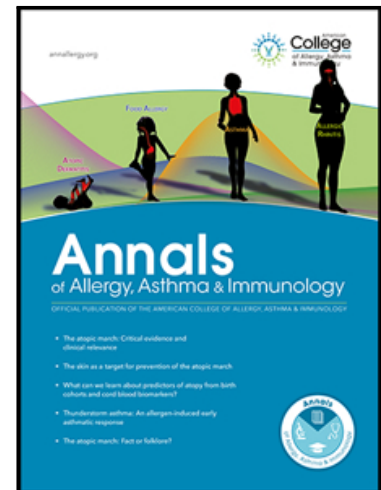


Antihistamine Premedication Improves Safety and Efficacy of Allergen Immunotherapy

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Title: Antihistamine Premedication Improves Safety and Efficacy of Allergen Immunotherapy.

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Key words: Allergen immunotherapy, antihistamine premedication, randomized clinical trials; systemic allergic reactions; target maintenance dose.

Abbreviations

AR Allergic rhinitis

AIT Allergen Immunotherapy

AE Adverse event

CI Confidence interval

IVA Insect venom allergy

LR Local reaction

OR Odds ratio

OIT Oral immunotherapy

PRISMA Preferred Reporting Items for Systemic Reviews and Meta-Analyses

RCT	Randomized controlled trial
SAR	Systemic adverse reaction
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SU	Sustained unresponsiveness
TMD	Target maintenance dose
VIT	Venom immunotherapy

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Background: Allergen immunotherapy (AIT)-associated adverse events are a major concern for safety and efficacy of AIT. Presently, there is no consensus to whether antihistamine premedication could improve such conditions.

Objective: To identify the superiority of antihistamine pretreatment in AIT.

Methods: A comprehensive literature search for randomized controlled trials (RCTs) reporting the effects of antihistamine premedication on safety and efficacy of AIT was performed in MEDLINE, Embase and Cochrane Library databases. Safety was assessed according to the number of patients reporting systemic adverse reactions (SARs; the primary outcome), efficacy according to the number of patients achieving target maintenance dose (TMD) and sustained unresponsiveness (SU) to allergen. Results: Eleven RCTs (including 609 patients) satisfied the inclusion criteria for the meta-analysis. All premedication protocols were temporary. Pooled analysis demonstrated that compared to control patients, significantly fewer antihistaminepretreated patients reported total and moderate-to-severe SARs (OR= 0.36; 95%CI,

0.23 to 0.56, $P<0.05$; and OR= 0.20; 95%CI, 0.06 to 0.74, $P<0.05$; respectively), as well as total and moderate-to-severe SAR episodes (OR= 0.42; 95%CI: 0.34 to 0.53, $P<0.05$; and OR= 0.09; 95%CI: 0.01 to 0.50, $P<0.05$; respectively). Similarly, antihistamine pretreatment significantly increased the number of patients achieving TMD (OR= 2.94; 95%CI: 1.72 to 5.03, $P<0.05$), but not SU (OR= 1.65; 95%CI: 0.77 to

3.54, $P=0.2$), compared with the control group. Subgroup analysis according to different allergens and dose escalating approaches also displayed superiority of antihistamine pretreatment over control.

Conclusion: Antihistamine premedication can significantly improve safety and efficacy of AIT by reducing frequency and severity of SAR and increasing TMD.

Introduction

Allergy is a common disorder that affects 20%-30% of the overall population throughout the world.^{1,2} The condition impairs the work and school performance of affected individuals, can lead to depression and mental illness, and impose a huge economic burden.³ Moreover, sometimes it may become life-threatening, for example when there is exacerbation of comorbid allergic asthma. Although recent

decades have seen tremendous advances in the diagnosis and treatment of allergic diseases, there is still increasing concern regarding the marked morbidity resulting from allergic disease.

Allergen immunotherapy (AIT) is the only potential disease-modifying treatment for allergic diseases.⁴ The typical process of AIT involves regular administration of increasing doses of sensitising allergen to a target maintenance dose (TMD). AIT aims to achieve sustained unresponsiveness (SU) when an allergic patient is challenged with specific allergen again. AIT involves administration of the allergen via different routes; including subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT) and oral immunotherapy (OIT).⁵ Furthermore, AIT can be administered according to different up-dosing schedules, classified as conventional, cluster and rush immunotherapies;⁶ of which the latter two are accelerated forms involving shorter treatment periods of immunotherapy.

Adverse events (AEs), which can be local or systemic, attract much attention during AIT. Local reactions (LRs) include erythema, pruritus at the injection site (in SCIT) or oromucosal symptoms (in SLIT),⁴ whereas systemic reactions (SRs) can manifest as allergic reactions including asthma, urticaria, and anaphylaxis.⁷ In general most AEs are LR, which appear within 30 minutes after allergen administration.⁸ In contrast, SRs appear with frequent contact with allergens, especially in rush schedule and can be severe.⁷ Frequent or severe SRs sometimes stop patients from continuing with and completing the prescribed course of AIT.

