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Comparison of adverse events between cluster and conventional immunotherapy for allergic rhinitis patients with or without asthma: A systematic review and meta-analysis

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ABSTRACT

Background: Cluster schedule of allergen-specific immunotherapy (AIT) is a cost-effective choice for allergic rhinitis (AR) patients, but its safety has been questioned due to the greater dosages required at each treatment compared with conventional immunotherapy. It remains a question that whether cluster schedule leads to a higher risk of side effects.

Objective: This study was designed to update the evidence and investigate whether cluster schedule leads to a higher risk of local adverse reactions (LARs) and systemic adverse reactions (SARs) than cluster schedule does.

Methods: We searched the Cochrane Central Register of Controlled Trials, EMBASE and Medline thoroughly and included studies comparing cluster and conventional schedules. A meta-analysis of 5 outcomes related to adverse events was performed after bias and heterogeneity assessments. And as a result of language limitations, we considered only articles in Chinese and English.

Results: 5 observational studies and 6 interventional studies were included in the meta-analysis. There were no differences between cluster and conventional schedules when analyzing SARs by the number of patients, delayed SARs, grade 2 SARs and LARs. Analyses of SARs by injection, grade 1 SARs and LARs by injection in observational studies showed that cluster schedule had a lower risk of adverse events than did conventional schedule.

Conclusion: Our data suggest that cluster schedule is as safe as or even safer than conventional schedule for AR patients with or without asthma (AS).

1. Introduction

Allergen-specific immunotherapy (AIT) is an important treatment strategy for allergic rhinitis (AR) patients with or without asthma (AS). AIT is currently the only curative intervention that potentially rebalances the immune system and thus affects the natural course of allergic disease. The long-term efficacy and safety of AIT have been confirmed by many clinical trials and studies. Moreover, AIT can prevent the development of new sensitization [1] and prevent development of AR into AS [2,3].

Subcutaneous immunotherapy (SCIT) is the most universal route and its efficacy has been widely confirmed in clinical trials. The standard procedure of SCIT contains two phases: a dose-increase phase and a maintenance phase. Depending on different dose-increase regimens, SCIT can be divided into conventional schedule, cluster schedule and rush schedule. With conventional schedule, one injection is administered per week, and a period of approximately 15 weeks is needed before reaching the maintenance dose. With cluster schedule, 2–3 injections are administered on a weekly visit, so the duration to reach the maintenance dose is shortened. Compared with conventional schedule, the cluster schedule cuts the time of the dose-increase phase nearly in half, so it is more convenient and more cost-effective for patients. However, this raises a question that whether cluster schedule leads to a higher risk of side effects and patients who are susceptible to adverse reactions should choose conventional schedule for safety concern. This systematic review aims to analyze the relevant literature comparing the risk of adverse reactions between these 2 schedules and provide evidence for clinical practice.

Abbreviations: AIT, allergen-specific immunotherapy; AR, allergic rhinitis; AS, asthma; LARs, local adverse reactions; SARs, systemic adverse reactions; SCIT, subcutaneous immunotherapy; RCTs, randomized controlled trials; PAR, perennial(or persistent) allergic rhinitis; SAR, seasonal allergic rhinitis; IAR, intermittent allergic rhinitis

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2. Material and methods

2.1. Criteria of studies for this review

2.1.1. Types of studies

Considering that adverse reactions during allergen immunotherapy are rare, we decided to include both randomized controlled trials (RCTs) and other studies such as nonrandomized controlled trials, case-control studies, cross-sectional studies and both prospective and retrospective cohort studies, provided that they included a comparison of adverse events between cluster and conventional schedule therapies.

2.1.2. Types of participants

Patients suffering AR with or without AS were qualified regardless of their age, gender, kinds of allergens, duration and severity of disease and other coexisting conditions. All patients underwent objective examinations such as positive skin prick tests and elevated serum allergen-specific IgE tests to confirm their allergies.

2.1.3. Types of interventions

Conventional immunotherapy involves a dose accumulation phase of 8–16 weeks, and one injection is given on a weekly basis; on the other hand, cluster immunotherapy involves 2–3 injections given during one visit at intervals of 30 min, and the dose maintenance phase is reached within 8 weeks. After the build-up phase, patients under both schedules receive weekly injections until the end of the treatment. Studies involving only the dose accumulation phase or both phases of these 2 schedules were considered.

