Allergology International xxx (2018) 1–11

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited Review Article

The efficacy of sublingual immunotherapy for allergic diseases in Asia

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ARTICLE INFO

Article history:
Received 22 January 2018
Received in revised form
5 February 2018
Accepted 14 February 2018
Available online xxx

Keywords:
Asia
Disparity
Efficacy
Randomized controlled trial
Sublingual immunotherapy

ABSTRACT

Sublingual immunotherapy (SLIT) has been proven to be safe and effective from an abundance of Western literature, but data from Asia is less complete. This review aims to examine the basic science, safety and efficacy of SLIT in Asian patients, and to determine future research needs in Asia. We performed a literature search on PUBMED, Scopus, and Cochrane Library database for articles on SLIT originating from Asian countries through Nov 2017. There were 18 randomized, double-blind, placebo-controlled trials, of which 9 involved solely paediatric subjects. Overall, sublingual immunotherapy is safe and is efficacious in Asian populations in allergic rhinitis (AR) and asthma. House dust-mite SLIT is effective in both mono- and polysensitized AR patients. Efficacy of SLIT is comparable to subcutaneous immunotherapy. Data on long term efficacy is lacking. A disproportionate majority of research originates from China and Japan, reflecting an asymmetry of access to SLIT within Asia. Significant disparities exist in the development of the allergy speciality, prescription patterns of SLIT, and pharmacological potencies of different SLIT products within and between Asian nations. We conclude that current available evidence suggests SLIT is efficacious in Asians but data quality of evidence is hampered by non-placebo controlled studies with methodological limitations. More data is needed in South and Southeast Asian populations. Future efforts may be directed towards improving access to SLIT in developing countries, standardization of SLIT dosage, and evaluating long term clinical outcomes.

Introduction

In the last two decades, sublingual immunotherapy (SLIT) earned a reputation as a safe and effective therapeutic modality for allergic diseases, particularly allergic rhinitis (AR) and asthma.[1] It is a treatment with disease-modifying properties having the potential to cure allergies, and does not have the systemic complication profile and invasiveness of subcutaneous immunotherapy (SCIT). Pooled data from extensive well-conducted randomized, double-blind, placebo-controlled trials in the West have shown that SLIT is safe and effective.[2] Data from Asia is less complete. As such, it is timely and important to review existing literature from Asia on the basic science, safety and efficacy of SLIT in Asian patients, and to determine future research needs in Asia.

Asia is an expansive continent supporting nearly 60% of the world's population, and is home to China and India, two of the world's fastest growing economies.[3] It is ethnically and culturally diverse, but more importantly, there exist huge disparities among Asian countries in economic development. One would therefore expect research into allergy and its management in Asia is to be inevitably confounded by the complex interplay of genetic, cultural, environmental and socioeconomic influences. In this review, we will focus primarily on the evidence for efficacy and safety of interventional studies on SLIT conducted in Asia. Secondarily, we will also explore some of the unique contextual details surrounding SLIT in Asia.

Literature search

Search strategy

A literature search was conducted using the search term “sublingual immunotherapy” on Pubmed, Scopus, and Cochrane Library.

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2018.02.007

Inclusion and exclusion criteria

We included articles originating from Asian countries, with a focus on East Asia. We excluded studies on non-human subjects and articles not directly relevant to sublingual immunotherapy in Asia, i.e. review articles on allergy management in general or on sublingual immunotherapy globally. Language of article was not an exclusion criterion.

Prioritization and analysis of studies

We identified and included for analysis all randomized, double-blind, placebo-controlled trials. Other interventional studies were evaluated on a case-by-case basis. While these trials inherently lack methodological strength, we acknowledge that relevant and useful clinical information that are otherwise not available (e.g. long term efficacy data) may be obtained, and are cited appropriately.

Characteristics of published work

The search yielded 5123 citations on sublingual immunotherapy, of which 441 were of potential interest. After excluding duplicates and applying our inclusion and exclusion criteria, we shortlisted 135 articles (Fig. 1). There were 18 randomized, double-blind, placebo-controlled trials, of which 9 involved solely paediatric subjects. The characteristics and salient results are summarized in Table 1.

Publications originated from 6 countries in Asia, chief among which are China and Japan, contributing to 51.9% and 29.6% of studies respectively. Together, these two countries are accountable for 81.4% of all articles and 83.3% of randomized, double-blind, placebo-controlled trials on SLIT from Asia (Fig. 2). South Asian (e.g. India, Sri Lanka) and Southeast Asian (e.g. Vietnam, Malaysia, Indonesia) countries are severely under-represented, even though these regions collectively make up more than 50% of Asia's population.[3]

The chronological distribution of research articles on SLIT in Asia, by year of publication, is presented in Figure 3. The rapid rise of interest in SLIT in Asia can be seen to parallel the rest of the world.

