Efficacy of Allergen Specific Immunotherapy for Treatment of Allergic Rhinitis: A systematic review and meta-analysis

ABSTRACT

Background: Allergic rhinitis is a common disease that affect nose causing sneezing, watery nose, nasal itching and redness that affect quality of life, productivity at work or school and may underlies complications (e.g. Asthma) for patients and are often accompanied by itchy eye, redness and lacrimation.

Aim of the Work: The objective of this study is to systematically assess the efficacy and safety of immunotherapy treatment for patients with Allergic Rhinitis.

Method: Our initial search generated a total of 23330 possible relevant titles. Titles, abstracts were preliminary screening so that 22565 were excluded. 154 articles were retrieved in full text the number of studies excluded after assessment of the full text 145, 9 articles met the eligibility criteria and fulfilled the inclusion and exclusion criteria for the review.

Data Sources: Medline databases (PubMed, Medscape, ScienceDirect. EMF-Portal) and all materials available on the Internet upto 2018.

Data Extraction: If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and defined assessment measures.

Conclusion: Our systematic review provides evidence that Sublingual Immunotherapy (SLIT) tablets effectively relieve rhinitis symptoms in adults with allergic rhinitis, improve their quality of life and provide data about safety of Sublingual Immunotherapy as there were no serious side effects of using SLIT tablets. Nevertheless, the current evidence may be limited due to sample size and the heterogeneity between studies. Large sample size and multiple center RCTs on the efficacy of different formulations of SLIT drugs are still needed to provide further evidence and more precise recommendations.

Keywords: Allergic rhinitis, house dust mite, immunotherapy, specific immunotherapy

INTRODUCTION

Allergic rhinitis is an inflammatory disease of nasal mucosa, induced by an immunoglobulin E (IgE)-mediated reaction caused by house dust mite (HDM) in allergen sensitized subjects. HDM is one of the commonest AR allergen in the world and the most common organisms are Dermatophagoides Pteronyssinus and dermatophagoides Farinae the two types are different from each other to some extent but AR patients are desensitized to both species. AR is characterized by sneezing, rhinorrhea, nasal congestion and nasal pruritus, which are often accompanied by ocular pruritus, redness and/or lacrimation. Allergic rhinitis (AR) is a common airway disease with a reported prevalence of 10-30%. Although AR is not a serious illness, it is clinically relevant because it underlies many and productivity at work or school. [(1)]

Current treatment modalities include allergen avoidance, antihistamine, nasal steroid and allergen specific immunotherapy. Compared to symptom releasing options (eg: antihistamine and nasal steroid), Specific Immunotherapy(SIT) (subcutaneous or sublingual route) represented the only immune-modifying and curative available option for the treatment of AR patients. Novel data demonstrated the efficacy of Subcutaneous Immunotherapy(SCIT) also as a preventive strategy to reduce onset of new sensitization to non-related allergens, progression from AR to asthma. [(2)]

The mechanisms of immunotherapy (IT) are still not fully understood. IT is based on administration of gradually increasing concentrations of allergen extracts and leads to the development of clinical allergen tolerance in selected patients. Tolerance is mainly accompanied by the induction of regulatory subsets of T and B cells, the production of IgG4 isotype allergen-specific blocking antibodies, and decreased inflammatory responses to allergens by effector cells in inflamed tissues. [(3)]

Despite the well-established benefits of Subcutaneous Immunotherapy(SCIT), only a small percentage of candidate AR patients were willing to accept this therapeutic option with good compliance. Moreover, based on the current published studies, we still could not conclude affirmatively that IT is a safe and efficacious option for the treatment of allergic rhinitis patients. A well designed systematic review of the literature is needed to evaluated the evidence based efficacy of IT in allergic rhinitis.[(4)]

AIM OF THE WORK

The objective of this study is to systematically assess the efficacy and safety of Immunotherapy treatment for patients with Allergic Rhinitis.

PATIENTS AND METHODS

Criteria for considering studies for this review

Types of Studies: All types of clinical studies, either randomized controlled trials (RCTs), prospective cohort, retrospective cohort, retrospective case control, or case series.

Types of Participants: Population: patients with diagnosed AR with or without asthma.

Types of Interventions: Immunotherapy (IT): whether subcutaneous immunotherapy (SCIT; cluster or conventional) or sublingual immunotherapy (SIT).

Types of Outcome measures: Rhinitis symptom scores, medication scores, overall quality of life, or adverse events

Search methods for identification of studies

We intend to conduct systematic searches for clinical trials with no study type, language, publication year or publication status restrictions.

1. Electronic Searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL; PubMed; EMBASE; LILACS; KoreaMed; IndMed; PakMediNet; ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform), Google and other sources.

Search terms included allergic rhinitis, immunotherapy, sublingual, subcutaneous.

All articles are classified as either randomized controlled trials (RCTs), prospective cohort, retrospective cohort, retrospective case control, or case series. Levels of evidence assigned based on guidelines of the Oxford Centre for Evidence-Based Medicine for therapeutic studies. Level 1 studies include RCTs. Level 2 studies include prospective cohort studies and poor quality or inhomogeneous random trials. Level 3 studies include both retrospective cohort and case-control trials. Level 4 studies include single-armed case series without controls. Level 5 evidence represents expert opinion.

2. Searching Other Resources

We searched the 'grey literature' such as books, journal articles, conference abstracts and table of contents for relevant studies that fulfill our inclusion criteria

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, we searched PubMed, TRIP database, NHS Evidence–ENT & Audiology, and Google to retrieve existing systematic reviews relevant to this systematic review, so that we scanned their reference lists for additional trials.

Data collection and analysis

1. Selection of Studies

Firstly, one reviewer evaluated the titles and abstracts to determine whether the study met the eligibility criteria. Secondly, abstracts and full texts evaluated independently by two reviewers for eligibility. Disagreements resolved by a discussion with a third reviewer.

2. Data Extraction and Management

Two review authors independently extract data from the full texts of included studies using a specifically developed extraction form. The data extraction form will be piloted previously.

Information collected on the following: Study characteristics (first author, year of publication, study design, number of arms, sample size, duration of follow-up). Participant characteristics (age, sex, numbers of participants, inclusion and exclusion criteria in the included studies) and possible confounders (previous insults, co-morbidities and other confounders as reported by the authors). Intervention and comparative intervention (SIT, cluster SCIT, conventional SCIT).