2.1.4. Types of outcome measures

Five aspects of adverse events related to AIT were analyzed: systemic adverse reactions (SARs), delayed SARs (happened 30 min after treatment), severity of SARs on the basis of a grade system in accordance with grading guidelines, local adverse reactions (LARs), delayed LARs (happened 30 min after treatment).

2.2. Search methods for the identification of studies

Published and unpublished articles in the EMBASE (1974 to 2019 February 01), Medline (1946 to February 01, 2019) and Cochrane Central Register of Controlled Trials (December 2018) databases were searched via OvidSP. The Medline search strategy is presented below, and the strategy when querying other databases was reorganized on the basis of the following example:

Search Strategy:

1 1 exp. Rhinitis, Allergic/ or exp Rhinitis, Allergic, Seasonal/ or exp Rhinitis, Allergic, Perennial/ (20374)
2 (allergic rhinitis or atopic rhinitis or (SAR or IAR or PAR)).af. (163365)
3 (hayfever or pollinosis or pollenosis or (hay and fever)).af. (5810)
4 ((allergen* or aeroallergen*) and rhinitis).af. (10767)
5 1 or 2 or 3 or 4 (177152)
6 exp immunotherapy/ or exp desensitization, immunologic/ (258009)
7 (immunotherapy or immunomodula*).af. (153720)
8 (immune or allergen* or antigen* or desensiti*).af. (1475094)
9 (therapy or vaccin* or inject*).af. (4559197)
10 8 and 9 (383754)
11 (cluster or accelerat*).af. (451277)
12 6 or 7 or 10 (634209)
13 5 and 11 and 12 (123)

2.3. Data extraction and analysis

2.3.1. Data extraction

Each study was viewed by 2 researchers. Four aspects of the data, including details of study design and methodology, characteristics of the population, description of the interventions and the statistics of the outcome measures, were collected with a prepared extraction sheet.

2.3.2. Quality assessment

The risk of bias of studies was assessed according to the Cochrane Collaboration tool and other scales recommended in the Cochrane handbook, such as the Newcastle-Ottawa Scale (NOS) for cohort studies and case-control studies. A total score more than or equal to 6 for NOS is qualified.

2.3.3. Data analysis

RevMan 5.3 was used for data processing. Trials and observational studies were analyzed separately. Chi-squared tests and the I^2 statistic were performed to assess heterogeneity, with $P < 0.1$ and $I^2 > 50\%$ indicating significant differences between studies and the necessity to develop critical explanations. The outcome measures mentioned above were all dichotomous. The Mantel-Haenszel method under fixed-effect model was used for analysis, and relative risks (RR) with 95% confidence intervals (CIs) were used to evaluate the safety of the schedules. All the tests were two-tailed. Sensitivity analysis and subgroup analysis would be applied when necessary.

3. Results

3.1. Description of studies

A total of 423 reports were identified through database searching, and 4 additional reports were identified from the reference lists. After removing duplicates, 359 records remained, of which 28 records were further assessed. Six studies were excluded because of the absence of full texts [4–9], 1 was excluded for repeated data [10]; therefore, 21 full-text articles were examined. Finally, 11 studies, including 5 RCTs [11–15] (1 full text was obtained by sending an e-mail request to the author [15]), 1 nonrandomized controlled trial [16] and 5 observational studies [17–21], met the eligibility criteria. The flow diagram of the study selection is illustrated in Fig. 1. The reasons for excluding the other 10 studies are as follows:

Five studies did not use a standardized conventional schedule [22–24] or cluster schedule [25,26],

One study compared a cluster schedule with a placebo [27],

Two were excluded for insufficient data [28,29], and

Two investigated only patients under the cluster schedule [30,31].

A total of 643 patients were investigated in the included trials: 319 were administered AIT under a cluster schedule, and 324 were administered AIT under a conventional schedule as a control (Table 1a). Five observational studies involved a population of 1907 participants: 966 were administered AIT under a cluster schedule, and 941 were administered AIT under a conventional schedule. Additional details about the characteristics of the studies are shown in Table 1b.

3.2. Risk of bias in the included studies

The risk of bias evaluation for trials was performed as recommended by the Cochrane handbook [32] and the accredited Newcastle-Ottawa Scale was used to evaluate the observational studies (Fig. 2 and Table 2). The result showed acceptable bias in all included studies.