Prescription of antihistamines before AIT might serve as an alternative to improve the safety of AIT. The majority of studies reporting premedication have generally involved rush protocols in SCIT, and to a lesser extent cluster protocols or OIT. To date, no study has reported premedication in SLIT. Premedication is usually recommended one or two hours before administration of the first dose of AIT on the day.⁹⁻¹¹ However, presently there is no consensus regarding the effect of antihistamine premedication on improvement in safety of AIT. The EAACI Guidelines on AIT for allergic rhinoconjunctivitis recommend premedication with an antihistamine because it reduces the frequency and severity of local and systemic cutaneous reactions, despite not eliminating the risk of other systemic reactions.¹² Similarly, the EAACI Guidelines on AIT for Hymenoptera Venom Allergy¹³ recommend premedication with an antihistamine as it can improve the tolerability of venom immunotherapy as well as reduce large local reactions and to some extent also systemic adverse events.^{9,10,14,15} The evidence for antihistamine pretreatment in AIT for house dust mite-driven allergic asthma and food allergy, however, is still lacking.^{16,17} On the other hand, whether the efficacy of AIT can be influenced by antihistamine also remains unclear. Thus, we have conducted a meta-analysis of studies involving premedication with antihistamines to determine whether these agents might contribute to improvements in safety and efficacy of AIT.

METHODS

This meta-analysis was conducted in full accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) Statement.¹⁸

Search strategy and selection criteria

The MEDLINE, Embase and Cochrane Library databases up to Aug 2020 were searched for randomized controlled trials (RCTs) evaluating the effect of antihistamine premedication on AIT in patients with an allergic condition. The literature search was limited to papers published in English, with no set time limit of publication. Studies were initially identified by a combination of medical subject headings and free terms, which were limited to the title and abstract. The search terms and strategies utilized in MEDLINE were as follows:

#1 "Premedication"[Mesh] OR Pretreatment

#2 "Histamine H1 Antagonists"[Mesh] OR "Loratadine" [Mesh] OR "Desloratadine" [Mesh] OR "Cetirizine" [Mesh] OR "Levocetirizine" [Mesh] OR "Fexofenadine" [Mesh] OR "Terfenadine" [Mesh] OR "Olopatadine Hydrochloride"[Mesh]

#3 "Immunotherapy" [Mesh] OR "Allergen specific immunotherapy" OR "Subcutaneous immunotherapy" OR "Sublingual Immunotherapy" [Mesh] OR Oral immunotherapy OR Conventional immunotherapy OR Accelerated immunotherapy OR Cluster immunotherapy OR Rush immunotherapy OR "Desensitization, Immunologic" [Mesh]

#4 "Rhinitis, Allergic"[Mesh] OR "Hypersensitivity"[Mesh]

#5 "Randomized Controlled Trial" [Publication Type] OR randomized OR placebo

#6 #1 OR #2

#7 #3 AND #4

#8 #5 AND #6 AND #7

The Embase and Cochrane Library databases were also searched for appropriate publications employing similar logical rules. Reference lists from the published papers and other appropriate reviews were additionally examined for potential studies meeting inclusion criteria, which had not been highlighted by the literature search of the MEDLINE, Embase and Cochrane Library databases.

Study selection and data extraction

Two independent investigators (LW, CW) evaluated the titles and abstracts of all publications for potential inclusion in the meta-analysis, and then assessed the full texts to select eligible studies. Studies were excluded for any of the following reasons: (1) case reports, reviews, observational studies, (2) no definite diagnosis criteria cited, (3) premedication without antihistamines, and (4) trials with inadequate clinical data.

Data from each eligible article were extracted as follows: (1) research region (2) disease and allergen, (3) type of AIT, (4) pretreatment regimens, (5) total numbers of patients in each trial, (6) numbers of patients with systemic adverse reactions (SAR)

and numbers of SAR episodes, (7) patient numbers and episode numbers of moderate to severe SAR, and (8) patient numbers achieving TMD and SU.

The included studies all compared the effects of antihistamine premedication with control group; without limitation posed on the protocols of antihistamine premedication. All subjects had a definite diagnosis of specific allergy. SARs were evaluated according to frequency and severity. Frequency was analysed by total number of patients reporting a SAR and total SAR episode numbers and severity was measured by total patient number and episode numbers of moderate to severe SAR. The total number of patients reporting SAR was selected as the primary endpoint and TMD and SU, which can be regarded as indicators of efficacy of AIT, were assessed as the secondary endpoints. To evaluate the correlations between TMD and SU, we analyzed three RCT studies reporting both TMD and SU.^{11,15,19} SAR severity in most studies was classified according to three levels: mild (transient or could be easily tolerated); moderate (causing discomforting and disrupting usual activities, but respond well to related medication) and severe (anaphylactic shock or other life-threatening onset).

Data from studies included in the meta-analysis were extracted and analysed by two investigators (LW, CW), and in case of any disagreement, were further evaluated by a third investigator (HL or LZ), until a consensus was reached among all parties involved.

Quality assessment

The quality of each study included in the meta-analysis was rated independently by two reviewers, in accordance with the Cochrane Collaboration tool for assessing risk of bias (<https://training.cochrane.org/handbook/current>, Accessed 14 Aug, 2020). A bias graph was prepared using Revman version 5.4 software (<https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>, Accessed 14 Aug, 2020). Any disagreement was resolved by further discussion among the reviewers and a consensus was reached accordingly.

Statistical analysis

Data included were analyzed using the software Revman version 5.4. Meta-analysis was performed to compare safety and efficacy of AIT in patients with and without antihistamine premedication. SAR, TMD and SU were all dichotomous variables, of which, differences were measured by weighted associated odds ratios (ORs) with 95% confidence interval (CI) in the different groups. To determine the potential impact of dose-escalating protocols and/or sensitizing allergens, a comprehensive subgroup analysis was carried out to estimate the effect of antihistamine pretreatment on the safety and efficacy of AIT. Descriptive analysis was performed for data that were not combinable.