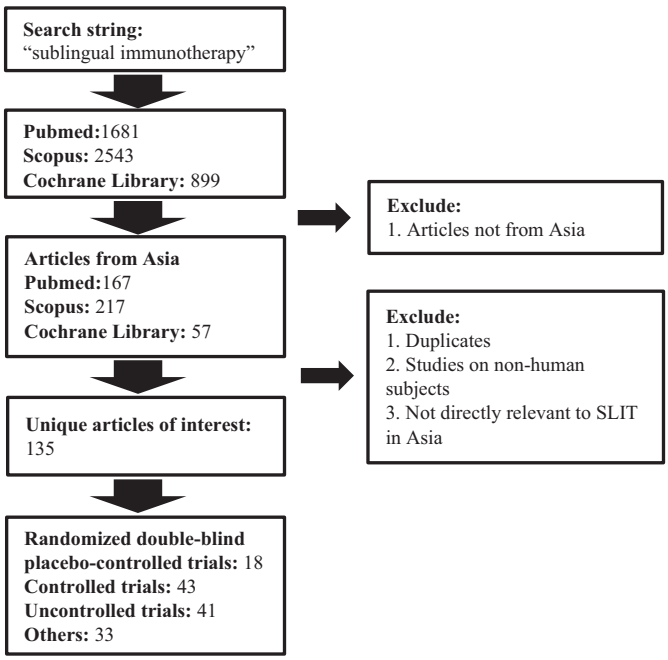

Fig. 1. Flowchart of results of literature search strategy.

Efficacy of SLIT in Asia

Overall clinical efficacy

In randomized, controlled trials (RCT) in Asia, SLIT is consistently shown to produce clinical improvement in allergy control, in AR[4–15] as well as asthma,[16–20] in all except one study[21] (Table 1). Additionally, it has been shown to produce objective improvements in lung function tests in asthmatic subjects.[16–18] Improvement in symptoms begin from 8 to 12 weeks of therapy and is sustained throughout course of treatment,[14,15,19] although it has been reported in two separate controlled trials on house dust mite (HDM)-induced AR to begin as early as 4 weeks.[22,23]

In a 6-month RCT, one Taiwan study failed to show statistically significant improvement in symptom and medication scores compared to placebo. The authors postulated possible reasons to be insufficient duration of therapy, dosage, and time in contact with oral cavity.[21] Fujimura *et al.* found SLIT to be not significantly different with placebo in ameliorating symptoms of Japanese cedar (JC) pollinosis after 1 year of treatment, although significant efficacy was found in the subsequent years of follow up.[6]

While demonstrating clear overall benefit over placebo comparing pooled inter-group data, it is recognized that SLIT does not work effectively for all users. Wang *et al.* reported achievement of well-controlled asthma in 80.5% with SLIT,[20] while Fujimura *et al.* reported clinical response in only 55%.[6] In a single-arm, uncontrolled trial of 6-month HDM SLIT in children, Lin *et al.* reported the rates for well-controlled, partly controlled and uncontrolled AR to be 43.1%, 32.8% and 24.1%, respectively.[24]

Monosensitized versus polysensitized patients

Polysensitization is a highly prevalent and clinically-significant phenomenon. In a large cross-sectional multi-centre study in China, more than 90% of atopic patients are sensitized to two or more allergens and 83.7% had concomitant sensitization to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.[25] The results of numerous trials are consistent in demonstrating that HDM SLIT is equally effective in controlling symptoms and reducing medication usage in polysensitized AR patients, in both adult and paediatric populations.[22,26–29] In one study, the authors found clinical symptom scores to show improvement earlier in the monosensitized group at 6 months and 1 year compared to the polysensitized group, but no difference at 1.5–2 years.[30] There are no studies directly comparing the clinical efficacy of single mite allergen SLIT against dual mite allergen preparations (e.g. SLIT containing *Der p and Der f* in 1:1 ratio).

It is speculated that the single HDM extract induces immune tolerance by activating inducible regulatory T cells which exert a partially nonspecific immunologic regulatory effect on immune responses even to unrelated antigens.[22,31] This biological phenomenon is termed "bystander effect". However, an important caveat is that existing data is only limited to HDM-induced AR in China. More studies are required to understand the treatment response profiles using different allergens, on different populations, and on asthma. A comparative trial on single-allergen versus multi-allergen SLIT may shed more light on the clinical significance of the bystander effect, and thus inform clinicians on the management of polysensitized patients.

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Table 1
Randomized, double-blind, placebo-controlled trials from Asia.