3.3. Effects of interventions

Considering design heterogeneity, trials and observational studies were analyzed separately. SARs and LARs were assessed by counting

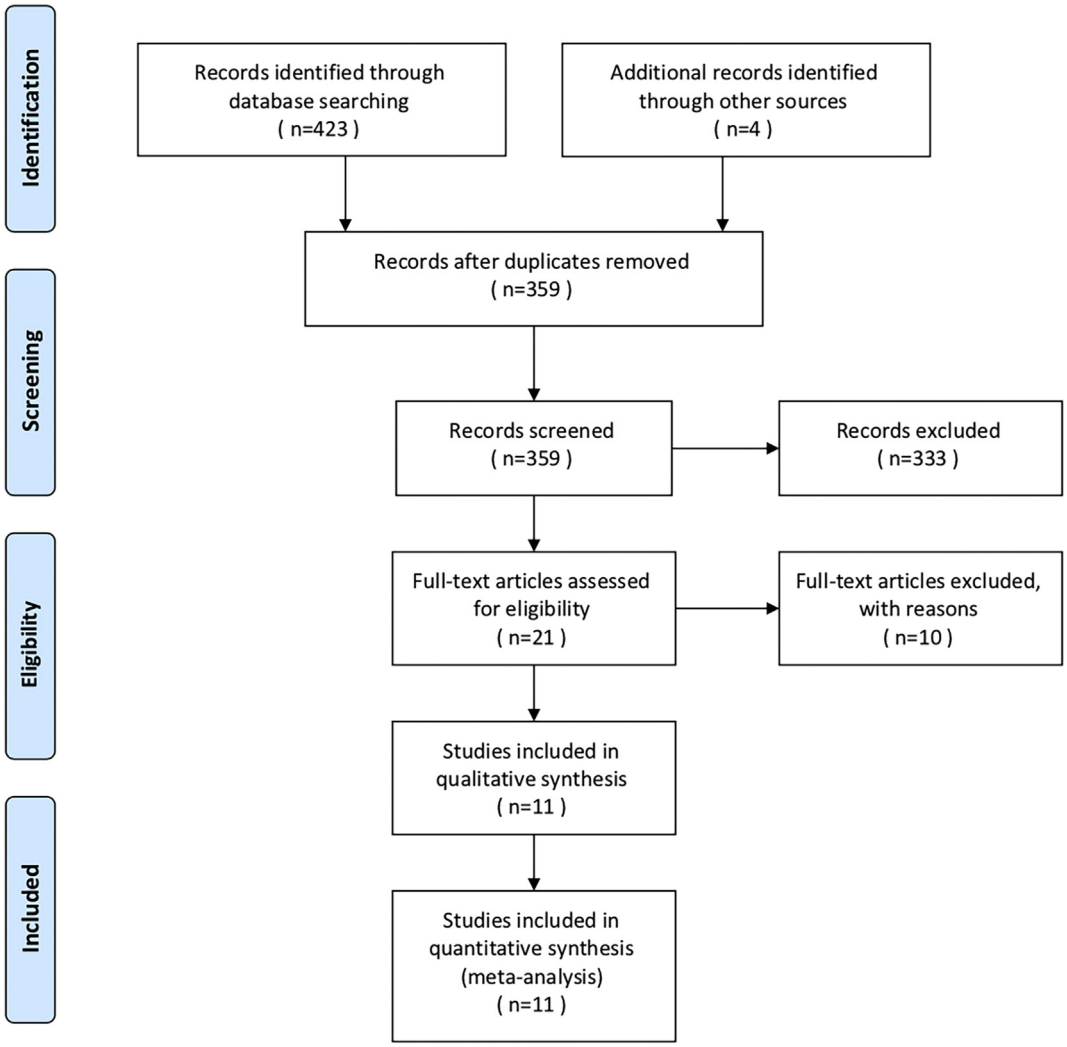


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram.

the number of injections and participants.

3.3.1. Systemic adverse reactions in the build-up phase (by injection and by patient)

4 trials [11–13,16] reported systemic reactions during the initial phase by injection. A total of 3514 doses were administered to patients under the cluster schedule, and 3293 doses were administered under the conventional schedule, with incidence rates of systemic reactions of 19 and 22, respectively. No difference (RR = 0.89; 95% CI 0.49–1.64; $P = 0.72$) and low heterogeneity ($P = 0.77$; $I^2 = 0\%$) was discovered between groups. 139 patients received cluster regimen and 142 patients received the conventional regimen in 4 trials [12,13,15,16], with 20 and 17 patients, respectively, having systemic reactions. Analysis showed low heterogeneity between studies ($P = 0.76$; $I^2 = 0\%$) and no differences in the effects of the 2 regimens (RR = 1.23; 95% CI 0.69–2.19; $P = 0.49$).