3. Assessment of Risk of Bias in Included Studies

The assessment of risk of bias performed by two reviewers independently considering the following domains according to the Cochrane risk of bias tool: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias for the RCTs. According to the Cochrane Handbook, these items are described as having a 'low', 'high', or 'unclear' risk of bias. For non-randomized studies, bias due to confounding, bias in selection of participants, bias due to departures from intended interventions, bias due to missing data, bias in measurements of outcomes of interventions, bias in selection of the reported results, and overall bias assessed according to the 'Cochrane risk of bias tool for non-randomized studies. According to the 'Cochrane risk of bias tool for non-randomized studies' these items are described as having a 'low',

'moderate', 'serious', 'critical', or 'unclear' risk of bias. According to the recommendations for the Cochrane RoB-tool for non-randomized studies, no studies assessed as having a 'critical' risk of bias included in any data synthesis.

4. Measures of intervention effect

We analyzed the outcomes "rhinitis score, medication score, quality of life" as dichotomous outcomes "significant or non-significant impact". With determination of cut-off point at which significance could be detected for each variable.

5. Unit of Analysis Issues

The unit of analysis is each patient recruited in the studies.

6. Dealing with Missing Data

In case of missing data we tried: Contact with the original investigators to request missing data. Analysing only the available data if they are thought to be missing at random. Calculate the missing values from other values such as calculating missing standard deviations through known confidence intervals, standard errors, t values, P values or F values. Using statistical models to allow for missing data.

7. Assessment of Heterogeneity

Heterogeneity among studies investigated by using the chi2 test and I2 test. If significant heterogeneity is detected ($I2 > 50\%$ or $p < 0.1$) for outcome measures, the calculations with a fixed effect model will be repeated using a random effects model as sensitivity analysis and we considered results from both.

8. Assessment of Reporting Biases

We planned to minimize the impact of reporting bias in our systematic review by ensuring a comprehensive search for eligible studies including three trial registries. A funnel plot and appropriate statistical tests for small study effects performed if ≥10 studies are available.

9. Data Synthesis

Intervention effects in divergent study designs are influenced differently by bias. Data from RCTs and non-randomized studies was not pooled, but rather was analyzed separately. Combined estimates were not provided for studies with considerable imbalances or differences in the included population or differences regarding interventions. Estimation of treatment effects was based on a fixed effect model; when we are faced with substantial heterogeneity (i.e., $I2 > 50\%$), a random effects model was calculated as well as sensitivity analysis. Pooling of data and meta-analysis of non-randomized studies was only considered among studies with similar design (e.g., prospective cohort studies were only combined with other prospective cohort studies) and limited heterogeneity. We calculate pooled RRs and 95% CIs across comparable studies. When considerable heterogeneity ($I2 > 80\%$) was found between comparable studies, pooled estimates were not provided. Instead, a descriptive synthesis of findings was performed.

10. Sensitivity Analysis

Sensitivity analysis was undertaken whenever there's uncertainty about a certain decision to know if the final findings are robust to these decisions

11. Summary of findings table

It included the following sections: Table header: included information about: population, Setting, Intervention. A list of all outcomes. Numbers of participants and studies addressing each outcome. A grade of the quality of evidence for each outcome grade approach was used. Space for comments.

RESULTS

Bergmann 2014 [5]

Participants	**509**
Age range **Mean ± SD**	**18-50 y** **300 IR : 29.0 ± 8.52 y** **500 IR : 30.1 ± 8.43 y** **Placebo : 30.0 ± 8.96 y**

Notle, 2015 [6]

Participants	**124**
Age range **Mean**	**18-58** **6 DU : 27** **12 DU : 28** **Placebo : 27**

Mosbech, 2014 [7]

Participants	**489**
Age range **Mean**	**17-58 y** **1 SQ-HDM : 33**

	3 SQ-HDM : 33 **6 SQ-HDM : 31** **Placebo : 31**

Okubo, 2016 [8]

Participants	**946**
Age range **Mean ±SD**	**12-64 y** **6 SQ-HDM : 27.2 ± 12.0** **12 SQ-HDM : 26.8 ± 12.1** **Placebo : 26.8 ± 11.7**

Roux, 2016[9]

Participants	**355**
Age range **Mean ±SD**	**18-55 y** **500 IR : 32.8 ± 9.33** **300 IR : 32.5 ± 8.56** **100 IR : 32.4 ± 10.09** **Placebo : 31.3 ± 8.75**

Demoly, 2015 [10]

Participants	**992**
Age range **Mean ±SD**	**18-65 y** **6 SQ=HDM : 32.5 ± 11.2** **12 SQ-HDM : 32.1 ± 10.6** **Placebo : 32.2 ± 10.9**

Okamoto 2016[11]

Participants	**927**
Age range **Mean ±SD**	**12-64 y** **300 IR : 30.0 ± 11.8** **500 IR : 30.5 ± 11.7** **Placebo : 30.2 ± 11.6**

Pfaar, 2018 [12]

Participants	**406**
Age range **Mean ±SD**	**18-65 y** **Active : 37.48 ± 11.43** **Placebo : 36.69 ± 10.77**

Kim, 2018 [13]

Participants	**39- 81 y**
Age range **Mean ±SD**	**Treatment : 67.0 ± 5.8** **Control ; 67.2 ± 6.5**

Sex

The nine trials included participants from both sexes.

Study	**Male**	**Female**
Bergmann, 2013[5]	267	242
Roux, 2016 [9]	172	183
Demoly, 2015 [10]	494	498
Okubo, 2016[8]	433	513
Okamoto, 2016[11]	408	519
Notle, 2014[6]	54	85
Mosbech, 2014 [7]	240	249
Kim, 2018[13]	22	17
Pfaar, 2018[12]	182	124

Setting

Study number	**Setting**
Bergmann, 2013[5]	Academic Medical Centre, Otorhinolaryngology, Amsterdam. Supported by Stallergenes S.A.
Roux, 2016 [9]	Allergy and Asthma Research Centre, Ottawa. This study was funded by Stallergenes S.A., France.
Demoly, 2015 [10]	Allergy Outpatient Clinic, Rennweg, Vienna, Department of Respiratory Medicine,

