

Meta Analysis

Sublingual Immunotherapy Tablets Relieve Symptoms in Adults with Allergic Rhinitis: A Meta-analysis of Randomized Clinical Trials

Yi Li¹, Shi-Yuan Yu¹, Rui Tang², Zuo-Tao Zhao³, Jin-Lyu Sun²

¹Emergency Department, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China

²Department of Allergy, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, Beijing 100730, China

³Department of Dermatology, Peking University First Hospital, Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing 100034, China

Abstract

Background: Sublingual immunotherapy (SLIT) has been proven to be effective against house dust mite-induced allergic rhinitis. However, the efficacy in adults with allergic rhinitis has never been reported on SLIT tablets. The current meta-analysis aimed to illustrate the differentiated efficacy of SLIT tablets on allergic rhinitis.

Methods: Our systematic review and meta-analysis were performed on allergic rhinitis patients and aimed to summarize those randomized controlled studies (RCTs). PubMed, EMBASE, Cochrane library, and MEDLINE were screened for associated articles. We included RCTs on allergic rhinitis patients undergoing SLIT therapy and reporting outcomes on symptom relief and serum-specific IgE levels. The effect of SLIT tablets on the Rhinitis Quality Life Questionnaire Score (RQLQ), Rhinitis Total Symptom Score (RTSS), and serum-specific IgE levels was evaluated using RevMan 5.3.

Results: Seven studies were included, with 2723 patients identified. All of the studies were RCT. The included seven studies were all conducted on adults. Among the included seven articles, five researches administered patients with SLIT tablets and were eligible for meta-analysis of RTSS, consisting of 1490 patients. Overall, RTSS was significantly reduced in the SLIT tablet group compared with that in the placebo group (standard mean difference = -0.33, 95% confidence interval [-0.54, -0.13], $P < 0.01$). There was no significant difference in specific IgE levels between SLIT and placebo patients.

Conclusions: 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.

Key words: Allergic Rhinitis; Meta-analysis; Sublingual Immunotherapy; Sublingual Immunotherapy Tablets

INTRODUCTION

Allergic rhinitis (AR) is a mild-to-moderate allergic disease affecting approximately 10% to 30% of the population worldwide.^[1] House dust mite (HDM) is one of the most common AR allergens in the world, and the most common species are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. The two types differ from each other to some extent, but patients are suffering from HDM-induced AR are usually cosensitized to both species.^[2] AR symptoms include runny nose, sneezing,

nasal itching, and nasal obstruction, among other symptoms. The symptoms vary by individual, and patients can be in

Address for correspondence: Dr. Jin-Lyu Sun, Department of Allergy, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, Beijing 100730, China
E-Mail: 18611382050@163.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2018 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 05-07-2018 **Edited by:** Li-Shao Guo

How to cite this article: Li Y, Yu SY, Tang R, Zhao ZT, Sun JL. Sublingual Immunotherapy Tablets Relieve Symptoms in Adults with Allergic Rhinitis: A Meta-analysis of Randomized Clinical Trials. Chin Med J 2018;131:2583-8.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.244108

great pain during exacerbations.^[3] The current therapeutic treatment includes allergen avoidance, antihistamine treatment, intranasal glucocorticoid treatment, and immunotherapy.^[4]

Immunotherapy modulates immune system function and is currently considered to be the only option with a potential long-term posttreatment effect on allergic diseases.^[5] The molecular and cellular mechanisms of AIT include early mast cell and basophil desensitization effects, regulation of T- and B-cell responses, regulation of IgE and IgG4 production, and inhibition of responses from eosinophils, mast cells, and basophils in the affected tissues.^[6] However, the mechanism has not yet been completely illustrated. Sublingual immunotherapy (SLIT) has been demonstrated as a potential effective treatment for HDM-induced allergic rhinitis.^[7] SLIT drugs contain a low dose of an extract from HDM, aiming to modulate the immune reaction and achieving long-term efficacy.^[8] SLIT is more convenient and safer than subcutaneous immunotherapy (SCIT), which is another commonly used immunotherapy against HDM-induced AR.^[9] The formulations of SLIT include drops and tablets, and there is a trend for the SLIT tablets to gradually replace the use of SLIT drops due to their more convenient transportation and safer and more effective outcomes.