Author, year[†]	Ages	Study arms	Dropouts	Disease	Duration	Allergen dose and administration	Manufacturer	Main positive results	Negative results	Adverse events	Limitations
China											
Cao, 2007[18]	4–18	SLIT: 139 PC: 139	19 (14%) 8 (6%)	Asthma +/-AR	25wk	HDM (Der f) 40 mcg/day Drops	ZHE	Reduced median variability of PEFR (−1.38 vs −0.90), asthma medication score (−0.08 vs 0.52), rhinitis symptom score (−1.96 vs −1.03) Increase in specific IgG4	Rescue medication usage FEV_1 Specific IgE	No severe AE Minor AE: 20 (12/8 A/P) cases – rashes, rhinorrhoea, headache, fatigue, mild asthma exacerbation (1 case)	Disproportionate drop-outs from SLIT group
Wang, 2013[7]	4–60	SLIT: 60 PC: 60	12 (20%) 23 (38%)	AR +/-Asthma	6mo	HDM (1:1 Der p:Der f) 75 mcg/day Drops	ZHE	Decrease in total symptom scores started in week 14 Increase in specific IgG4		No severe AE Mild AE: 22 (15/7) cases – exacerbation of rhinitis, rashes, abdominal pain, oral pruritus	
Luo, 2014[8]	5–16	SLIT: 36 PC: 36	0 (0%) 0 (0%)	AR	1y	HDM (Der f) 40 mcg/day Drops	ZHE	Reduced symptom, medication, and combined symptom medication score Decreased BAFF associated with decreased Th2 cytokine and enhanced Th1 cytokine expression	-	No severe AE	
Tian, 2014[19]	4–18	SLIT: 30 PC: 30	NS	Asthma	48wk	HDM (Der f) 40 mcg/day Drops	ZHE	Reduced mean symptom score Decline in percentage of Th17 cells in both SLIT and control groups Increase in $CD4^+CD25^+$ Treg cells in SLIT group	-	NS	
Wang, 2014[20]	14–50	SLIT: 322 PC: 162	23 (7%) 8 (5%)	Asthma	1y	HDM (1:1 Der p:Der f) 300 IR/day Drops	STA	Achievement of control greater with SLIT in moderate asthma (81% vs 66%)	SLIT not better than placebo in mild asthma	No treatment-related severe AE Mild AE: (number NS) – abdominal pain, swollen tongue, oral pruritus, glossitis, cheilitis and mouth oedema	
Wang, 2016[11]	6–16	SLIT: 25 PC: 25	NS	AR	1y	HDM (Der f) 40 mcg/day Drops	ZHE	Decreased expression of osteopontin and Th2 cytokines with increase in IL-10 and TGF-β expression. Children with low baseline serum OPN level acquired better improvement of symptom and medication scores.		NS	
Chen, 2017[12]	6–12	SLIT: 21 PC: 21	NS	AR	6mo	HDM (Der f) 40 mcg/day Drops	ZHE	Inhibition of platelet activation Decreased expression of platelet factor-4 (PF4) and β-Thromboglobulin (BTG) correlated with decreased symptom scores		NS	
Guo, 2017[13]	5–55	SLIT: 32 PC: 16	2 (6%) 2 (13%)	AR	1y	HDM (1:1 Der p:Der f) NS Drops	ALK	Improved nasal symptoms score, allergic conjunctivitis score, and medication score	No difference between adults and children No difference between monosensitized (HDM) and polysensitized	No severe AE Mild AE: 14 (11/3) cases – urticaria, stomach pain, mouth and throat irritation, headache, diarrhoea, asthma exacerbation (2)	

(*continued on next page*)

Table 1 (*continued*)

Author, year[†]	Ages	Study arms	Dropouts	Disease	Duration	Allergen dose and administration	Manufacturer	Main positive results	Negative results	Adverse events	Limitations
Japan											
Okubo, 2008[4]	25–55	SLIT: 37 PC: 22	2 (treatment arm not known)	Seasonal AR	6mo	JC (Cry j 1) 2000 JAU/week Drops	TOR	Reduced nasal and ocular symptom scores and medication scores Improved QOL (JRQLQ)	-	No systemic AE Local AE: 6 cases – mild oral pruritus in first 2–3 doses	
Yonekura, 2010[5]	7–15	SLIT: 20 PC: 11	1 (5%) 2 (18%)	AR	10mo	HDM (Der f) 0.5 mcg	TOR	Symptom scores	Symptom-medication scores	No systemic AE Local AE: 1 (A) case – bitter taste	Small study population
Fujimura, 2011[6]	16–73	SLIT: 58 PC: 45	7 (12%) 8 (18%)	Seasonal AR	2y	JC (Cry j 1) 2000 JAU/week Drops	TOR	Reduced symptom medication scores in second pollen season. Symptom medication score in SLIT group remained attenuated compared with placebo in third season 1 year after 2-year SLIT. Symptom medication score correlates with the sIgE/tIgE ratio in the SLIT group. Improved QOL-symptom and total QOL scores in the increased iTreg subgroup compared with placebo.	No significant difference in symptom medication score in first pollen season compared to placebo Specific IgG4	No severe AE Mild AE: 7 (6/1) cases – oral pruritus, gingivostomatitis, asthma, rash in nose, bitter taste	
Hou, 2015[9]	18–52	SLIT: 6 PC: 9	0 (0%) 0 (0%)	Seasonal AR	5mo	JC (Cry j 1) 2000 JAU/week Drops	TOR	SLIT prevented development of pollinosis symptoms Changes in miRNA levels in response to pollen exposure (miR-223, let-7b)	-	NS	
Okamoto, 2015[10]	12–64	SLIT: 266 PC: 265	26 (10%) 24 (9%)	Seasonal AR	2 seasons (~18mo)	JC (Cry j 1&2) 2000 JAU/day Drops	TOR	Reduced nasal, ocular and combined symptom score (17–32%) Reduced medication usage Improved QOL score Increased specific IgG4 and reduced IgE	-	No treatment-related severe AE Mild AE: 50 (36/14) cases – mouth edema, stomatitis, throat irritation, oral pruritus.	
Okamoto, 2016[14]	12–64	SLIT 300 IR: 322 SLIT 500 IR: 323 PC: 323	7 (2%) 27 (8%) 7 (2%)	AR	1y	HDM (1:1 Der p:Der f) 300–500 IR/day Tablets	STA	Reduced adjusted average symptom score (up to 18.2%), rhinitis symptom and combined scores Reduced rescue medication usage Improved QOL Increased specific IgE and IgG4	Ocular symptoms No difference between 300 and 500 IR dosage groups	No treatment-related severe AE Mild AE: 66.8–73.1% in SLIT groups, 18.6% in PC group – throat irritation, edema mouth, oral pruritus, and ear pruritus.	Higher dropouts in 500 IR group
Okubo, 2017[15]	12–64	SLIT 10,000 JAU: 313 SLIT 20,000 JAU: 314 PC: 319	27 (9%) 33 (11%) 34 (11%)	AR	1y	HDM (1:1 Der p:Der f) 10,000–20,000 JAU Tablets	ALK	Reduced total combined rhinitis score (19–22%) Improved QOL score (JRQLQ)	No difference between adult and adolescent age groups	No treatment-related severe AE Mild-mod AE: 63.6% in SLIT 16.9% in PC groups – mouth edema, oral pruritus, and throat irritation	
Taiwan											
Lue, 2006[16]	6–12	SLIT: 10 PC: 10	0 (0%) 0 (0%)	Asthma	6mo	HDM (1:1 Der p:Der f) 300 IR/day Drops	STA	Improvement in nighttime symptom score compared to placebo Within-group (but not compared to placebo) improvement of lung function tests, daytime symptom score, medication score Increase in specific IgG4	SPT reaction Specific IgE	No severe AE	Small study population