	Bispebjerg University Hospital, Copenhagen; and Allergy & Asthma Center Westend, Outpatient Clinic & Research Center, Berlin. Supported by ALK, Hørsholm, Denmark.
Okubo, 2016[8]	Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, Yamanashi University; Association of Pollen Information of Japan, Tokyo; dTorii, Tokyo.
Okamoto, 2016[11]	Department of Otorhinolaryngology-Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Department of Otorhinolaryngology- Head and Neck Surgery, University of Fukui, Fukui; Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; Department of Otorhinolaryngology-Head and Neck Surgery, Graduate School of Medical Science, University of Yamanashi, Yamanashi, Japan
Notle, 2014[6]	Department of Medicine, Division of Allergy and Immunology, National Jewish Health, Denver, Bernstein Allergy Group and the Division of Allergy and Immunology, University of Cincinnati, Cincinnati; and, Vienna Challenge Chamber, Vienna. Supported by Merck & Co.
Kim, 2018[13]	Division of Respiratory, Allergy and Critical Care Medicine, Konyang University College of Medicine, Daejeon, Korea, Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea, Division of Allergy and Immunology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, Division of Respiratory and Critical Care Medicine, Korea University College of Medicine, Seoul, Korea, Division of Pulmonary, Allergy, and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea, Department of Statistics, Clinical Trial Center, Ajou University Medical Center, Suwon, Korea
Pfaar, 2018 [12]	Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg. Division of Internal Medicine, Asthma and Allergy, Medical University of Lodz; the Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University.

Location and year

Study	Location	Year of publication
Bergmann, 2013 [5]	Germany	November, 2013
Roux, 2016 [9]	Canada	March, 2016
Demoly, 2015 [10]	France	2016
Okubo, 2016[8]	Japan	September, 2016
Okamoto, 2016[11]	Japan	July, 2016
Notle, 2014[6]	USA	December, 2024
Mosbech, 2014[7]	Germany and Denmark	November, 2014
Kim, 2018[13]	Korea	August, 2018
Pfaar, 2018[12]	Germany	November, 2018

Sample size and compliance

Study	Sample size	Lost in follow up
Bergmann, 2013[5]	313	82
Roux, 2016 [9]	180	67
Demoly, 2015 [10]	656	115
Okubo, 2016 [8]	633	94
Okamoto, 2016[11]	612	115
Notle, 2014[6]	83	18
Mosbech, 2014 [7]	241	115
Kim, 2018[13]	39	6
Pfaar, 2018[12]	406	32

Risk of bias in included studies:

Tables of assessment of risk of bias provide more details on this domain.

Intervention:

Study	Intervention groups	Control
Bergmann, 2013 [5]	1. 300 IR 2. 500 IR	Placebo tablets
Roux, 2016 [9]	1. 100 IR 2. 300 IR 3. 500 IR	Placebo tablets
Demoly, 2015 [10]	1. 6 SQ-HDM 2. 2 SQ-HDM	Placebo tablets
Okubo, 2016 [8]	1. 6 SQ-HDM 2. 12 SQ-HDM	Placebo tablets
Okamoto, 2016 [11]	1. 300 IR 2. 500 IR	Placebo tablets
Notle, 2014 [6]	1. 6 DU 2. 12 DU	Placebo tablets
Mosbech, 2014 [7]	1. 1 SQ-HDM 2. 3 SQ-HDM 3. 6 SQ-HDM	Placebo tablets
Kim, 2018 [13]	Treatment group	Control group
Pfaar, 2018 [12]	Active group	Placebo group

Effect of outcome predictive values

Predictive variables	Assessing studies
RTSS	**5/9**
IgE level	**2/9**
RQLQ	**3/9**
Adverse drug reaction	**9/9**

RTSS

Among the included nine articles, five of the studies that administered patients with SLIT tablets were eligible for meta-analysis of RTSS and consisted of 1490 patients. A randomized model was used due to the high heterogeneity (I^2= 99.32%). Meta-analysis demonstrated a significant reduction in RTSS in patients receiving SLIT tablets compared to placebo (mean difference = -0.98, 95% CI = -1.41 to -0-56).