However, the currently reported outcomes of SLIT tablets are highly variable while the outcomes of SLIT tablet in China have never been reported due to government regulations. Numerous randomized controlled studies (RCT) have been conducted worldwide, although the parameters and outcome measurement are still highly variable. In addition, the different efficacies of SLIT due to different drug formulations were varied according to clinical experience.^[10-13] It is difficult to determine whether SLIT does or does not work overall. There has been no published meta-analysis concerning the efficacy of SLIT tablets on relieving AR patient symptoms. Our current meta-analysis aims to evaluate the outcome of SLIT tablets on HDM-induced AR patients to determine the efficacy of symptom relief and to provide the evidence for the further investigation and administration of SLIT tablet in China.

METHODS

Published literature was systematically reviewed through the PubMed, EMBASE, and Cochrane Library databases. Search items included “allergic,” “hypersensitive,” “anaphylactic,” “rhinitis,” “nasitis,” “SLIT,” etc., The articles were restricted to those published in English or Chinese and human studies.

The database search results were evaluated independently by two experienced researchers and strictly followed the inclusion and exclusion criteria and article quality evaluation protocol. If divergence occurred, a discussion was performed until a final consensus was reached. Next, full-text screening

was conducted, and the included articles were identified for meta-analysis.

Inclusion criteria

(1) Reports should include patients with HDM-induced AR, with or without allergic asthma (AA). (2) Statistics should include Rhinitis Quality of Life Questionnaire scores (RQLQ), Rhinitis Total Symptom Scores (RTSS), and/or specific serum IgE level. (3) Only RCT and prospective controlled study were included. (4) Studies should be performed on adolescents, adults, or both. (5) Articles published in English or Chinese.

Exclusion criteria

(1) Experiment not performed on humans was excluded. (2) Main parameters were impossible to extract. (3) Reports recruited patients merely suffering from AA but not AR. (4) Statistics consisted of patients with SLIT and other immunotherapy combined, which cannot be separated. (5) Experiment administered non-SLIT therapy as the main treatment.

Data of the endpoint of each clinical study was then extracted and collected by the researchers using Microsoft Excel 2013 including RTSS and serum-specific IgE levels. Risk of bias, mean value, standardized mean deviation (SMD), and sample size were collected to perform a meta-analysis using Review Manager 5.3. The results are shown in forest plot and funnel plot format. Heterogeneity was considered high when $I^2 > 50\%$, and a randomized model was conducted to pool these statistics; a fixed model was used if I^2 is no more than 50%. Next, a meta-regression analysis was performed using STATA 12.0 to determine the source of heterogeneity. $P < 0.05$ is considered to indicate a significant difference.

RESULTS

Study inclusion

Database screening included 1193 related articles identified by reviewing PubMed, EMBASE, Cochrane Library, and MEDLINE. In total, 972 articles were removed because the studies were not performed on human subjects. After full-text screening and quality evaluation conducted by our researchers, seven articles meeting the inclusion criteria were included. The selection process is illustrated in Figure 1.

Among the included seven articles, all of the studies were RCTs conducted on adult patients suffering from AR. RTSS was used to evaluate the symptom level, and specific IgEs were evaluated to elucidate the effect on the individual immune system. Study details are shown in Table 1.

Risk of bias

The methodological quality of selected trials was assessed using the Cochrane Collaboration's tool. All of the studies included suggested randomization, with the proper method of random sequences generation and six studies reported detailed allocation concealment. However, the risk was unclear regarding outcome assessment. The reasons for dropout between groups are similar in included studies. The risk of selective reporting bias is low. Six included

studies had low risk of other bias while the other is unclear. Therefore, all studies were judged to be of a good methodological quality [Figures 2 and 3].