The level of heterogeneity between the studies was assessed using the Chi-squared (χ^2) and I^2 test; with the P value <0.1 or $I^2 >50\%$ regarded to be moderate-to-high heterogeneity. The random effect model was applied for an instance of considerable

heterogeneity, or else the fixed effect model was applied. Test for overall effect was also considered as statistically significant when P was <0.05 . Pearson correlation coefficient r and P value were calculated by Graphpad Prism (Version 8.0.2 GraphPad Software, Inc., La Jolla, CA, USA). Potential publication bias was evaluated by inspecting the symmetry of a funnel plot, and Begg's test through Stata version 16 was additionally used to quantify the publication bias.

RESULTS

Study selection

A total of 430 articles were identified. Based on the title and abstract evaluation, 416 articles were excluded as shown in Figure 1. Subsequent screening of the full texts of the remaining 14 articles indicated that one study did not focus on premedication in AIT,²⁰ one study reported only local reactions in AIT,²¹ which was not an endpoint for this study, and one study was a conference abstract that lacked full text (eTable 1²²). Thus, these three articles were not included in the meta-analysis. Finally, 11 studies met all the inclusion criteria for the study and were included in the meta-analysis.⁹⁻

11,14,15,19,23-27

Characteristics of studies included in the meta-analysis

Characteristics of the included studies are summarised in Table 1. The eleven studies enrolled a total of 609 patients, of which 325 received antihistamine premedication and 284 controls without antihistamine premedication. Seven trials were performed in Europe, two in the United States, one each in Canada and Japan. All trials were double-blinded with regards to antihistamine premedication, apart from one trial which was of open-label design.²⁸ Seven studies investigated AIT for insect venom allergy (IVA), three for inhaled allergy and one for food allergy; with all IVA studies investigating Hymenoptera (bee, fire ant) venom. With regard to the up-dosing protocols, eight rush protocols, one conventional and one cluster protocol were employed over the course of SCIT. A 40-week up-dosing phase was employed in

peanut OIT, which was considered as non-rush protocol.²⁶ None of the studies employed antihistamine premedication throughout the whole AIT treatment. Eight premedication protocols were employed in up-dosing phase and one premedication protocol in up-dosing phase and part of the maintenance phase.¹⁰ The premedication protocols employed in the remaining studies^{14,24} were not clarified.

Risk of bias

The risk of bias of all included studies is shown in Figures 2A and 2B. All reported complete outcome and there was no selective reporting bias. Most studies referred to “randomized controlled trial”. However, one study showed high risk of performance bias, particularly as evidence for blinding of participants and personnel or randomization procedure used was reported inadequately.

Funnel plots were prepared to assess the potential publication bias. No obvious asymmetry was observed (Figure 2C) and the *P* value of 0.64 was calculated for Begg’s test, indicating no significant publication bias.

Comparison of SAR during AIT in antihistamine premedication group versus control group

All studies (n=609 participants) assessed systemic adverse events over the course of treatment and compared the number of patients who reported SAR between premedication group and control group. Pooling the data of these studies showed that SARs to AIT were significantly lower with antihistamine premedication (18.8%) than without antihistamine premedication (36.3%; total OR, 0.36; 95%CI, 0.23 to

0.56, $P<0.05$; $I^2=35\%$) (Figure 3A). Additionally, the total numbers of SAR episodes^{23,26} were significantly reduced in the premedication group compared to the control group (total OR, 0.42; 95%CI, 0.34 to 0.53, $P<0.05$; $I^2=0\%$) (Figure 3B).

Moreover, four studies^{19,24,25,27} measured the severity of SAR by recording the number of patients who experienced at least one moderate to severe SAR during AIT. A combined analysis suggested that pretreatment with antihistamine may alleviate moderate to severe systemic reactions in AIT (total OR, 0.20; 95%CI, 0.06 to 0.74, $P=0.02$; $I^2=0\%$) (Figure 3C). Sub-analysis of data from studies demonstrating severe SARs^{24,27} indicated that compared to control group, antihistamine premedication might also afford protection against severe SARs, including anaphylaxis (total OR, 0.13; 95%CI, 0.02 to 0.79, $P=0.03$; $I^2=0\%$) (eFigure1). Similarly, combined assessment of the SAR episodes over the course of AIT demonstrated that use of antihistamines as premedication before AIT could significantly reduce episodes which potentially posed a threat to the life of patients (total OR, 0.09; 95%CI, 0.01 to 0.50, $P<0.05$; $I^2=4\%$) (Figure 3D).

Subgroup analysis between different escalating schedules was conducted as indicated in Figure 4A. Eight rush and three non-rush studies were included in this subgroup analysis and the total numbers of patients with SAR were assessed. This analysis demonstrated that pretreatment with antihistamine significantly decreased SARs in both rush (total OR, 0.45; 95%CI, 0.28 to 0.73; $P<0.05$; $I^2=36\%$) and non-rush (total OR, 0.12; 95%CI 0.04 to 0.38; $P<0.05$; $I^2=0\%$) subgroups. Furthermore,

compared with rush schedules (OR=0.45), non-rush schedules (OR=0.12) had a greater SAR reduction after antihistamine pretreatment ($P=0.04$).