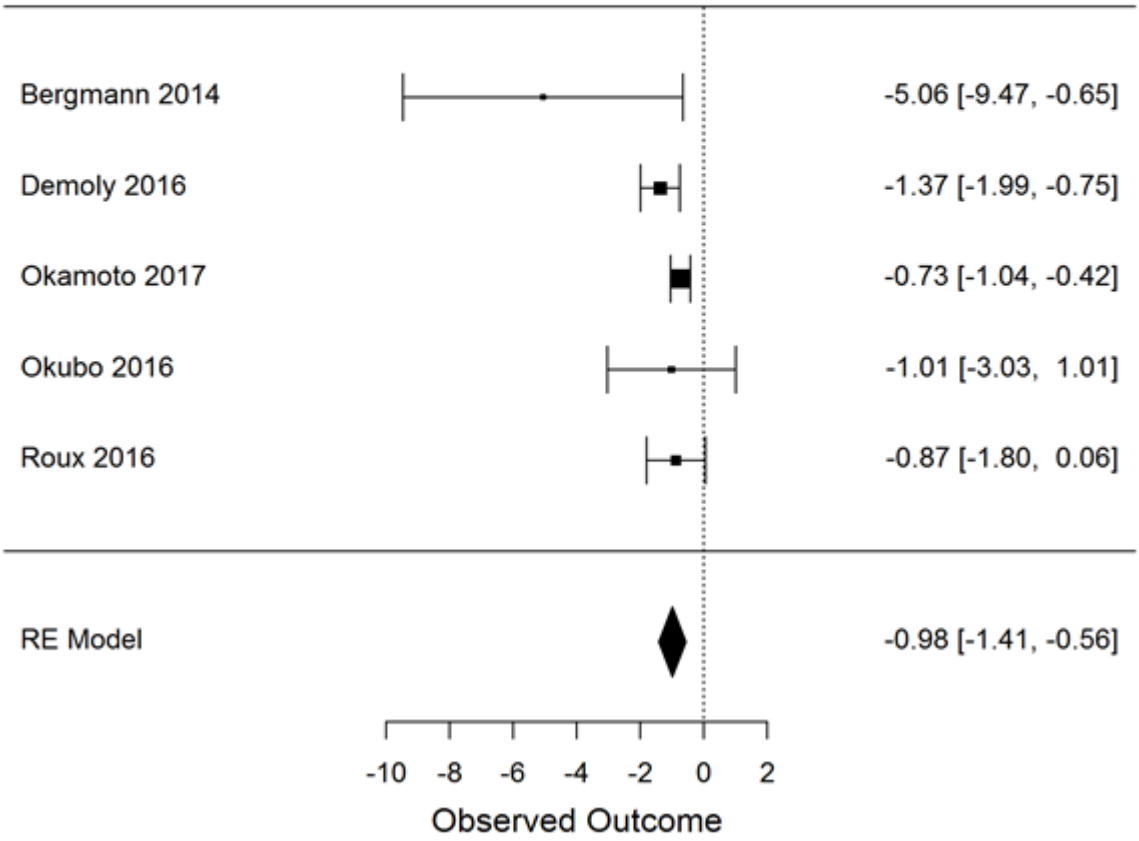

Figure 1A. Forest plot for difference between SLIT and placebo as regards RTSS. There is considerable heterogeneity across studies (I^2 = 99.32%). Difference between SLIT and placebo is statistically significant (mean difference = -0.98, 95% CI = -1.41 to -0-56) favoring SLIT over placebo.

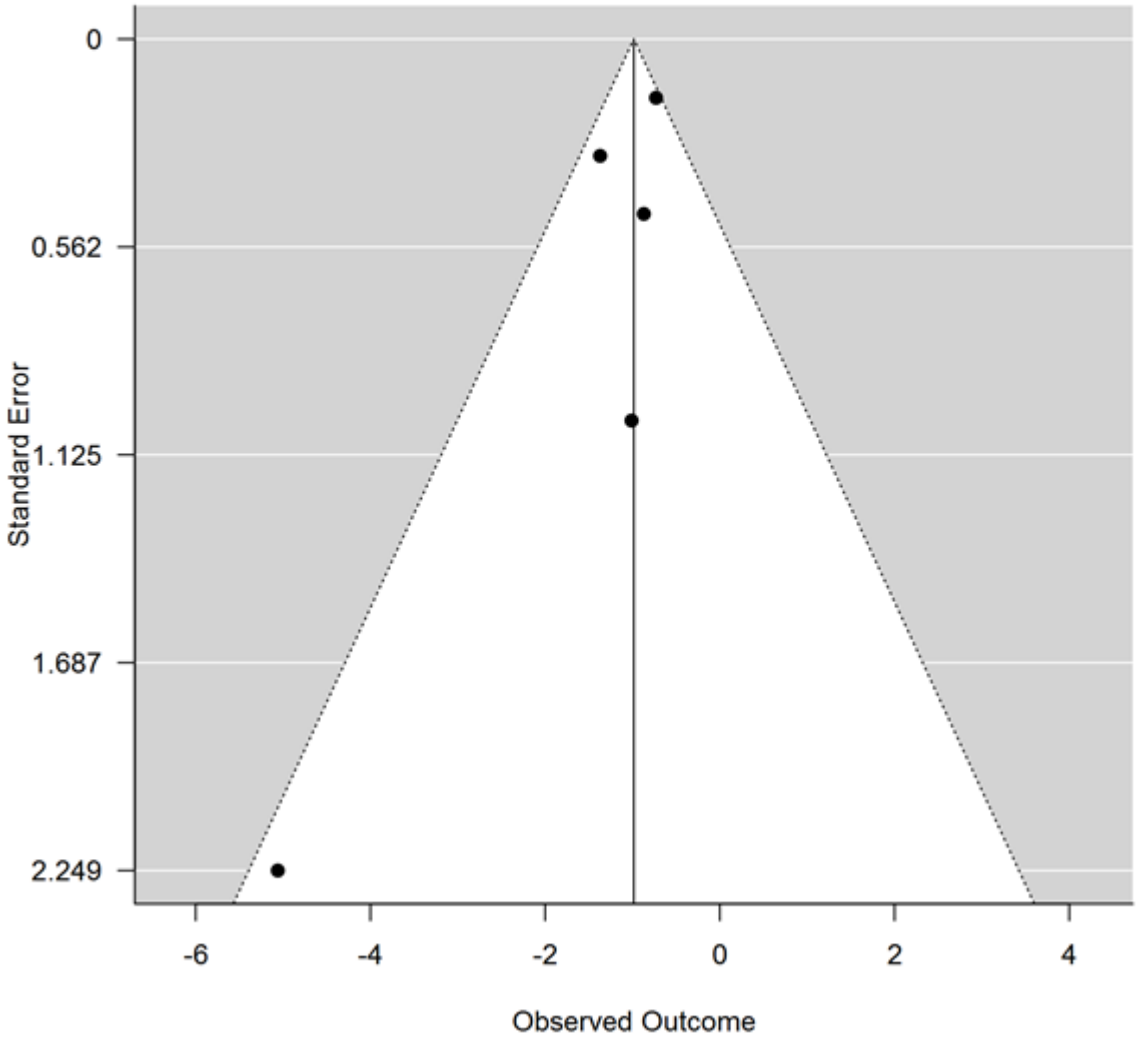

Figure 1B. Funnel plot for difference between SLIT and placebo as regards RTSS. There is evidence of publication bias with asymmetrical funnel plot. Begg-Mazumdar rank correlation test P-value = 0.233, Egger regression test P-value = 0.077, Rosenthal fail-safe N = 68.

Serum immunologic outcomes

Two of the nine articles on SLIT tablets included descriptive data for meta-analysis on specific IgE levels. Data from these two articles consisted of 103 patients. A randomized model was used due to high heterogeneity (I^2= 96.812 %, Cochran Q test P-value = 0.045). There was no significant difference in IgE levels in the patients undergoing SLIT tablets compared to placebo (mean difference = 11.70, 95% CI = -56.54 to 79.94).