Efficacy of sublingual immunotherapy

Among the included seven articles, five of the studies that administered patients with SLIT tablets were eligible for meta-analysis of RTSS and consisted of 1490 patients.^[14-18] A randomized model was used due to the high heterogeneity ($I^2 = 74\%$). Meta-analysis demonstrated a significant reduction in RTSS in patients receiving SLIT tablets compared to placebo (SMD = -0.33 , 95% confidence interval [CI]: $[-0.54, -0.13]$, $P = 0.001$) [Figure 4].

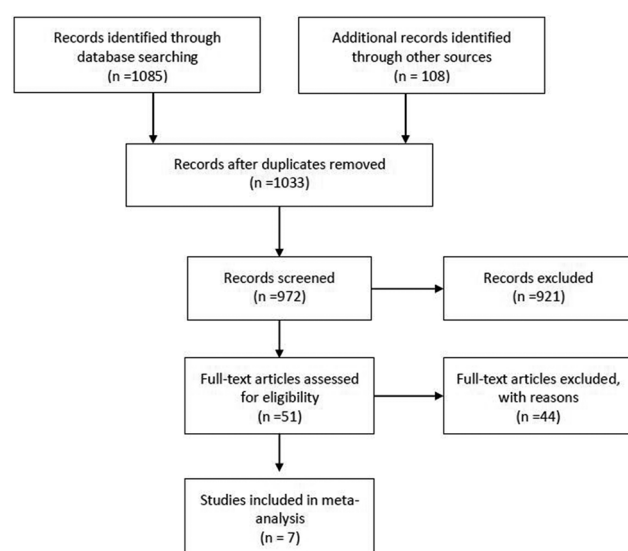


Figure 1: Flow diagram of the meta-analysis study on house dust mite sublingual immunotherapy tablets relieve symptoms of adults allergic rhinitis.

Two of the seven articles on SLIT tablets included descriptive data for meta-analysis on specific IgE levels. Data from these two articles consisted of 103 patients.^[19,20] A randomized model was used due to high heterogeneity ($I^2 = 69\%$). There was no significant difference in IgE levels in the patients undergoing SLIT tablets compared to placebo (SMD = 0.14 , 95% CI $[-0.72, 1.07]$, $P = 0.74$) [Figure 5].

Meta-regression analysis showed no association between SLIT dose, treatment duration, publication year, or patient age and the level of RTSS or specific IgE level ($P > 0.05$).

Adverse drug reaction

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; however, there were still nine serious ADRs reported among the three of the seven included studies such as respiratory distress, laryngeal edema, severe eczema, or vaginal laceration. However, among the included seven articles, no systemic anaphylactic reaction was reported, and only one case required epinephrine administration due to respiratory distress caused by laryngeal edema and followed by dysphonia, throat irritation, and dry cough. No case of death was reported.

DISCUSSION

Immunotherapy is considered to be the only approach with promising and long-term effects on allergic diseases. SLIT is one of the most commonly used therapies involving HDM-induced AR; however, the efficacy and outcome vary among the studies.

SLIT tablets combine two major species together^[21] and may better target allergic diseases with high heterogeneity such

Table 1: Characteristics of included studies on adult patients suffering from allergic rhinitis