Niu, 2006[17]	6–12	SLIT: 56 PC: 54	7 (13%) 6 (11%)	Asthma	6mo	HDM (1:1 Der p:Der f) 300 IR/day Drops	STA	Improved asthmatic symptom scores and medication scores Improved FVC, FEV_1, PEF	SPT reaction Serum total and specific IgE	No severe AE		No measurement of IgG
Tseng, 2008[21]	6–18	SLIT: 30 PC: 33	2 (7%) 2 (6%)	AR	6mo	HDM (1:1 Der p:Der f) 300 IR/day Drops	STA	Increased specific IgG4 and IgG4/IgE ratio	Mean total nasal symptom scores and medication scores	No severe AE Mild AE: 26 (19/7) cases – tongue numbness, epistaxis, oral ulcer, asthma exacerbation		Low sample size Placebo group had higher symptoms score at baseline

† citation number; NS, not stated; PC, Placebo control; Con, Control; IR, index of reactivity, an in-house standardization unit of allergen quantity; JAU, Japanese allergy unit; AR, Allergic rhinitis; AC, Allergic conjunctivitis; HDM, House dust mite; JC, Japanese cedar pollen; ALK, ALK-Abelló; STA, Stallergenes S.A.; TOR, Torii Pharmaceutical Co., Ltd.; ZHE, Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd.; A/P, Active/Placebo.

SLIT versus SCIT

There are no randomized, double-blind, double-dummy, placebo-controlled trials in Asia comparing the efficacy of SCIT with SLIT. Several controlled, open-label trials demonstrated efficacy of SLIT to be comparable to SCIT in controlling symptoms of HDM-induced AR,[31–33] HDM-induced asthma,[34,35] and pollen-induced seasonal AR.[36,37] SCIT may be superior to SLIT in a few discrete aspects, but results are peculiar to the specific studies. Zhu *et al.* found that SCIT was significantly better in relieving nasal obstruction compared to SLIT, while being comparable to SLIT with regard to all other symptoms of AR.[32] Wang *et al.* found SCIT to be superior in reducing medication usage in HDM-induced AR.[33] In a large prospective comparative trial with Japanese cedar (JC)pollen-induced seasonal AR, Yuta *et al.* found SCIT to be quantitatively better than SLIT in most clinical scores in the first year of follow up, but the difference did not meet statistical significance.[36] By the second follow up year, this difference was no longer observed.[37] Interestingly, in this study, visual analogue scale (VAS) and symptom score for nasal congestion both favoured SLIT over SCIT. Overall, there is no convincing evidence of superiority in efficacy of one treatment method over the other. Considering the small scale of the studies and methodological limitations (absence of blinding), the unique findings should be interpreted with circumspection.

Long term efficacy

With relatively few exceptions, SLIT is studied for short periods between 6 months to one year, while the recommended duration by World Allergy Organization is 3 years.[1] There are no RCTs with follow up periods extending beyond 2 years (Table 1). Long term data in Asia can only be found in a number of open-label intervention trials or retrospective cohort studies.

