only Tu et al[32] and Song et al[33] studies reported AEs per administration on HDM SCIT with an incidence rate of 1.4% and 1.6%, respectively. Song et al[33] reported 11 grade 3 AEs (0.2%), including asthma attack and airway hyper-responsiveness, which responded well to a single dose of dexamethasone. Ma et al[39] reported the decline of AE incidence over time following HDM AIT from 44.4%-50% at 1 month to 12.5%-16.7% at 12 months. Only Zhang et al[40] study reported that a polysensitized patient who developed 2 episodes of wheezing recovered well with symptomatic medications; however, these AEs led to discontinuing the AIT. None of the studies reported severe systemic AEs resulting in epinephrine administration.

Discussion

This systematic review included 13 studies conducted on patients with allergic rhinitis. HDM AIT in polysensitized patients with allergic rhinitis was as effective in improving TNSS, TMS, CSMS, VAS, and RQLQ as in monosensitized ones. The AEs were mild and comparable between the 2 groups. The immunological indices remained inconsistent and were not predictive of clinical responses. Before implementing this approach to clinical practice, specific issues have to be addressed and considered.

Polysensitization can be categorized into 2 distinct subgroups: cross-reactivity/cross-sensitization and co-sensitization. Cross-reactivity refers to common structures of different allergens that bind to the same sIgE, whereas co-sensitization indicates the concurrent presence of different sIgE that bind to their allergen epitopes. HDM has been known for being cross-reactive with cockroaches and mugwort but not with other non-homologous allergens.[43] Therefore, the simultaneous presence of sIgE to HDM, animal danders, and pollens tends to be co-sensitization rather than cross-reactivity.

HDM allergy in polysensitized patients could be classified into 3 subgroups: 1) HDM as the only clinically relevant allergen and other allergens only being co-sensitized; 2) HDM being major and other non-homologous allergens being minor and relatively less significant in contributing to patient' symptoms; 3) Both HDM and other non-homologous allergens being clinically relevant in contributing to patient' symptoms. The efficacy of HDM AIT should be highest in the first subgroup, diminishing in the second subgroup, and likely least effective in the third subgroup, whose symptoms may fluctuate when exposed to other causal allergens. Based on the details of included studies, polysensitized patients but not polyallergic in Soyyigit et al[34] study were consistent with the first subgroup. In contrast, those in Zhang et al[40] study who were obviously polyallergic were likely consistent with the second subgroup as their clinical responses to HDM AIT were not significantly different from those of monosensitizied ones. In the remaining studies, polysensitized patients with unreported polyallergy status also responded favorably to HDM AIT, indicating that they likely belonged to either the first or the second subgroups.

Adequate maintenance dose of HDM AIT directly affects the clinical effectiveness. The HDM SCIT dosages used in Soyyigit et al,[34] Song et al,[33] and Tu et al[32] studies were close to the dose being demonstrated the efficacy by a controlled clinical trial.[44] The dosages of HDM SLIT drops containing HDM allergens of 50 to 100 μg in most of our included studies were close to the dose being demonstrated the efficacy by a well-designed RCT.[45] Although the SLIT drops used in Kim et al 2019[41], Lee et al[38] studies, and allergoid SLIT tablets in the De Castro et al[42] study differed from those in the remaining studies; they followed the dosing regimens recommended by the manufacturers.

Baseline immunologic indices and their alteration following HDM AIT have been investigated in 4 studies.[34,36,40,41] One of the basophil surface biomarkers reflecting its degranulation in the early phase of allergic reaction is CD203c.[46] At baseline and after HDM AIT, the level of CD203c expression in polysensitized patients was higher than in monosensitized ones, indicating a higher baseline level of allergic inflammation.[34] In addition, polysensitized patients have demonstrated their immunologic shift toward predominant type 2 cytokines, as evidenced by an increase in IL4 and a decrease in IL10 and IFNγ levels.[47,48] Of interest, a reduction in type 2 cytokines following HDM AIT was observed by Zhang et al[40] study with no difference between monosensitized and polysensitized patients.

Biomarkers associated with clinical responses following AIT have been extensively studied, some of which were assessed in our included studies. Soyyigit et al[34] reported that the sIgE/total IgE ratio was significantly higher in polysensitized patients; however, no correlation was found between the ratio and clinical responses. The sIgE/total IgE ratio was reported to be a valuable biomarker for predicting effective responses to HDM AIT in monosensitized patients, with a sensitivity and specificity of 97.9 % and 93.1 %, respectively.[49] However, another open-labeled RCT was unable to replicate the benefits of this ratio.[50] An additional potential biomarker is allergen sIgG4, a blocking antibody that competes with allergens for binding with sIgE on mast cells and basophils.[51] The studies examining the relationship between increased sIgG4 and improved clinical outcomes following HDM AIT showed inconclusive results.[52,53] Of note, a more significant increase in sIgG4 in monosensitized subjects in Kim et al 2019[41] was not predictive of AIT responders.

This systematic review and meta-analysis carry some limitations. First, all of the included studies were observational in design. Thus, the meta-analytic results were subjected to confounding and should be interpreted with caution. We have provided the summary tables with ratings on the quality of evidence according to GRADE to emphasize the certainty of each pooled outcome. Second, the clinical efficacy of AIT in monosensitized and polysensitized patients was evaluated without placebo as a control group. However, the superiority of HDM AIT over placebo has been repeatedly demonstrated by previous RCTs.[45,54] Therefore. the efficacy

of HDM AIT, which may differ between the 2 groups, could be evaluated through non-randomized studies in which the monosensitized patients would serve as a control group. In addition, substantial real-world evidence from non-randomized studies will complement RCTs with rigorous methodology.[55] Third, the total number of patients included within the quantitative synthesis was relatively low and may not contain sufficient power to identify minimal clinically important differences in treatment effects. A trial sequential analysis was one alternative to help conclude the futility of the results;[56] however, owing to statistical reasons, the trial sequential analysis could not be performed for the standardized mean difference.[57] Finally, several outcome values used during analysis were not directly reported in the included original articles and, therefore, had to be extracted from graphs, imputed, or calculated from other reported values. This certainly affects the quality of data and the pooled results. However, we believed that the effects would be minimal as standard methods were used as references, and leave-one-out sensitivity analyses of all outcomes showed robust and consistent results.

In conclusion, since HDM allergens may play a dominant role in specific subgroups of polysensitized patients, thus, carefully selecting clinically relevant HDM-allergic patients to be treated with HDM AIT could be a reasonable treatment option as opposed to being restricted to monosensitized ones.

Acknowledgement

We thank Professor Harold S. Nelson, MD, for his valuable comments on the manuscript. This study was partially supported by the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, and the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Conflict of interests

The authors declare the following financial interests/relationships which may be considered as a potential conflict of interests:

- P. Phinyo, T. Krikeerati, and P. Wongyikul declare no conflict of interests;
- M. Lao-Araya has received honoraria for scientific lectures from Abbott, A. Menarini, Astra-Zeneca, GSK, Novartis, Organon, Takeda, and Viatris
- T. Thongngarm has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, Sanofi, Takeda, and Viatris; research supports from Abbott and Sanofi; has served on the advisory board for Sanofi and Viatris.

Funding

No funding has been received for this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

T. Krikeerati is an essentially intellectual contributor involving in research design, data analysis, data interpretation, result summary, comprehensive comments, and writing the manuscript.

Ethics approval

Ethics approval was considered exempt due to the nature of systematic review and meta-analysis.

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