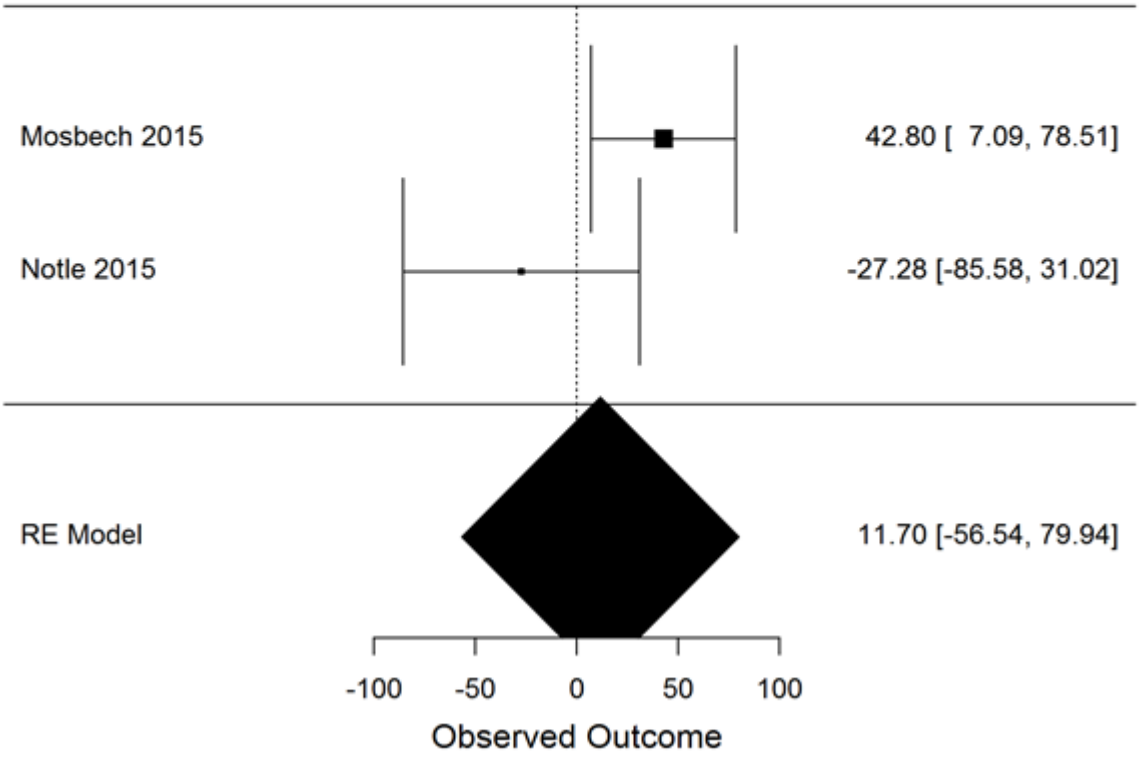

Figure 2A. Forest plot for difference between SLIT and placebo as regards specific IgE level. There is considerable heterogeneity across studies (I^2 = 96.812%, Cochran Q test P-value = 0.045). Difference between SLIT and placebo is not statistically significant (mean difference = 11.70, 95% CI = -56.54 to 79.94).

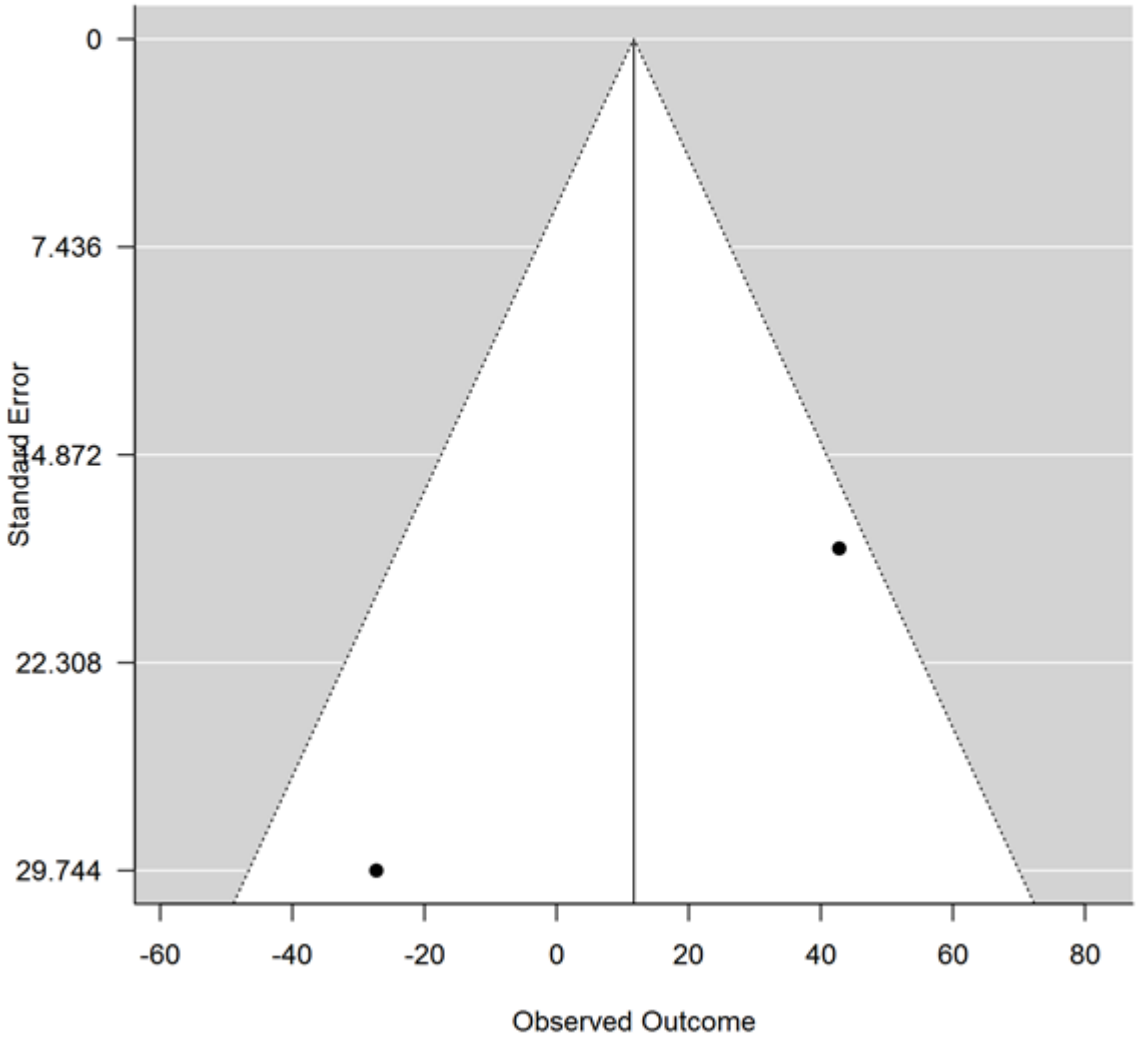

Figure 2B. Funnel plot for difference between SLIT and placebo as regards RTSS. There is no evidence of publication bias with symmetrical funnel plot. Begg-Mazumdar rank correlation test P-value = 1.000, Rosenthal fail-safe N = 0.