3 observational studies [17,19,20] reported SARs data by injection during the initial phase including 4830 and 4006 injections in the cluster and conventional groups, with 17 and 29 total cases of SAR, respectively. The cluster schedule group was at a lower risk of SARs (RR = 0.47; 95% CI 0.25–0.88; $P = 0.02$) than was the conventional schedule group although significant heterogeneity was observed ($P = 0.01$; $I^2 = 77\%$;) (Fig. 3). 19 out of 914 patients in the cluster group and 29 out of 899 patients in the conventional group experienced SARs in 4 observational studies [17,19–21]. The tests for overall effect showed no significant differences between 2 groups (RR = 0.59; 95% CI 0.33–1.06).

3.3.2. Severity of systemic reactions in the build-up phase

4 trials [11–13,16] classified SARs by injection according to the guidelines of the Immunotherapy Subcommittee of the European Academy of Allergology and Clinical Immunology (EAACI) [33]. No grade 3 or grade 4 SARs were reported. There was no significant difference in the SAR incidence between the cluster and conventional schedule groups for grade 1 SARs (RR = 0.90; 95% CI 0.37–2.16; $P = 0.81$) and grade 2 SARs (RR = 0.89; 95% CI 0.38–2.07; $P = 0.79$) with accredited heterogeneity.

Analysis for 3 observational studies [17,19,20] indicated that the cluster schedule group was less likely to present grade 1 SARs (RR = 0.28; 95% CI 0.13–0.62; $P = 0.002$), although heterogeneity was observed between studies ($P = 0.09$, $I^2 = 58\%$) (Fig. 4a). For grade 2 SARs, the test revealed no difference (Fig. 4b).

3.3.3. Delayed systemic reactions

Two trials [12,14] reported no late-phase systemic reactions, while another trial reported that all SARs occurred after 30 min [16]. Thus, analysis was not applicable.

No difference was observed between cluster and conventional schedules according to the result for observational studies (Fig. 5).

Table 1a
Characteristics of the trials.

	Study design	Schedule	No. of patients	Age	Patients withdrawn	Patients with AR and AS	Vaccine	Build-up phase	Premedication	Outcomes
Fan, Q 2017	Controlled trial	Cluster	30	23.5 (8.5–20)	2	5	*D. pteronyssinus* extract (Alutard SQ, ALK-Abelló)	6w	–	SAR, clinical efficacy
		Conventional	30	22.0 (5.5–32.5)	1	4		14w	–	
Tabar, A.I 2005	Double-blind RCT	Cluster	120	19.34 ± 9.8*	13	94	Pangramin Depot UM D. pteronyssinus (ALK-Abello)	6w	–	SAR, LAR, PEF, VAS, SPT, sIgE, IgG, IgG4, etc.
		Conventional	119	18.47 ± 9.49*	9	82		12w	–	
Wang, C.S 2011	RCT	Cluster	40	26 (18,38)	2	0	D. pteronyssinus extract (Alutard SQ, ALK-Abelló)	6w	–	LAR, SAR, T5SS, medication score, sIgE, IgG4
		Conventional	40	26 (16,42)	1	0		14w	–	
Zhang, L 2009	RCT	Cluster	48	25 (15–36)	3	7	D. pteronyssinus extract (Alutard SQ, ALK-Abelló)	6w	Loratadine	LAR, SAR, medication score, QOL, VAS, SPT, IgE, etc.
		Conventional	48	25 (12–34)	4	8		14w		
Luo, Z 2015	RCT	Cluster	53	–	1	0	D. pteronyssinus extract (Alutard SQ, ALK-Abelló)	6w	Cetirizine	SAR, RQLQ, medication score, clinical efficacy, etc.
		Conventional	57	–	7	0		15w		
Sandilos, C 2016	RCT	Cluster	28	34.45 ± 13.575*	0	35	Stallergenes (France) and Inmunotek (Spain)	3w	–	SAR
		Conventional	30		0			7w	–	

Note: "*": Data in these cells is described by the mean ± standard deviation, while others is presented as median (25–75th percentiles). "–": Data is not available. AR: allergic rhinitis. SAR: systemic adverse reaction. LAR: local adverse reaction. PEF: peak expiratory flow. VAS: visual analog scale. SPT: subcutaneous prick test. T5SS: total 5 symptom score. QOL: quality of life. RQLQ: mini rhinoconjunctive quality of life questionnaire.