Long term data on HDM-driven allergic disease originate predominantly from China. In an open-label, uncontrolled study involving 206 patients aged 4–60 undergoing SLIT for HDM-induced AR, Li *et al.* compared clinical efficacy in groups completing 1 year, 18 months, and 2 years of SLIT therapy, and found significant improvement in symptom scores in all three groups, but the highest proportion of patients who maintained withdrawal from symptom-relief medications at 1 year after stopping SLIT was in the 2-year group (76.2%). The authors proposed 2-years treatment is important for the consolidation of improved symptoms.[38] Two other prospective, randomized, open-label on HDM-induced AR in China demonstrated similar findings on sustained efficacy of SLIT 1 year after discontinuation following completion of 2-years therapy.[39,40] In one retrospective study, however, Han *et al.* found a significant rebound in symptom scores at 1 year following completing 2-year SLIT.[41] The longest follow up duration was 4 years in a retrospective study of 100 children with HDM-induced AR and asthma. The authors found clinical efficacy improved with each successive year of therapy from 1 to 3 years, but failed to find a significant difference between 3 and 4 years of therapy. The authors suggested 3 years to be the optimal length of SLIT.[42]

In Japan, long term data is available for perennial AR due to JC pollinosis. Fujimura *et al.* found symptom medication scores in the 2-year SLIT group to be significantly attenuated compared to the placebo group in the pollen season 1 year following completion of SLIT.[6] The longest follow up period of 4 years is reported in a small study by Yuta *et al.* In this study, clinical efficacy was also demonstrated to improve with increasing duration of SLIT up to 4 years. Comparing the patients at 1 year following discontinuation of 3-year SLIT ($n = 12$) with patients who continued SLIT for 4 years ($n = 5$), symptom scores and medications scores were found to be

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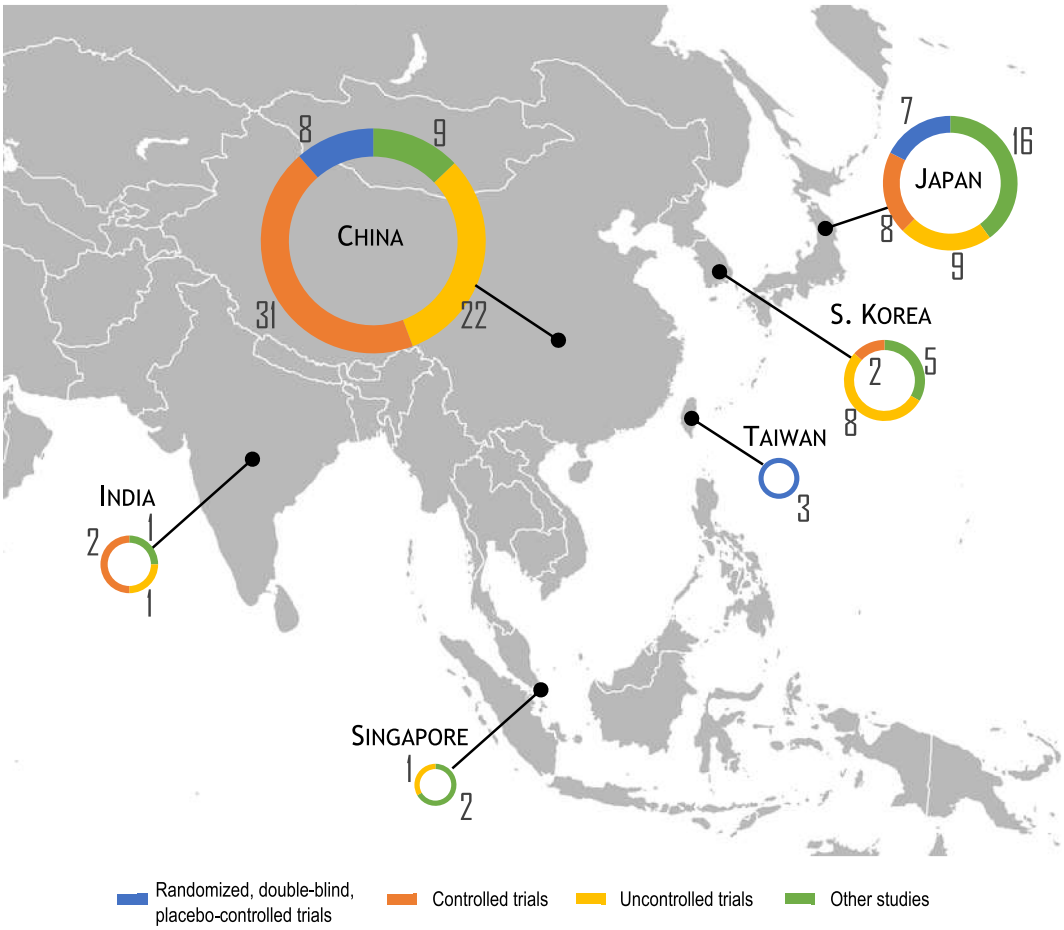

Fig. 2. Geographic distribution of origin of SLIT research from Asia.