Research	n	Type	Age (years)	Recruited patients	Formulation	Amount*	Duration	Primary endpoint	Secondary endpoint
Karl-Christian Bergmann 2014 ^[14]	313	RCT	Drug 30.1 ± 8.43 Control 30 ± 8.96	Diameter of SPT >3 mm, or sIgE >0.7 kU/L, or ARTSS >4	Tablet	500 IR tablet QD	24 m	AAaSS	ARTSS, ARSS, ARMS
Hendrik Nolte 2015 ^[20]	83	RCT	Drug 28 (18–58) Control 27 (19–43)	Diameter of SPT >3 mm, or sIgE >0.7 kU/L	Tablet	12 DU of MK-8237	24 w	Not reported	Not reported
Holger Mosbech 2015 ^[19]	241	RCT	Drug 31.6 (15–68) Control 31.6 (14–74)	Diameter of SPT >3 mm, or sIgE >0.7 kU/L	Tablet	6 SQ-HDM	12 m	RTSS, RQLQ	Not reported
Kimihiro Okubo 2016 ^[15]	633	RCT	Drug 26.8 ± 12.1 Control 26.8 ± 11.7	sIgE >3.5 kU/L	Tablet	12 SQ-HDM	12 m	TCRS	Symptoms and life quality scores
Michel Roux 2016 ^[17]	180	RCT	Drug 32.8 ± 9.33 Control 31.3 ± 8.75	Diameter of SPT >3 mm, or sIgE >0.7 kU/L, or ARTSS >5	Tablet	500 IR tablet QD	6 m	ARTSS	ARSS, AVASS
Pascal Demoly 2016 ^[16]	656	RCT	Drug 32.1 ± 10.6 Control 32.2 ± 10.9	Not reported	Tablet	12 SQ-HDM	12 m	TCRS	Symptoms and life quality scores
Y. Okamoto 2017 ^[18]	612	RCT	Drug 30.5 ± 11.7 Control 30.2 ± 11.6	sIgE >0.7 kU/L, or ARTSS >5	Tablet	500 IR tablet QD	12 m	AASS	Nasal and ocular symptom scores, RQLQ

*Amount is described as the highest does in a certain clinical trial. TCRS: Total combined rhinitis score; AASS: Average Adjusted Symptom Score; AAaSS: Average adjusted symptom score; ARTSS: Average Rhinitis Total Symptom Score; ARSS: Average Rhinitis Symptom Score; ARMS: Average Rescue Medication Score; AVASS: Average Visual Analog Scale Score; RQLQ: Rhinitis quality of life questionnaire score; SPT: Skin prick test; RCT: Randomized controlled studies; HDM: House dust mite; RTSS: Rhinitis Total Symptom Score.

as AR.^[22] In addition, SLIT tablets ensure better modulation of the drug amount and higher compliance than SLIT drops due to its safety and convenience for transportation, administration, and follow-up.^[23] A majority of current RCTs showed some benefit from immunotherapy on RQLQ and RTSS. SCIT and SLIT are two forms of immunotherapy on

allergic rhinitis while SLIT has proven to be potentially safer than SCIT.^[24] Although some of our included articles reported side effects, such as oral pruritus, resulting from SLIT tablets, none of the studies reported severe complications. However, the long-term efficacy of SLIT remains under investigation. For instance, a multicenter, large sample size RCT conducted in Europe revealed that SLIT reduces RTSS and RQLQ in patients suffering from allergic rhinitis.^[16] Similar outcomes were shown in another meta-analysis studying AR patients treated with probiotics.^[25]

Our study illustrated a significant reduction of RTSS in patients undergoing treatment with SLIT tablets, and all the included patients were adults. These findings are consistent with our observation during clinical work that SLIT drops may not work at times.^[19,26] de Bot *et al.*^[13] also noted that SLIT drops with HDM allergens are no better than placebo regarding the efficacy of reducing rhinitis symptoms in adolescents suffering from allergic rhinitis. The sample size was 251 patients. Allergic diseases are of high heterogeneity due to various molecular and age differences.^[27] However, Ippoliti *et al.*^[10] reported a significant reduction of RTSS in a sample of 86 adolescent patients suffering from allergic rhinitis and allergic asthma undergoing SLIT drops. However, the different immune system functions modulated by different drug formulations may serve as another reason for treatment response heterogeneity.^[10] 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.^[17,20] However, only two of the seven included studies were carried out following EEC guidelines, resulting in high heterogeneity in our meta-analysis. 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.^[28] 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.^[29] Moreover, the inclusion