RQLQ

Three of the nine articles on SLIT tablets included descriptive data for meta-analysis on quality of life. Data from these 3 articles consisted of 2069 patients. A randomized model was used due to high heterogeneity (I^2= 98.926 %). There was no significant difference in quality of life in the patients undergoing SLIT tablets compared to placebo (mean difference = 0.26, 95% CI = -0.67 to 1.19).

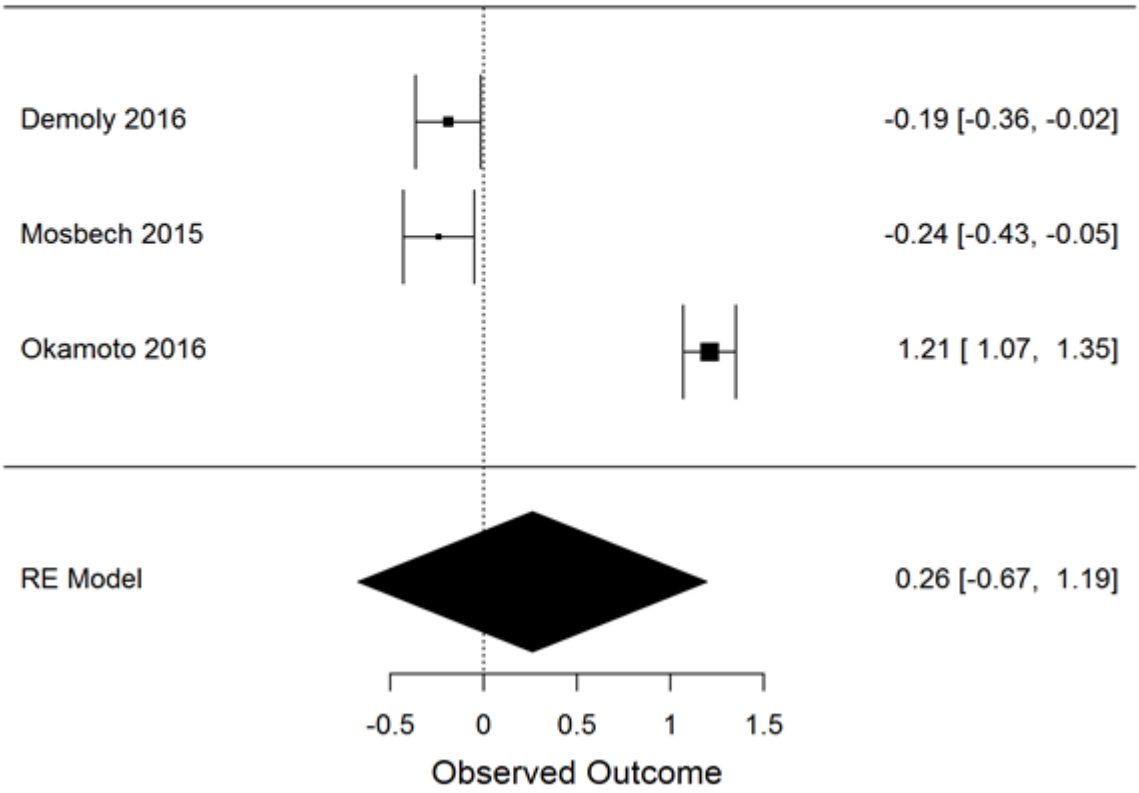

Figure 3A. Forest plot for difference between SLIT and placebo as regards RQLQ score. There is considerable heterogeneity across studies (I^2 = 98.926%, Cochran Q test P-value <0.001). Difference between SLIT and placebo is not statistically significant (mean difference = 0.26, 95% CI = -0.67 to 1.19).