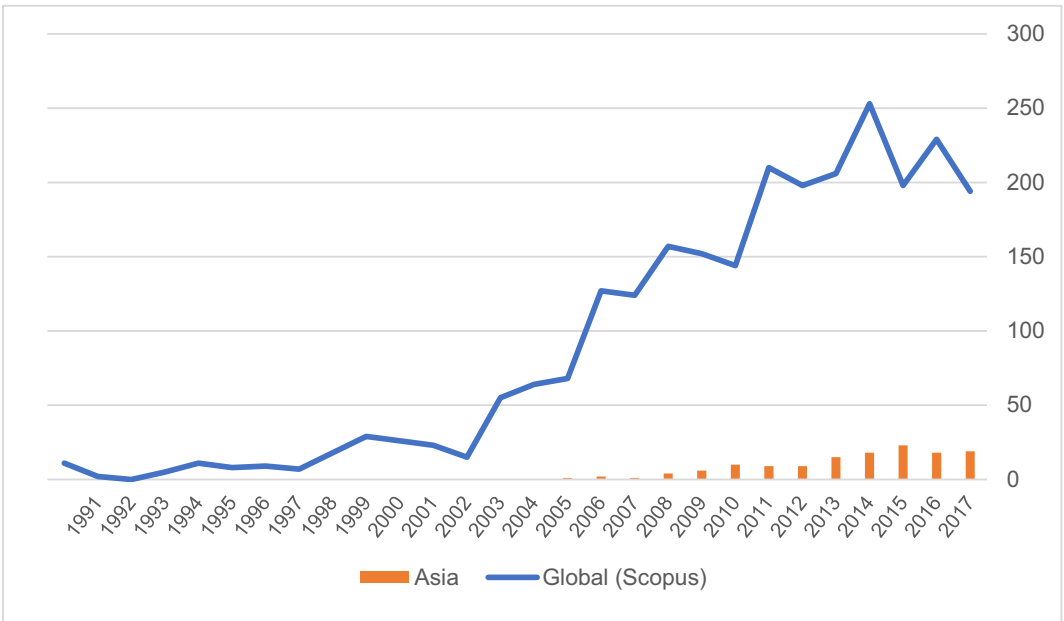

Fig. 3. Chronological distribution of SLIT research articles (by year of publication) in Asia.

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lower in the latter group. However, the small sample size limits the derivation of meaningful conclusions.[43]

Prevention of new sensitizations

SLIT is shown to reduce new sensitizations and prevent the progression from AR to asthma.[44] However, there is a paucity of Asian data in this aspect. In a randomized, controlled, open-label study on children with HDM-induced AR who underwent SLIT for 1 year, the onset of new sensitizations at the end of the trial period was observed in 3.55% of children in the SLIT group and 27.27% of children in the standard pharmacotherapy control group, with a decrease in number of positive allergens in 11.35% of children in the SLIT group.[45] A South Korean prospective cohort study on children with HDM-induced AR reported negative findings in this aspect, although it is constrained by a small sample size in the SLIT group and methodological limitations.[46]

Safety and adverse events

Consistently, none of the RCTs reported severe systemic adverse events (AE). There were no reports of anaphylaxis or use of adrenaline. Globally, the rate of anaphylaxis SLIT has been estimated at 1 case/100,000,000 administrations.[47] None of these cases were reported from Asia.

Most AEs were mild and involved local allergic reactions (Table 1). The most commonly encountered reactions were localised to the oral cavity, including oral pruritus, oral edema, tongue numbness, and bitter taste. These included inflammatory reactions, such as cheilitis,[20] glossitis,[20] gingivostomatitis[6] and oral ulcers.[21] Gastrointestinal symptoms such as abdominal pain[7,20] and diarrhoea[13] were less common. Relating to exacerbation of underlying allergic disease, rhinorrhoea was a commonly observed AE,[13,18,21] but exacerbation of asthma was rare.[7,18]

The incidence of AE in the SLIT groups vary widely from study to study, from as low as 5%[5]–73%,[14] with many reporting rates between 10 and 30%.[4,6,7,10,18] These mild AEs tended to recover without the need to discontinue SLIT, and were managed without treatment in most cases.[14] A majority occurred during the up-dosing phase in the first few weeks.[4,13] Dropouts due to AEs were rare, reported in two studies to be 1.5%[18] and 2.2%[10] of the respective SLIT groups.

A comparison in safety profiles between SLIT and SCIT was addressed in one controlled clinical trial for HDM-induced AR in Chinese children and adults. The authors concluded there was no significant difference in the overall incidence of systemic adverse effects between the SCIT and SLIT groups.[48]

Special populations

Use of SLIT in the paediatric population

It is recognized that SLIT is especially favourable for young children and their caregivers due to its good safety profile and that treatment does not require use of needles or frequent trips to the medical clinic.[1] The efficacy of SLIT has been validated in many Western studies. In a review article, Lee *et al.* evaluated evidence for the efficacy of SLIT in Asian children. The authors concluded that barring limitations in methodology, available studies performed in Asia are suggestive of benefit of SLIT for HDM allergies in Southeast Asian children.[49]

Among the 18 RCTs, 9 involved exclusively paediatric subjects, and 6 studies recruited paediatric patients as a subset of the study cohort (Table 1). Overall, SLIT has been demonstrated to be effective in children for AR and asthma. There is only one study on Taiwanese children reporting negative results, as discussed in the previous section.[21]