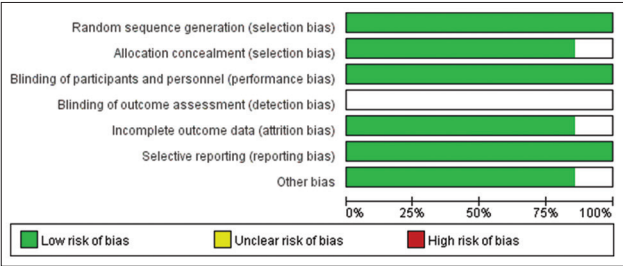


Figure 2: Risk of bias among included articles.

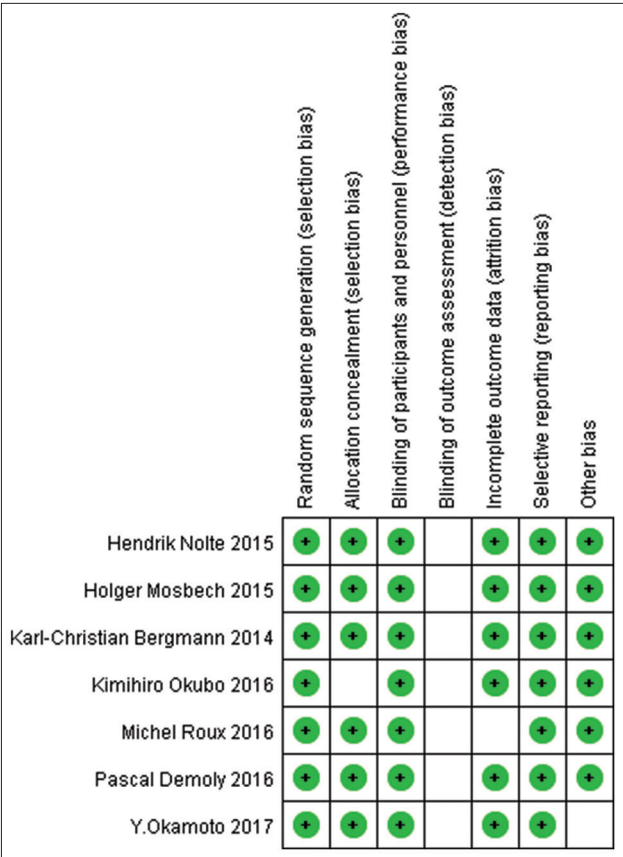


Figure 3: Risk of bias summary among included articles.

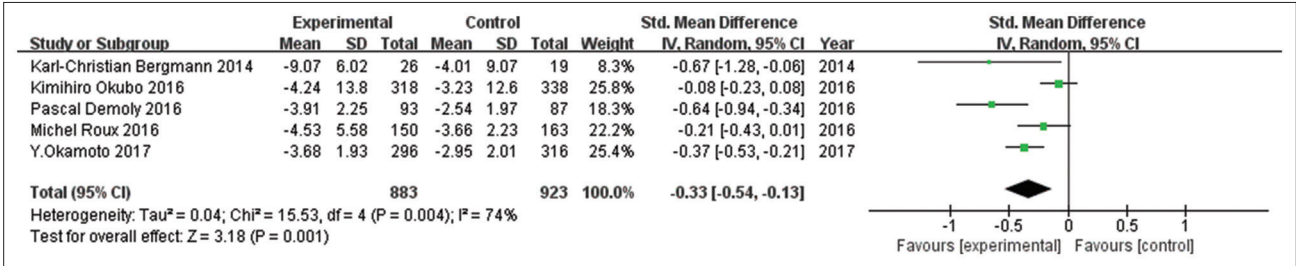


Figure 4: Efficacy of sublingual immunotherapy tablets on Rhinitis Total Symptom Score between experimental and placebo groups.