Subgroup analysis based on different allergens indicated that antihistamine premedication provided significant protection against SARs irrespective of patients receiving AIT for insect venom allergy (total OR, 0.49; 95%CI, 0.30 to 0.82; $P<0.05$; $I^2=35\%$) or other types of allergy (total OR, 0.13; 95%CI, 0.05 to 0.34; $P<0.05$; $I^2=0\%$) (Figure 4B). However, the protection afforded by antihistamine treatment against SARs was lower in patients with insect venom allergy (OR=0.49) compared to other types of allergy (OR=0.13) ($P=0.02$).

A total of six trials recorded local reactions, however, there was no consistent grading of these reactions.^{9,10,14,23,25,27} Most of these studies demonstrated that antihistamines before AIT was beneficial in controlling LR. Portnoy and colleagues²⁷ found that antihistamine pretreatment could significantly reduce LR occurrence rate and erythema size among subjects. Two trials reported that antihistamine pretreatment could significantly reduce LR grading, as measured by the diameter of injection site swelling.^{9,23} Similar results were seen in another trial, which systemically evaluated LR according to its extension and duration, and demonstrated that besides extension, antihistamines could also shorten the duration of LRs.¹⁰ Moreover, the study by Brockow and colleagues¹⁴ demonstrated that the proportion of severe LRs was significantly lower in the antihistamine pre-treated group than in

the placebo pre-treated group. However, one trial also demonstrated that pretreatment with antihistamine did not decrease the size of LR in subsequent AIT.²⁵

Efficacy of AIT in antihistamine premedication group compared to control group

In our meta-analysis, all 11 studies (n=609 participants) assessed TMD during AIT. Overall, 92.6% patients in the antihistamine pretreatment group achieved TMD (323/349) compared to 84.1% patients in the control group (253/301). Statistical analysis demonstrated that premedication with antihistamine significantly increased the number of patients reaching TMD compared to control (total OR, 2.94; 95%CI, 1.72 to 5.03; $P<0.05$; $I^2=0\%$) (Figure 5A).

Sustained unresponsiveness was also measured by a re-challenge test using corresponding allergen in three trials.^{11,15,19} Sustained unresponsiveness was also achieved in a greater number of patients after pretreatment with antihistamines (65/81, 80.2%), compared to control group (61/84, 72.6%). However, the difference in numbers of patients with sustained unresponsiveness between the two groups was not statistically significant (total OR, 1.65; 95%CI, 0.77 to 3.54; $P=0.2$; $I^2=0\%$) (Figure 5B).

Assessment of an association between TMD and SU in three trials,^{11,15,19} which evaluated both TMD and SU demonstrated that there was no significant correlation between TMD and SU rates ($r = 0.53$, $P = 0.29$).

DISCUSSION

There are always concerns about adverse reactions in AIT, especially systemic reactions, which restrict AIT from being a more extensively accepted application. Anaphylaxis rates have been estimated to be 1 per 33300 injections in SCIT and 1 per 100 million administrations of SLIT,²⁹ and severe, even life-threatening adverse reactions, have been reported in patients receiving SCIT^{30,31}, but very rare in patients receiving SLIT.^{32,33} Thus, most of the studies investigating the effect of premedication have focused on patients receiving SCIT. In this regard, the current meta-analysis included ten SCIT trials and one OIT trial. No study was found to document the effect of antihistamine premedication in patients receiving SLIT; which possibly suggests superior overall safety of SLIT than SCIT and OIT.

According to the recent guidelines,^{12,13,16} the duration of AIT is generally about three years. Most of the studies included in the current meta-analysis employed antihistamine premedication during the up-dosing phase of AIT. One of the probable reasons for this may be the relatively higher occurrence of adverse reactions (ARs) during the up-dosing phase due to more frequent contact with allergens, especially in rush schedules.³⁴ On the other hand, premedication in up-dosing phase might provide considerable protection by significantly reducing the ARs. However, evidence comparing the effects of different courses of premedication in AIT is still lacking and needs to be addressed in the future.

Although antihistamine premedication is generally believed to reduce AIT-related SARs,²³ two trials from a single centre^{19,35}, one of which was excluded from this

meta-analysis because it was not a RCT,³⁵ have failed to demonstrate a significant effect of antihistamine premedication on the rates of SARs. To our knowledge, this is the first meta-analysis to systemically explore the effect of antihistamine premedication on AIT. Based on analysis of data from 11 RCTs, our results confirm the advantage of antihistamine premedication over control by demonstrating significant reductions in both episodes and severity of systemic adverse reactions. Furthermore, our findings suggest that antihistamine premedication may also improve the efficacy of AIT as indicated by an increase in the TMD. Although there was also a trend in greater number of patients pretreated with antihistamines in achieving SU to specific allergen challenge, this was not significantly different from that in the patients without antihistamine premedication.