Safety and efficacy has been demonstrated in children as young as 3 years old.[45,50,51] In a few non-randomized, open-label trials for HDM-induced allergic disease, it was consistently found that the efficacy of SLIT was not significantly different for different age groups, comparing pre-school with school-going children,[45,50,52] and comparing children with adults.[52,53] Single-allergen SLIT was as equally effective in monosensitized and polysensitized children with HDM-induced AR and/or asthma.[22,27,29]

Data on duration of therapy and long term efficacy of SLIT in Asian children is generally lacking. In a prospective case-control study involving Chinese children with HDM-induced AR or asthma, Ding *et al.* found SLIT to provide effective control in 85% and 100% of children with AR after one and two years of treatment, respectively. Asthma control was achieved in 76% and 92% of children after one and two years of treatment, respectively.[54] In two Chinese studies, sustained efficacy was observed one year after discontinuation of 2-year SLIT for HDM-induced AR[39] and asthma.[55] No data is available for sustained follow up beyond 1 year after completion of SLIT.

Use of SLIT in pregnancy

Data on use of SLIT in pregnant patients is extremely limited. In one prospective controlled trial conducted in India, Shaikh *et al.* studied 155 pregnant patients who received SLIT, of which 24 patients initiated SLIT during the pregnancy. Outcomes were compared with the control group, who were managed with standard pharmacotherapy. Six-year follow-up data revealed a lower incidence of complications in the SLIT group than that of the general population and the control group.[56] The authors concluded that SLIT is safe during pregnancy and is also safe when initiated for the first time in a pregnant patient.

Pharmacological aspects

Most studies from China and Japan tend to use products from locally-licenced SLIT manufacturers, namely Zhejiang Wolwo. Bio-Pharmaceutical Co. Ltd. in China, and Torii Pharmaceutical Co. Ltd. in Japan. Each SLIT product has its own standardization measures and manufacturer's dosing guidelines, with most recommending dosing schedules with gradual up-dosing phase of 2–4 weeks. As a result, direct comparisons in SLIT dosage between countries becomes difficult. The problem is made more complex with the different allergenicities of different products. In an *in vitro* study comparing the relative allergen potencies of 3 SLIT products, Park *et al.* compared Staloral (Stallergenes, France), SLITone (AlkAbello, Spain), and Zhejiang Wolwopharma (China), and found marked differences in the allergen potencies of maintenance doses. Staloral HDM reagent was 17-fold higher than that of SLITone and 42-fold higher than that of Wolwopharma.[57] The authors however acknowledged that using an ELISA-based test kit in the study may have limited the detection of isoallergens of a major allergen, and the *in vivo* effects are not assessed. In addition, SLIT tablet allergen bioavailability is dependent on the tablet formulation. In an experimental study, Ohashi-Doi *et al.* found that only fast-dissolving freeze-dried (as opposed to compressed) tablets allow delivery of soluble allergens to achieve allergen concentrations that reflect the nominal tablet strengths within the recommended sublingual holding time.[58] Head-to-head comparison studies of different SLIT products are required to determine the relative *in vivo* efficacies of each product. These may improve the strength of evidence for SLIT in the Asian population, and also assist in determining the optimal dosing for SLIT.

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There is a paucity of literature in Asia on determining the effective dose of SLIT. We found only one Japanese study on HDM-induced AR which compared the efficacy of two dosing regimes in the same study. In this trial using HDM SLIT from Stallergenes S.A., Okamoto *et al.* randomized study participants by dosage into a 300 IR (Index of Reactivity, a measure of standardisation of allergen potency by the manufacturer) group and a 500 IR group. At the end of 1 year, the authors found no difference in clinical response between the two groups.[14]

Basic science research

It is recognized that genetics play a crucial role in determination of ethnicity-specific susceptibility to allergy.[59] Research of allergic disease highlighting unique genetic polymorphisms in Asians has been summarized in a comprehensive review by Leung and Wong.[60] It is not known, however, if these genetic differences influence the way Asian patients respond to SLIT. We present a summary of the existing body of literature from Asia evaluating the biomolecular aspects of SLIT.

Biomolecular mechanisms of SLIT efficacy

SLIT has been found to:

- Induce IL-10-producing regulatory T cells (Tr1) to suppress of $CD4^+$ lymphocyte proliferation linked to reactivity against cedar pollen, via a cytokine-mediated mechanism. The high T-cell repertoire diversity of these Tr1 populations explain the mechanism of tolerance against multiple allergens.[61]
- Downregulate T helper 2 (Th2)-type immune responses mediated by the thymic stromal lymphopoietin (TSLP-OX40L) signalling pathway.[62]
- Increase percentage of circulating Tr1 cells and IL-10-producing B cells.[63]
- Reduce Th17 cells and increase $CD4^+$ $CD25^+$ Treg cells.[19]
- Increase relative expression of miR-146a and Foxp3 mRNA, increase ratio of post-treatment to baseline IL-10^+ $CD4^+$ T cells and the serum IL-10 level, decrease TRAF6 protein level and serum IL-5 level.[64]
- Reduce IL-4 and elevate levels of IFN-γ in allergic asthma patients after SLIT.[65]
- Downregulate IL-4 and IL-5 producing Th2 cells in response to allergen.[66]
- Reduce expression of B-cell-activating factor of the TNF family (BAFF), positively related to Th2 cytokines (IL-4, IL-5, IL-13) and increased IL-10 expression. Eosinophil cationic protein (ECP), IgA, and IgE also decreased as the same trend with BAFF.[8]
- Reduce levels of IL-4 and IL-13 in nasal lavage specimens.[67]
- Block the upregulation of mRNA miR-223 and downregulation of miRNA let-7b which are implicated in developing pollinosis.[9]
- Change mRNA levels of IL-5 (suppressed) and IL-10 (induced), which were associated with the clinical control of AR.[24]
- Reduce level of serum ECP and reduce eosinophil aggregation and activation.[68]
- Decrease expression of platelet factor-4 and β-Thromboglobulin protein.[12]