Table 1b
Characteristics of the observational studies.

	Study design	Schedule	No. of patients	Age	Patients withdrawn	Patients with AR and AS	Vaccine	Build-up phase	Premedication	Outcome
Garde, J. 2005	Prospective	Cluster	66	28 ± 11.6	4	19	*Salsola kali* (25 BU/ml, Pangramin® Depot BU, ALK-Abelló, S.A.)	4w	No	LAR, SAR
		Conventional	22					13w		
Martines-Canavate, A. 2005	Retrospective	Cluster	52	9.6 ± 3.1	–	60	*Alternaria alternata* 100% (Pangramin® Depot-UM, ALK-ABELLÓ)	4w	–	LAR, SAR
		Conventional	42					7w		
Barth, C. 2010	Retrospective	Cluster	72	31 (6–71)*	11	43	Allergopharma-Joachim Ganzer, ALK-Scherax, Bencard Allergie, HAL Allergie, Leti Pharma and Stallergenes	–	–	LAR, SAR
		Conventional	75					–		
Quiralte, J. 2013	Retrospective	Cluster	339	26.2 ± 13.3	–	164	Alustal Rapid®, Stallergenes Ibérica SA	4w	–	LAR, SAR
		Conventional	319	26.7 ± 13.8		143		8w		
Rodriguez Del Rio 2017	Prospective	Cluster	437	11.7 ± 3.9	–	–	Mites, pollen, alternaria, dander	–	–	SAR
		Conventional	483					–		

Note: "*": Data in this cell is presented as mean(range), while others are presented as mean ± standard deviations. "–": Data is not available. AR: allergic rhinitis. LAR: local adverse reaction. SAR: systemic adverse reaction.

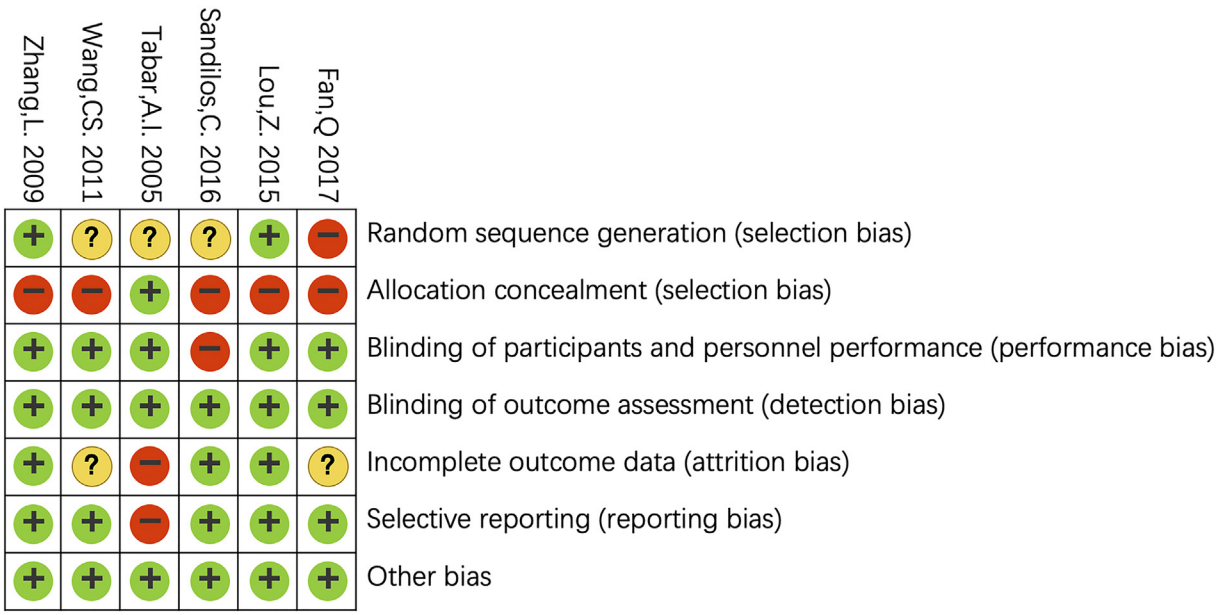


Fig. 2. Risk of bias summary for the included trials.