Accelerated protocols, such as rush schedule, may result in more adverse reactions than the conventional protocols because of more frequent contact with the specific triggering allergens during the up-dosing phase.^{36,37} One retrospective study compared the incidence of SARs in 11982 patients during 5 years-period, and demonstrated that per-shot incidences of SAR were 0.01%, 0.06% and 0.33% in conventional, cluster and rush build-up AIT, respectively. Similarly, the per-patient incidences of SARs were found to be 2.84%, 2.52% and 11.86%, respectively,³⁸ suggesting that the frequency of SR is linked to the density of allergen exposure, and consequently rush protocols are likely to lead to greater incidence of SARs than the conventional and cluster protocols. We performed a subgroup analysis according to rush or non-rush escalating schedules to determine whether this impacted the effect

of antihistamine premedication on SARs. Our present meta-analysis suggests antihistamine premedication may be effective in reducing the incidence of SARs in AIT, regardless of the build-up protocol employed. Moreover, the degree of protection of antihistamine premedication in non-rush schedule was greater than that in rush schedule. This finding supported that SAR incidence was not only higher, but harder to control in rush immunotherapy, compared to non-rush immunotherapy. Antihistamine premedication is well worth recommending in AIT, especially with more benefit in conventional and cluster immunotherapy.

Insect sting, food allergy and allergic rhinitis are common allergic disorders in daily life. A recent meta-analysis reported the median incidence of adverse events was 28.9% by collecting 46 Venom AIT case series and cohorts.³⁹ Boyle and colleagues⁴⁰ and Park and colleagues⁴¹ have reported comparable rates of 14.2% and 14.5% systemic adverse reactions, respectively, in venom immunotherapy. Rueff and colleagues⁴² have reported that about 8.4% of total subjects on venom immunotherapy developed severe adverse reactions requiring emergency intervention. Moreover, patients developing systemic adverse reactions faced a 38% relapse rate, bringing into question the safety of venom AIT. In contrast, both the frequency and severity of SARs in AIT for food allergy and allergic rhinitis have been shown to be lower than in venom allergy. One recent meta-analysis of food allergy indicated that the systemic adverse reaction rate was 13.2%.⁴³ Chu and colleagues⁴⁴ have reported a comparatively low rate of 6.1% severe SARs in OIT for peanut allergy. One prospective European survey evaluated the safety of AIT in over 1500

patients, of which 90% of the patients had allergic rhinitis, and found that only 1.53% of the patients developed systemic adverse reactions, which were mostly mild.⁴⁵ Thus, we have also performed a subgroup analysis of the reported data of AIT for venom allergy and AIT for other allergens (food and respiratory allergens). This meta-analysis revealed that pretreatment with antihistamines can also provide protection against various allergens. Although the protective effect of antihistamine premedication in reducing SARs in venom AIT was lower than that observed for other allergens (e.g. peanut, house dust mite and pollen), patients nevertheless achieved significant benefits from antihistamine premedication in venom immunotherapy. Thus, antihistamine premedication can be recommended in AIT targeting specific allergy mentioned above.

Antihistamines have generally been employed as the main option for pretreatment in AIT as most studies have supported the notion that the safety of AIT was increased after antihistamine pretreatment.⁴⁶ Consistent with this opinion, the current meta-analysis on pooled data also provide evidence to support this view. Moreover, Brockow and colleagues¹⁴ compared the effect of terfenadine and terfenadine combined with ranitidine, and were not able to demonstrate additional efficacy of the drug combination in reducing adverse reactions. In two trials^{19,27}, prednisone was prescribed as the combined premedication with the daily dose of 60mg but lasted no more than 4 days. It was usually considered not so harmless as the total amount of systemic corticosteroids taken in a life-time has been linked to systemic adverse effects on the long run. Interestingly, some studies have

investigated the potential impact of premedication on efficacy of AIT. Yoshihiro and colleagues²⁴ have indicated that antihistamines applied 2 hours before AIT can significantly promote TMD achievement with shorter time. In accordance with these findings, the current meta-analysis has also demonstrated that antihistamines can increase the numbers of patients achieving TMD. Similarly, Müller and colleagues¹¹ found that antihistamines could enhance the efficacy of AIT by increasing SU to specific allergen challenge. Pooled analysis in the present meta-analysis demonstrated a trend in increased SU with antihistamines premedication, however, this was not statistically significantly compared to control group. Moreover, correlation analysis showed that achieving TMD was not associated with achieving SU. Collectively, these findings suggest that antihistamines may help to improve the efficacy of AIT; however, further studies are required to both confirm the benefit of pretreatment with antihistamine on AIT efficacy and to explore the underlying mechanisms.

There are some limitations to this meta-analysis. First, the sample sizes in some of the trials were relatively small, which could potentially lead to selection bias. Second, most of studies with antihistamine premedication employed the rush protocol, which obviates information on the potential of other build-up protocols, in particular the cluster protocol. Thus, further studies with premedication provided in cluster AIT are worth considering. Third, the findings of our meta-analysis were based on data from 11 eligible trails, the majority of which employed SCIT. Whether antihistamine premedication is able to improve safety and efficacy of SLIT or OIT is

presently not clear and therefore warrants extensive investigation in such AIT trials in the future. Similarly, data for the effect of antihistamine premedication in AIT with other common allergens including HDM and pollens is presently scarce and should be elaborated on. Last, there are comparatively few data on this topic in the literature and the vast majority of the studies included in the present meta-analysis were published over a decade ago. Nevertheless, the efficacy of antihistamine premedication during AIT is worth exploring.

In conventional teaching, there is some concern that antihistamine premedication might mask minor reactions, which could be alert signs for subsequent severe AEs.³⁶ However, to date no study has reported such masking effects of antihistamine premedication. Indeed, the finding from the present study supported that antihistamine premedication significantly reduced moderate to severe SARs overall, and might even convey protection against specifically severe SARs and anaphylaxis. These findings nevertheless need to be confirmed in further studies with large sample sizes and long follow-up periods.