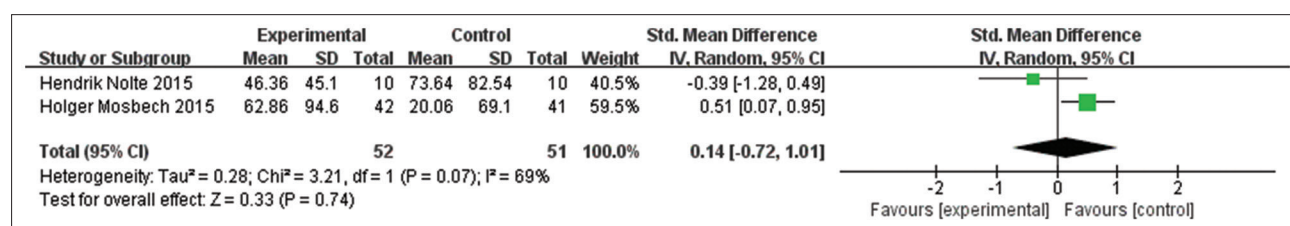


Figure 5: Efficacy of sublingual immunotherapy tablets on specific IgE levels between experimental and placebo groups.

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 cells.^[30] 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.^[25] 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^[31-33] 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.^[18,34] 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 and may be more efficacious than SLIT drops according to our clinical observations.^[26] 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 meta-analysis consisted of seven 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.^[22,33] 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.^[26,35,36] The current systematic review and meta-analysis 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.

In conclusion, Our current meta-analysis 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. Future RCTs and translational studies with larger sample sizes are needed to provide further evidence.

Acknowledgement

We would like to thank professor Ji-fu Wei for the important advice on our study.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (No. 30671943 and No. 81771725) and CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1003).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: Significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. *Allergy* 2001;56:301-6. doi: 10.1034/j.1398-9995.2001.00834.x.
2. Turner P, Dear J, Scadding G, Foreman JC. Role of kinins in seasonal allergic rhinitis: Icatibant, a bradykinin B2 receptor antagonist, abolishes the hyperresponsiveness and nasal eosinophilia induced by antigen. *J Allergy Clin Immunol* 2001;107:105-13. doi: 10.1067/mai.2001.111145.
3. Wood JP, Traub SJ, Lipinski C. Safety of epinephrine for anaphylaxis in the emergency setting. *World J Emerg Med* 2013;4:245-51. doi: 10.5847/wjem.j.1920-8642.2013.04.001.
4. Russell WS, Farrar JR, Nowak R, Hays DP, Schmitz N, Wood J, et al. Evaluating the management of anaphylaxis in US emergency