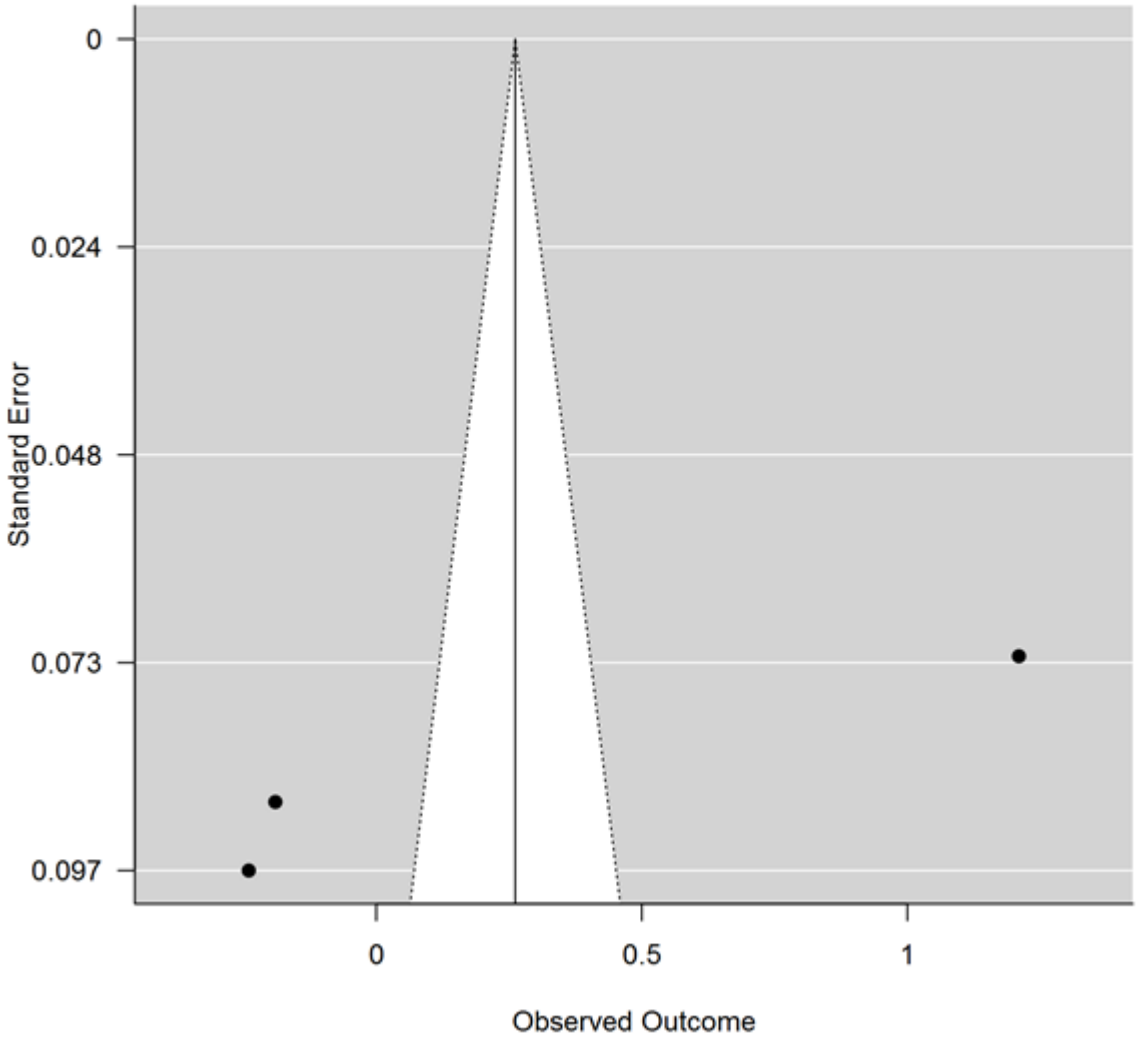

Figure 3B. Funnel plot for difference between SLIT and placebo as regards the RQLQ score. There is no evidence of publication bias with symmetrical funnel plot. Begg-Mazumdar rank correlation test P-value = 0.233, Egger regression test P-value <0.001, Rosenthal fail-safe N = 52.

Safety

In general, most of the cases of adverse drug reaction (ADR) were mild-to-moderate local allergic reactions such as mouth edema, oral pruritus, and throat irritation, occurring in 5–20% of the cases in the therapeutic groups**.** Serious ADRs are not common. No case of death was reported.

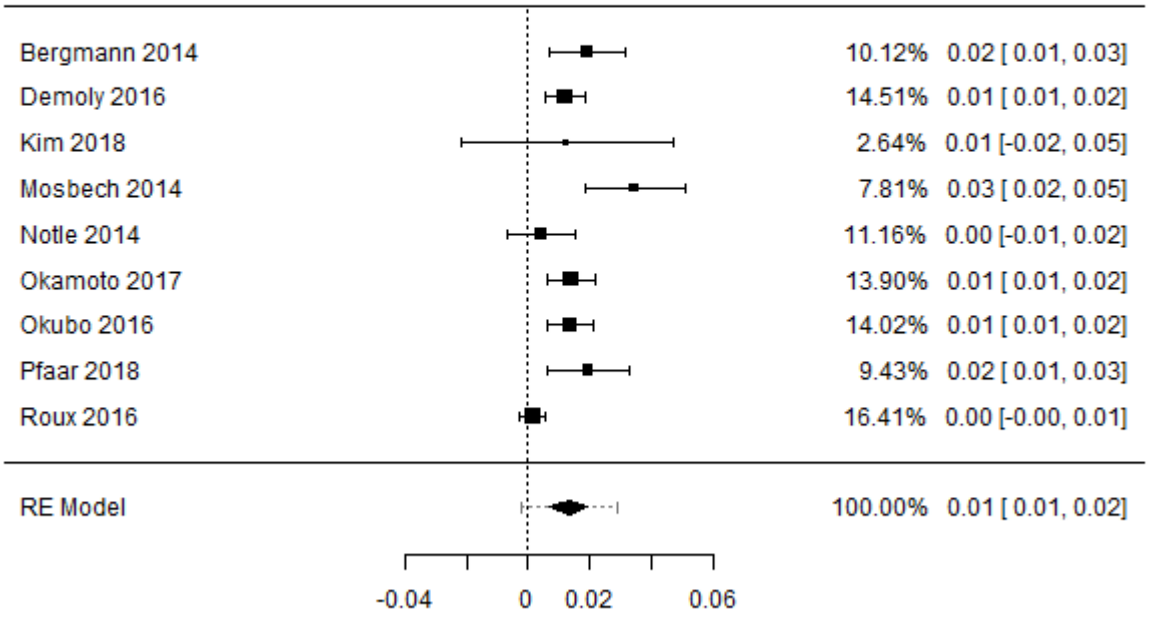

Figure 4A. Forest plot for the incidence rate of serious side effects associated with administration of SLIT. There is substantial heterogeneity across studies (I2 = 73.51%, Cochran Q test P-value <0.001). Pooled rate =1%, 95% CI = 1% to 2%.