In conclusion, this meta-analysis confirms that pretreatment with antihistamine before AIT can significantly reduce the episode frequency and severity of systemic adverse reactions. H1-antihistamines provide protection in AIT with different escalating approaches and distinguished allergens ranging from insect venoms to aeroallergens. Furthermore, antihistamine premedication might help to enhance efficacy of AIT by significantly augmenting the number of patients and reducing the

time needed to reach TMD. In view of these findings, antihistamines should be recommended as pretreatment in AIT.

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FIGURE LEGENDS

Figure 1. Flowchart of study retrieval, screening and inclusion in the meta-analysis following PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Figure 2. Assessment of risk of bias in the meta-analysis. (A) Quality assessment graph of risk of bias; (B) Risk of bias summary; and (C) Funnel plots for potential publication bias.

Figure 3. Systemic adverse reaction (SAR) assessments. (A) SAR patient numbers; (B) SAR episode numbers; (C) patient numbers with moderate to severe SAR (MSSAR); (D) moderate to severe SAR episode numbers.

Figure 4. Subgroup meta-analysis of the effect of antihistamine premedication on systemic adverse reactions (SAR) in (A) rush or non-rush up-dosing schedules and (B) allergic disorders with different allergens.

Figure 5. The benefit of antihistamine on the efficacy of allergen immunotherapy. (A) Target maintenance dose (TMD) with and without antihistamine premedication and (B) sustained unresponsiveness (SU) with and without antihistamine premedication.

TABLES

Table 1 Characteristics of studies included in the meta-analysis

Study (⁹⁻²⁶)	Country	Diagnosis	Allergen	Approach	Premedication	Patients N (P/C)	Total injection N (P/C)	TMD N (P/C)	SU N (P/C)	Total SARs N (P/C)	Total SAR episodes N (P/C)	Moderate to severe SAR N (P/C)	Moderate to severe SAR episode N (P/C)
Berchtold 1992 ⁹	Switzerland	IVA	Bee venom	SCIT /rush	Ter 240mg	52(26/26)		26/26		17/18			
Portnoy 1994 ²⁷	United states	AR/ Asthma	Inhalant allergens	SCIT /rush	Ast 30mg +Ran 300mg +Pre 60mg	22(11/11)		11/11		3/8		2/5	
Brockow 1997 ¹⁴	Germany	IVA	Hymenoptera venom	SCIT /rush	Ter 120mg ± Ran 300mg	121(82/39)		69/28		1/6			
Müller 2001	Switzerland	IVA	Bee venom	SCIT	Ter 240mg	52(26/26)		21/20	20/15	7/14			

Study (⁹⁻²⁵)	Country	Diagnosis	Allergen	Approach	Premedication	Patients N (P/C)	Total injection N (P/C)	TMD N (P/C)	SU N (P/C)	Total SARs N (P/C)	Total SAR episodes N (P/C)	Moderate to severe SAR N (P/C)	Moderate to severe SAR episode N (P/C)
				/rush									
Müller 2008 ¹⁵	Switzerland	IVA	Bee venom	SCIT /rush	Lev 5mg	54(27/27)	261/252	27/23	18/18	11/19			
Nielsen 1996 ²³	Denmark	AR	Birch/grass pollen	SCIT /cluster	Lor 10mg	45(21/24)	294/336	20/17		7/19	18/39		1/11
Reimers 2000 ¹⁰	Switzerland	IVA	Bee venom	SCIT /rush	Fex 180mg	54(28/26)		28/26		12/9			
Tankersley 2002 ¹⁹	United states	IVA	Fire ant venom	SCIT /rush	Ter 120mg + Ran 300mg +Pre 60mg	59(28/31)		27/29	27/28	1/2		1/2	

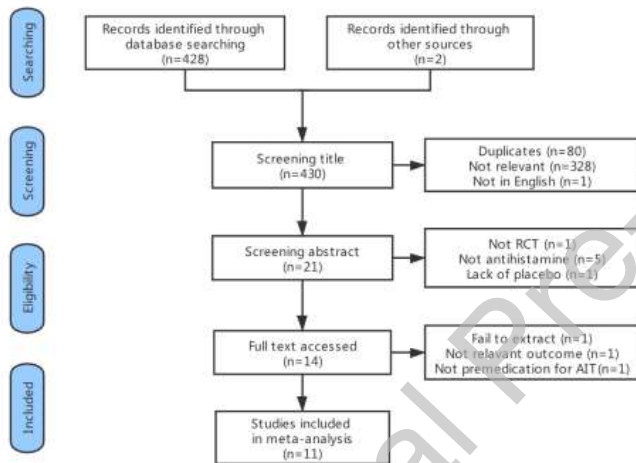
Study (⁹⁻²⁵)	Country	Diagnosis	Allergen	Approach	Premedication	Patients N (P/C)	Total injection N (P/C)	TMD N (P/C)	SU N (P/C)	Total SARs N (P/C)	Total SAR episodes N (P/C)	Moderate to severe SAR N (P/C)	Moderate to severe SAR episode N (P/C)
Yoshihiro 2006 ²⁴	Japan	AR	Cedar pollen /dust mite	SCIT /conventional	Fex 60mg	134(67/67)		86/67		0/6		0/6	
Wöhrl 2007 ²⁵	Austria	IVA	Hymenoptera venom	SCIT /rush	Des 5mg	10(5/5)		5/5		1/1		0/0	
Jagdis 2014 ²⁶	Canada	Food allergy	Peanut	OIT	Ket 4mg	6(4/2)	1430/49 4	3/1		1/1	240/159		6/11