Table 2
Newcastle-Ottawa Scale results for the observational studies.

	Garde, J 2005	Martines Canavate, A. 2005	Barth, C.2010	Quiralte, J. 2013	Rodriguez Del Rio, P 2017
Selection					
Representativeness of the exposed cohort	1	1	1	1	1
Selection of the nonexposed cohort	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1
Demonstration that outcome of interest was not present at start of study	1	0	0	0	1
Comparability					
Comparability of cohorts on the basis of the design or analysis	0	0	0	2	1
Outcome					
Assessment of outcome	1	1	1	1	1
Was follow-up long enough for outcomes to occur	1	1	1	1	1
Adequacy of follow up of cohorts	1	1	1	1	1
Total	7	6	6	8	8

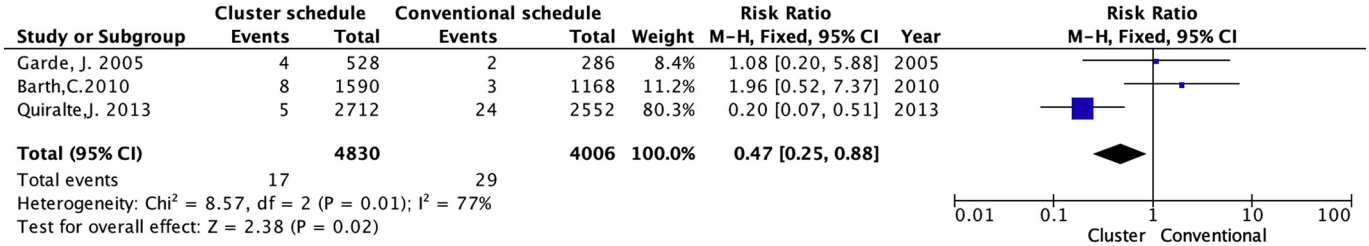


Fig. 3. SARs in the build-up phase by injection in observational studies.

3.3.4. Local adverse reactions in the build-up phase (by injection and by patient)

Only 2 trials [12,16] reported LARs, including 22 LAR cases out of 1026 injections in the cluster schedule group and 24 LAR cases out of 1112 injections in the conventional schedule group, during the build-up phase. Test showed no significant difference (RR = 1.01; 95% CI 0.57–1.78; $P = 0.99$) with a I^2 value of 0%. There was not enough data for analysis by patient.

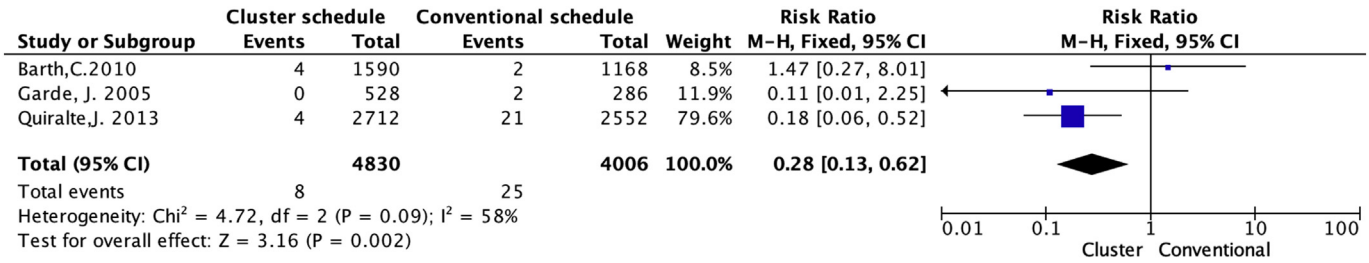
Three observational studies [17,19,20] reported LARs, including 219 LAR cases out of 4830 injections in the cluster schedule group and 303 LAR cases out of 4006 injections in the conventional schedule group. Test indicated that cluster schedule caused a lower risk of LARs in the build-up phase (RR = 0.64; 95% CI 0.54–0.76; $P < 0.0001$) (Fig. 6) with heterogeneity ($I^2 = 67\%$; $P = 0.05$). No difference in LARs by patient between 2 groups (RR = 1.00; 95% CI 0.79–1.28; $P = 0.98$).