- departments: Guidelines vs. practice. *World J Emerg Med* 2013;4:98-106. doi: 10.5847/wjem.j.920-8642.2013.02.003
5. Geller-Bernstein C, Pibourdin JM, Dornelas A, Fondarai J. Efficacy of the acaricide: Acardust for the prevention of asthma and rhinitis due to dust mite allergy, in children. *Allerg Immunol (Paris)* 1995;27:147-54.
6. Berings M, Karaaslan C, Altunbulakli C, Gevaert P, Akdis M, Bachert C, *et al.* Advances and highlights in allergen immunotherapy: On the way to sustained clinical and immunologic tolerance. *J Allergy Clin Immunol* 2017;140:1250-67. doi: 10.1016/j.jaci.2017.08.025.
7. Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, *et al.* House dust mite allergen reduction and allergy at 4 yr: Follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17:329-36. doi: 10.1111/j.1399-3038.2006.00410.x.
8. Peng GC, Hsu CH. The efficacy and safety of heat-killed *Lactobacillus paracasei* for treatment of perennial allergic rhinitis induced by house-dust mite. *Pediatr Allergy Immunol* 2005;16:433-8. doi: 10.1111/j.1399-3038.2005.00284.x.
9. Tabar AI, Echechipia S, García BE, Olaguibel JM, Lizaso MT, Gómez B, *et al.* Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol* 2005;116:109-18. doi: 10.1016/j.jaci.2005.05.005.
10. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, *et al.* Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003;14:216-21. doi: 10.1034/j.1399-3038.2003.00025.x
11. Corren J, Diaz-Sanchez D, Saxon A, Deniz Y, Reimann J, Sinclair D, *et al.* Effects of omalizumab, a humanized monoclonal anti-IgE antibody, on nasal reactivity to allergen and local IgE synthesis. *Ann Allergy Asthma Immunol* 2004;93:243-8. doi: 10.1016/S1081-1206(10)61495-0.
12. Guimarães Junqueira de Queirós M, Oliveira Silva DA, Alves R, Fukuhara Chiba H, Soares de Amaral VB, de Almeida KC, *et al.* Mite-specific immunotherapy using allergen and/or bacterial extracts in atopic patients in Brazil. *J Investig Allergol Clin Immunol* 2008;18:84-92.
13. de Bot CM, Moed H, Berger MY, Röder E, Hop WC, de Groot H, *et al.* Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol* 2012;23:150-8. doi: 10.1111/j.1399-3038.2011.01219.x.
14. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, *et al.* Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133:1608-14.e6. doi: 10.1016/j.jaci.2013.11.012.
15. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, *et al.* Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. *J Allergy Clin Immunol* 2017;139:1840-48.e10. doi: 10.1016/j.jaci.2016.09.043.
16. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J, *et al.* Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016;137:444-51.e8. doi: 10.1016/j.jaci.2015.06.036.
17. Roux M, Devillier P, Yang WH, Montagut A, Abiteboul K, Viatte A, *et al.* Efficacy and safety of sublingual tablets of house dust mite allergen extracts: Results of a dose-ranging study in an environmental exposure chamber. *J Allergy Clin Immunol* 2016;138:451-8.e5. doi: 10.1016/j.jaci.2016.03.039.
18. Okamoto Y, Fujieda S, Okano M, Yoshida Y, Kakudo S, Masuyama K, *et al.* House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. *Allergy* 2017;72:435-43. doi: 10.1111/all.12996.
19. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, *et al.* SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol* 2015;114:134-40. doi: 10.1016/j.anai.2014.11.015.
20. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, *et al.* Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol* 2015;135:1494-501.e6. doi: 10.1016/j.jaci.2014.12.1911.
21. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study. *J Allergy Clin Immunol* 2010;126:969-75. doi: 10.1016/j.jaci.2010.08.030.
22. Patel DD, Antoni C, Freedman SJ, Levesque MC, Sundry JS. Phase 2 to phase 3 clinical trial transitions: Reasons for success and failure in immunologic diseases. *J Allergy Clin Immunol* 2017;140:685-7. doi: 10.1016/j.jaci.2017.04.029.
23. Di Gioacchino M, Cavallucci E, Ballone E, Cervone M, Di Rocco P, Piunti E, *et al.* Dose-dependent clinical and immunological efficacy of sublingual immunotherapy with mite monomeric allergoid. *Int J Immunopathol Pharmacol* 2012;25:671-9. doi: 10.1177/039463201202500313.
24. Bush RK, Swenson C, Fahlberg B, Evans MD, Esch R, Morris M, *et al.* House dust mite sublingual immunotherapy: Results of a US trial. *J Allergy Clin Immunol* 2011;127:974-81.e1-7. doi: 10.1016/j.jaci.2010.11.045.
25. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol* 2013;31:233-41. doi: 10.12932/AP0276.31.3.2013.
26. Mauro M, Boni E, Makri E, Incorvaia C. Pharmacodynamic and pharmacokinetic evaluation of house dust mite sublingually administered immunotherapy tablet in the treatment of asthma. *Expert Opin Drug Metab Toxicol* 2015;11:1937-43. doi: 10.1517/17425255.2015.1113255.
27. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, *et al.* Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;114:838-44. doi: 10.1016/j.jaci.2004.05.070.
28. Larenas Linnemann DE, Singh J, Rosario N, Esch R, Matta JJ, Maspero J, *et al.* Similar biological activity in skin prick test for Oralair® (8200 BAU) and Grazax® (6200 BAU) reinforces effective SLIT dosing level. *Allergy* 2016;71:1782-6. doi: 10.1111/all.12998.
29. Zhen AC. Efficacy and safety of sublingual dust mite allergen extract tablets in the treatment of adult allergic rhinitis (in Chinese). *Chin Med Abstr* 2014;22:65-6. doi: 10.1111/j.1398-9995.2004.00456.x.
30. Ferreira MB, Santos AS, Santos MC, Carlos ML, Barbosa MA, Carlos AG, *et al.* Nasal ECP patterns and specific immunotherapy in mite-allergic rhinitis patients. *Eur Ann Allergy Clin Immunol* 2005;37:96-102.
31. Lou W, Wang C, Wang Y, Han D, Zhang L. Enhancement of the frequency and function of IL-10-secreting type I T regulatory cells after 1 year of cluster allergen-specific immunotherapy. *Int Arch Allergy Immunol* 2012;159:391-8. doi: 10.1159/000338995.
32. Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, *et al.* A novel approach in allergen-specific immunotherapy: Combination of sublingual and subcutaneous routes. *J Allergy Clin Immunol* 2011;128:808-15.e7. doi: 10.1016/j.jaci.2011.04.033.
33. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev* 2015;28:CD011293. doi: 10.1002/14651858.CD011293.pub2.
34. Fujimura T, Yonekura S, Horiguchi S, Taniguchi Y, Saito A, Yasueda H, *et al.* Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clin Immunol* 2011;139:65-74. doi: 10.1016/j.clim.2010.12.022.
35. Nelson HS. Update on house dust mite immunotherapy: Are more studies needed? *Curr Opin Allergy Clin Immunol* 2014;14:542-8. doi: 10.1097/ACI.0000000000000104.
36. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, *et al.* Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.e7. doi: 10.1016/j.jaci.2014.03.019.