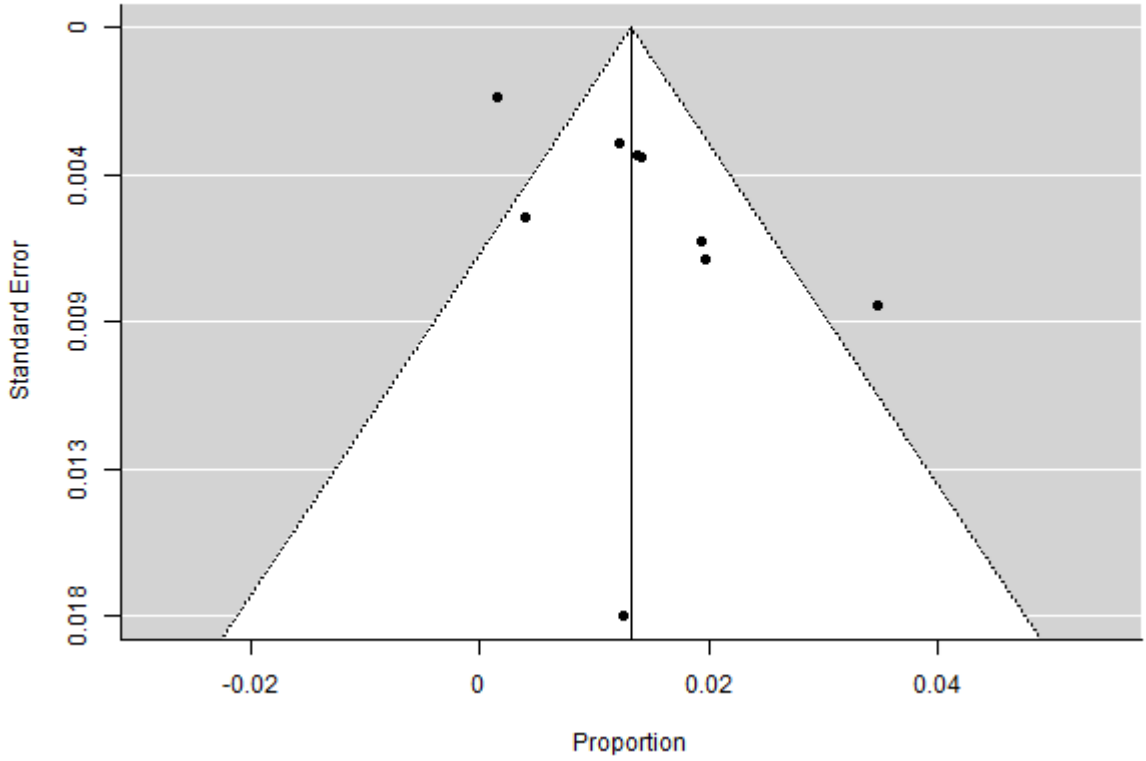

Figure 4B. Funnel plot for the incidence rate of serious side effects associated with administration of SLIT. There is evidence of publication bias with symmetrical funnel plot. Begg-Mazumdar rank correlation test P-value = 0.119, Egger regression test P-value = 0.044, Rosenthal fail-safe N = 186. Duval & Tweedie's Trim-and-Fill analysis shows no missing studies and effect size is unchanged.

DISCUSSION

Our study illustrated a significant reduction of RTSS in patients undergoing treatment with SLIT tablets, and all the included patients were adults. Allergic diseases are of high heterogeneity due to various molecular and age differences However, the different immune system functions modulated by different drug formulations may serve as another reason for treatment response heterogeneity[17].

It is well known that environmental exposure levels affect immunotherapy outcomes. The model of environmental exposure chamber (EEC) enables a better assessment of AR outcomes[18,19]. However, only two of the nine included studies were carried out following EEC guidelines, resulting in high heterogeneity in our metaanalysis.

The limited number of recruited patients is likely to interfere with the conclusion and future multiple centers, and RCTs with large sample sizes are still needed, particularly in AR patients undergoing therapy with SLIT tablets. Although the heterogeneity cannot currently be explained by SLIT tablet dose and treatment duration due to the results of the meta regression, the different transmucosal concentration gradient may cause a significant difference even in patients undergoing a similar dose of SLIT tablets.

These findings suggest that in addition to the concentration of the extract, the biological activity of SLIT tablets, transmucosal diffusion gradient, and other parameters should also be evaluated as well as the SLIT tablets dose. Moreover, the inclusion criteria of each RCT varied slightly from each other on characteristics, such as age range and dose of SLIT tablets, resulting in the relatively high heterogeneity.

The mechanism of SLIT is likely to be the modulatory effect on the immune system and cell[20]s. However, we did not identify a significant reduction of specific IgE levels in AR patients after SLIT tablet administration. Interestingly, there is a trend toward a reduction of serum specific IgE level in the placebo group, suggesting that the potential mechanism may be unrelated to the modulation of specific IgE. The mechanism through which SLIT tablets act on AR has not been completely defined.

The frequency and function of interleukin 10 secreting Tr1 cells are enhanced after immunotherapy on patients with allergic rhinitis; however, there was no significant reduction regarding serum specific IgE levels regardless of the drug formulations. However, serum specific IgE levels and the ratio of specific IgE to total IgE can potentially represent a mark for treatment response evaluation and evaluation of the prognosis. Collectively, these studies suggest that SLIT tablets may act as an adaptive modulator of the immune system.

In addition, future translational investigations are still needed to further illustrate the mechanisms of SLIT tablets. Our current study suggests that SLIT tablets are effective at reducing RTSS and relieving rhinitis symptoms[21]. Positive outcomes of the effect of SLIT tablets have been reported in most of the RCTs; however, there are still some limitations preventing the formation of a complete guideline for the treatment of AR.

Although our metaanalysis consisted of nine studies with more than 2000 patients, the heterogeneity is high, and the number of identified adolescent patients is still relatively small. Furthermore, the included studies lack the population of adolescents with AR undergoing SLIT tablet therapy.

Moreover, the index indicating immunostate of the receivers such as Th1/Th2 and Treg is not extractable in all included studies as these are not regular clinical observing outcomes. The evidence for the level of serum sIgE is rather limited currently due to few articles reporting such outcomes. Despite these limitations, our study was able to synthesize the most current studies regarding the efficacy of SLIT tablets on AR patients.

A majority of our identified articles showed a significant reduction in RTSS in AR patients undergoing SLIT tablets. Our meta analysis also illustrated the improvement of rhinitis symptoms, although no significant improvement of serum specific IgE level was observed. SLIT tablet administration for allergic rhinitis patients is a widely adopted and safe immunotherapy. The current systematic review and metaanalysis suggest that SLIT tablets are effective in reducing RTSS in AR adults but are perhaps not as effective regarding the serum specific IgE level.

However, the mechanism of SLIT tablets on AR patients has not been completely defined. Future RCTs and translational studies with larger sample sizes are still needed to provide a higher level of evidence regarding the efficacy of SLIT tablets in AR patients, particularly on adolescent AR patients. In addition, the outcomes in AR patients with or without allergic asthma should be evaluated independently to determine the potentially different outcomes between patients with or without comorbidities.

CONCLUSION

Our current metaanalysis suggests that SLIT tablets may serve as a safe and effective treatment in reducing rhinitis symptoms in patients suffering from HDM induced allergic rhinitis, despite the limitation of high heterogeneity. However, the efficacy in adolescents is still under investigation.. SCIT and SLIT are two forms of immunotherapy in allergic rhinitis while SLIT has proven to be potentially safer than SCIT

SLIT tablets combine two major species together and may better target allergic diseases with high heterogeneity such as AR[16]. In addition, SLIT tablets ensure better modulation of the drug amount and higher compliance due to its safety and convenience for transportation, administration, and follow- up[15].

Future RCTs and translational studies with larger sample sizes are needed to provide further evidence. SLIT tablets effectively relieve rhinitis symptoms in adults with allergic rhinitis. Nevertheless, the current evidence may be limited due to sample size and the heterogeneity between studies. Large sample size and multiple center RCTs on the efficacy of different formulations of SLIT drugs are still needed to provide further evidence and a more precise recommendation.

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