3.3.5. Delayed local adverse reactions

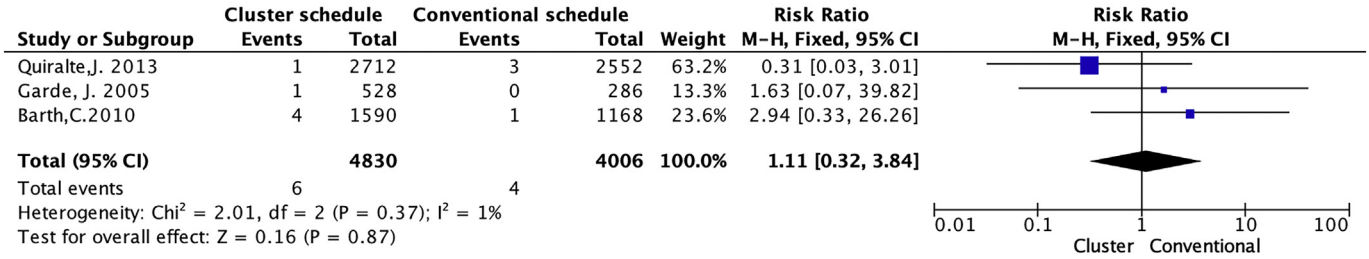
The data were insufficient for analysis.

3.3.6. Sensitivity analysis and publication bias

We made a sensitivity analysis by adding studies which was excluded for lacking full texts. Data relevant to our outcomes were acquired from the abstracts of 2 studies [6,8] and pooled into analysis for SARs by patient. The result illustrated that the risk of SARs by patient in



(a)



(b)

Fig. 4. a. Grade 1 SARs in observational studies.
b. Grade 2 SARs in the observational studies.

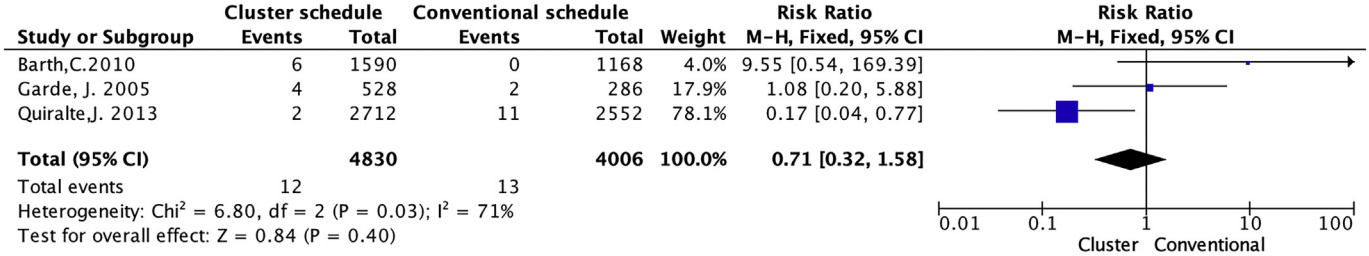


Fig. 5. Delayed SARs in observational studies.

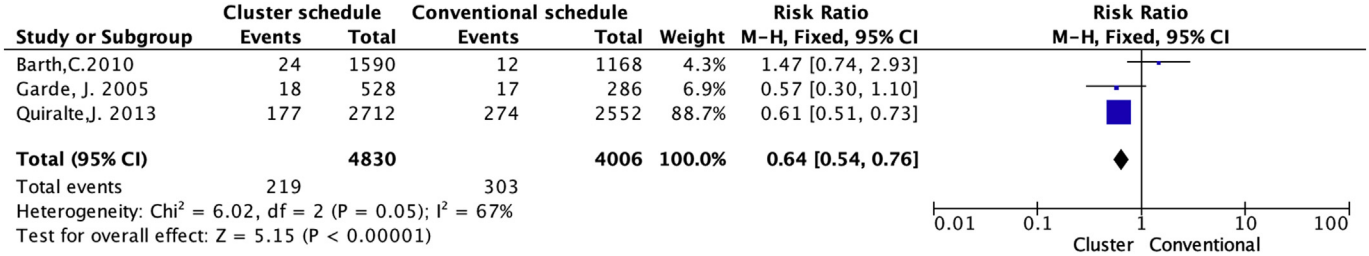


Fig. 6. LARs in the build-up phase by injection in observational studies.