尘螨过敏性鼻炎成年患者使用舌下含服片剂可缓解临床症状：随机临床试验荟萃分析

摘要

背景：舌下免疫疗法（SLIT）已被证明可有效对抗屋尘螨诱发的过敏性鼻炎。然而，目前尚无SLIT片剂对成人过敏性鼻炎的报道。我们的系统评价旨在分析讨论SLIT片剂对成人过敏性鼻炎的疗效。

方法：通过检索PubMed，EMBASE，Cochrane图书馆和MEDLINE筛选相关文章，本研究应用RevMan 5.3对数据进行整合分析，报告过敏性鼻炎患者经SLIT片剂治疗后症状缓解情况和血清特异性IgE水平。

结果：该荟萃分析纳入7项研究，总计包含2723成年名患者。所有研究均为随机对照研究（RCT）。7篇文章中，5名给予SLIT片剂的患者并且报道了鼻炎总症状评分。总体而言，与安慰剂组相比，SLIT片剂组中的RTSS显著降低[标准平均差异（SMD）=-0.33，95%置信区间（95%CI）（-0.54， -0.13）， $P=0.00$]。SLIT和安慰剂患者之间IgE水平没有显著差异。

结论：SLIT片剂可有效缓解成人过敏性鼻炎的鼻炎症状。然而，由于样本量和研究之间的异质性较大，目前的证据尚不足以形成指南。目前仍需大样本量、多中心RCT对不同种类SLIT药物的作用提供进一步的证据。