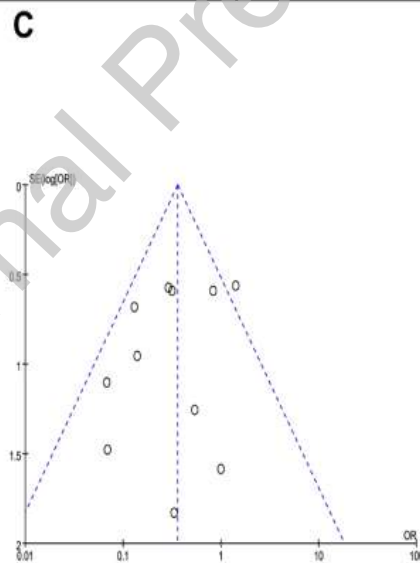
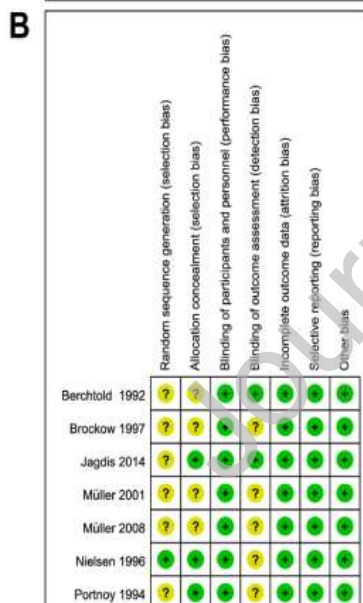
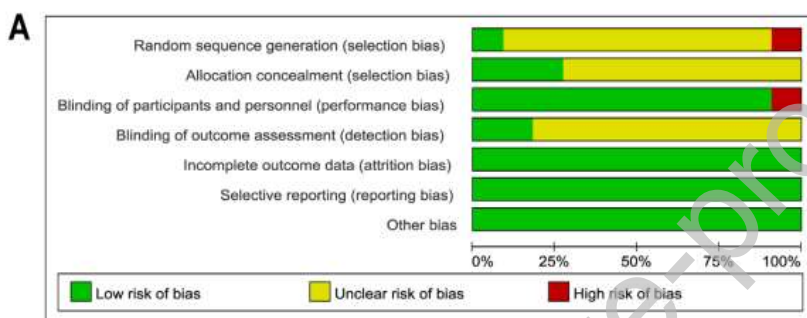
Abbreviations: AR, allergic rhinitis; Ast, astemizole; C, control/placebo group; IVA, insect venom allergy; Des: desloratadine; Fex:

fexofenadine; HDM, house dust mite; IVA, insect venom allergy; Ket: ketotifen; Lev: levocetirizine; Lor: loratadine; OIT: oral immunotherapy;

N: number of patients; P, premedication group; Pre: prednisone; Ran: ranitidine; SAR: systemic adverse reaction; SCIT, subcutaneous

immunotherapy; SU: sustained unresponsiveness; Ter: terfenadine; TMD: target maintenance dose