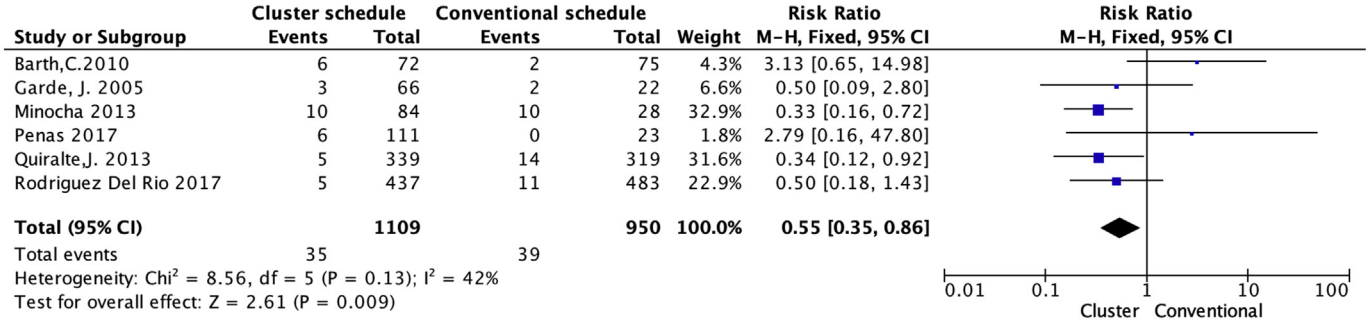


Fig. 7. SARs by patients in included observational studies and 2 observational studies lacking full texts.

cluster group is significantly lower (RR = 0.55; 95% CI 0.35–0.86; $P = 0.009$) with an acceptable heterogeneity ($I^2 = 42\%$; $P = 0.13$) (Fig. 7). The number of studies was inadequate for analyzing publication bias.

4. Discussion

As presented above, we analyzed statistics from trials and observational studies separately. Among the included studies, we detected statistical heterogeneity in some observational studies thus the result should be interpreted critically.

The tests for all outcomes in included trials showed a similar risk of adverse events between 2 schedules. However, significant lower RRs of cluster schedule were revealed in observational studies with respect to SARs in the build-up phase by injection, grade 1 SARs and LARs in the build-up phase by injection because of high statistical heterogeneity between Quiralte, J's study and others, which may indicate some publication bias.

Here, we attribute the variance to 4 main reasons. First, rare adverse events are less likely to be observed in clinical trials when the sample size is small. Apart from the double-blind RCT by Tabar [11], which included 239 individuals, the trials all included a relatively small sample size, although analyses by the number of injections could enlarge the sample size and eliminate some errors.

Second, every participant was given an antihistamine drug before the injections as premedication in 2 trials [12,14], 1 cohort study [17] reported no pretreatment, and relevant information was not available in the other studies. Previous studies suggested that premedication such as antihistamines and leukotriene antagonists could significantly reduce the incidence of adverse reactions [34,35]; however, further studies are necessary to confirm this idea.

Third, the duration of the dose-increasing phase and the number of doses administered at each visit were well controlled in the trials, except for one [15], but were variable in the observational studies. Finally, different types of allergens, including pollen, fungi, dander and mites were considered in the observational studies. In contrast, all but one trial applied vaccines of dust mite only.

Beyond the aforementioned factors, there are still some other varying elements, such as age and sex distribution and the number of patients with asthma, which may contribute to heterogeneity.

A 10-year retrospective study demonstrated that half of the systemic reactions to AIT were delayed and 10% occurred after 90 min when patients had already left the hospital [36]. Most of these reactions required medical treatment. Therefore, more attention should be paid to delayed reactions when assessing the risk of adverse reactions to immunotherapy.

Sensitivity analysis for included studies was not necessary since only one study showed inconsistent result, while analysis by adding 2 observational studies lacking full texts showed cluster schedule had lower hazard to develop SARs. This could be reliable because of acceptable statistical heterogeneity between studies.

5. Conclusion

Based on the above outcomes analyzed, our study suggests that cluster schedule is as safe as or even safer than conventional schedule for AR patients with or without AS. Large-scale and well-controlled RCTs are needed to address whether the exact duration of the build-up phase and the number of injections per visit for each schedule influence the occurrence of adverse reactions.

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