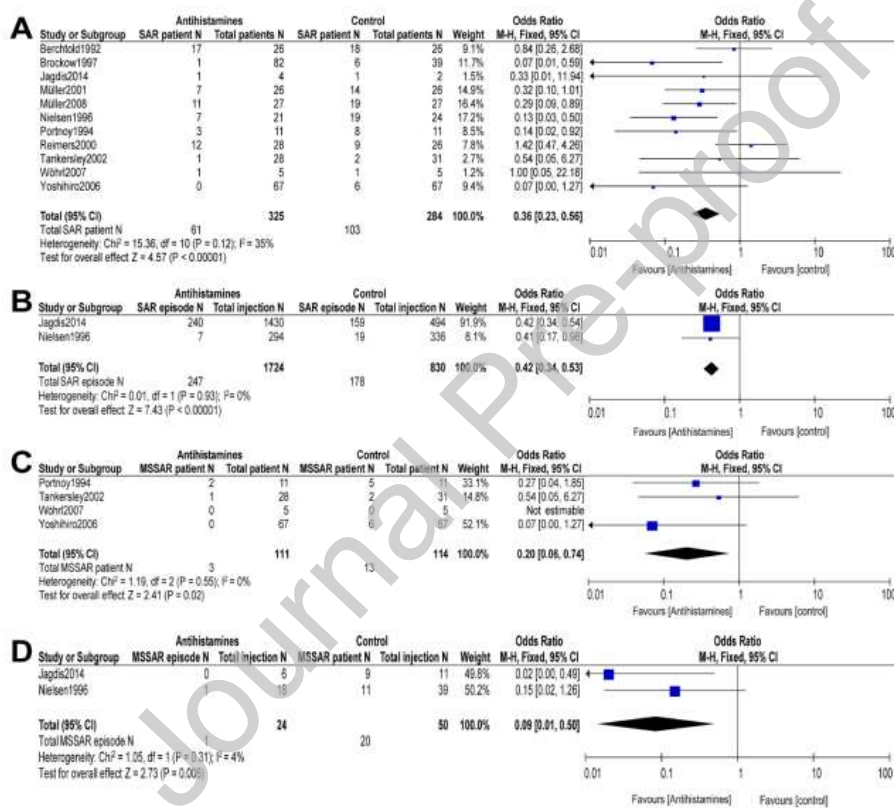


Figure 3

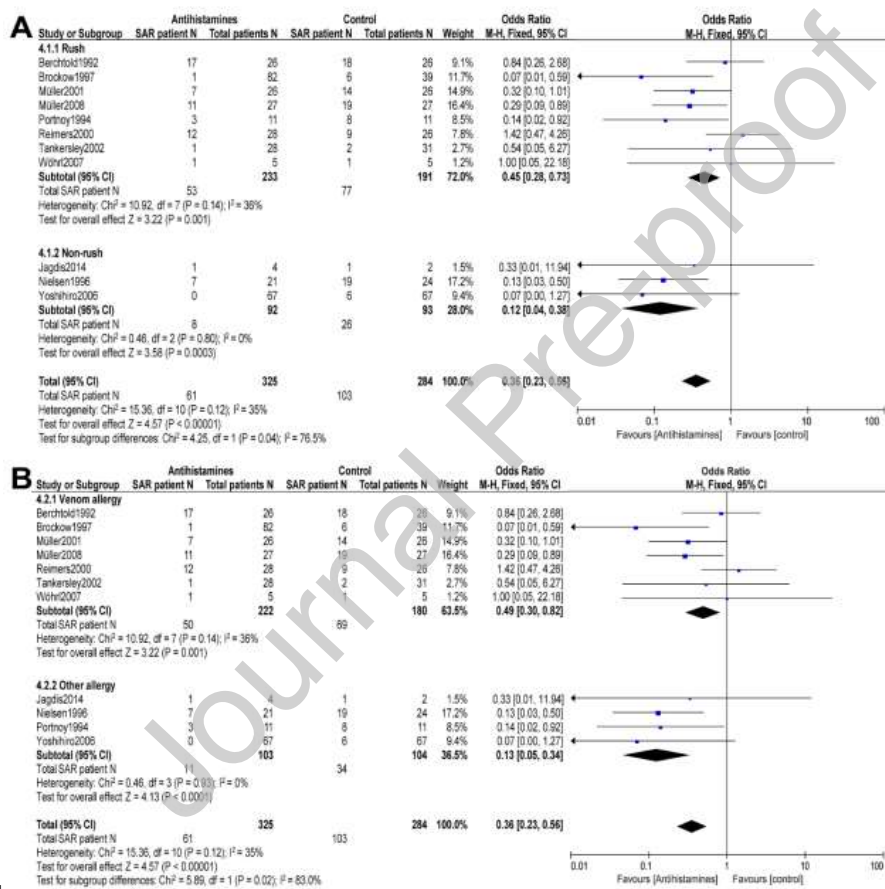


Figure4

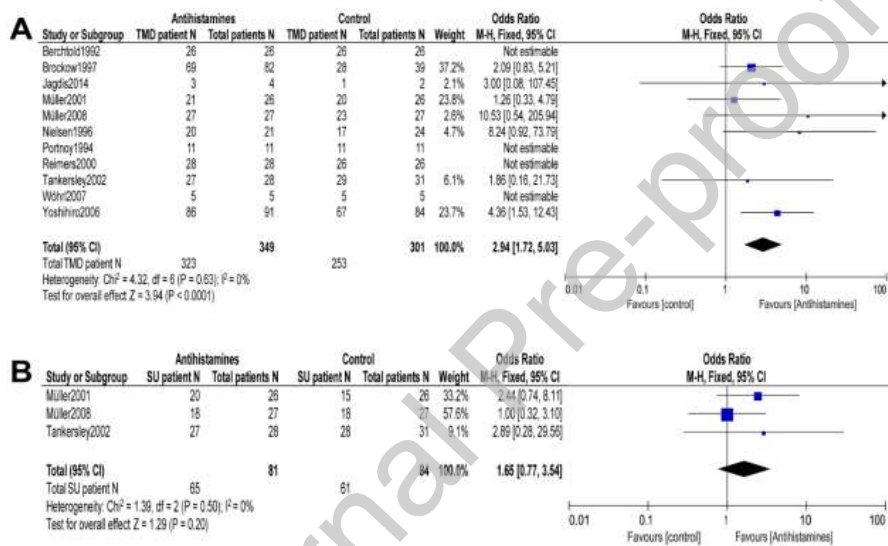


Figure5

Supplementary Table**eTable 1.** Conference abstract excluded from the meta-analysis.

Study	Source	Abstract description	Reasons for exclusion
Olgac et al. 2015	<i>Allergy</i> . 2015;70:113.	This study was an RCT to determine the possible preventive effects of premedication on systemic and local reactions during cluster immunotherapy. The total frequency of hypersensitivity reaction was higher in patients without premedication [14 (14.7%) vs. 13 (31.0%)]. Premedication group experienced fewer local reactions ($P=0.033$), but no significant difference was shown on the frequency of systemic adverse reaction (SAR).	Failed to extract SAR patient number, SAR episode number, TMD and SU (Conference Abstract, no full text)

Supplementary Figure

eFigure 1. Forest plot comparing patient numbers with severe systemic adverse reactions (SARs) between premedication and control groups.