Role of evaluation of serum IgE and IgG

- In an RCT on SLIT for JC pollinosis, total nasal symptom and medication score during pollinosis season in low serum IgE/total IgE (sIgE/tIgE) subgroup was significantly lower than that in the respective high sIgE/tIgE subgroup.[69]
- In another RCT on SLIT for JC pollinosis, subjects with a low sIgE/tIgE ratio before treatment were more likely to be responders to 2-year SLIT, and the ratio correlated with the symptom-medication score only in patients treated with SLIT, suggesting that SLIT was more effective in patients with a low sIgE/tIgE ratio than in those with a high sIgE/tIgE ratio.[6]
- In another RCT on SLIT for JC pollinosis, SLIT was found to increase levels of specific IgG4 antibody. However, no relationship between the IgG4 responses and the clinical efficacy was observed.[70]

Biomarkers for prediction of efficacy

- During SLIT, decreased Osteopontin (OPN) expression was related to low Th2 cytokine expression and enhanced IL-10 and TGF-β expression. High serum OPN expression predicts poor treatment efficacy.[11]
- A small study by Fujimura *et al.* involving 19 subjects sensitized to JC pollen showed the increase in induced regulatory T cells (Tregs) (IL-10^+ $Foxp3^+$ $CD25^+$ $CD4^+$ leukocytes) to be correlated with improved symptom and QOL scores after treatment with SLIT, and this effect is confirmed in a randomized, double-blind, placebo controlled trial.[6,71]
- Sakurai *et al.* had similar findings with IL-10^+ $Foxp3^+$ Tregs, raised only in good responders.[72] The authors conclude this is a valuable and prognosticator but deserves further evaluation.
- TIM-1 mRNA was significantly decreased in well controlled AR patients after 6-month SLIT. Moreover, change of TIM-1 mRNA was associated with the IL-5 mRNA suppression and IL-10 mRNA induction, suggesting TIM-1 suppression may contribute to modulating the balance of Treg/Th2 response in AR children. The authors suggested that TIM-1 may act as the therapeutic target of SLIT, and TIM-1 suppression may be used as an immunological indicator for successful SLIT in AR children.[24]
- BAFF may be used as a biomarker for SLIT treatment.[8]
- A high ECP level may be a useful parameter to predict the effectiveness of SLIT and select the patient for the treatment.[73]

Contextual aspects of SLIT in Asia

As an ethnically and culturally diverse region, many disparities exist in Asia related to allergic disease and the prescription patterns of SLIT. While there exists considerable evidence for efficacy of SLIT in Asia, its impact on the modification of allergic disease is much less certain. The following section highlights interesting information from a few articles in literature that shed light on the noteworthy disparities in Asia.

China

In China, HDM is the most prevalent allergen in patients with AR and/or asthma.[25] Allergen-specific immunotherapy was first used clinically in the 1950s, but early extracts were not standardized. In 2006, “Chanllergen,” a vaccine made with a single extract of *D. farinae* by Zhejiang Wolwo Bio-Pharmaceutical Co. Ltd. It was introduced for clinical use in China and was approved by the Chinese State Food and Drug Administration (SFDA).[7] This is currently the only SLIT vaccine available and used in China, estimated to cost 600 US dollars per year during the treatment of one patient.[74] In an article published in 2015, through a cross-sectional survey examining the diagnosis and treatment of allergic disease in Zhejiang province, Wang *et al.* examined the major barriers to the prescription of allergen immunotherapy (AIT). Overall, the allergy speciality was not well developed, while the body of doctors

Please cite this article in press as: Liu X, et al., The efficacy of sublingual immunotherapy for allergic diseases in Asia, Allergology International (2018), https://doi.org/10.1016/j.alit.2018.02.007

prescribing AIT face inexperience and lack of proper expertise as major issues. Significant disparities exist in the system. A clustering of resources and allergists meant that larger, more influential cities with academic medical institutions were the main drivers in allergy diagnosis and treatment, while smaller cities fell behind, despite the comparable prevalence of allergic diseases in each city.[75]

Japan

In Japan, AR is highly prevalent, affecting an overall 39.4% of the population, with 23.4% having perennial AR, and 26.5% suffering from JC pollinosis.[76] Perennial AR is common among young people and that JC pollinosis is common among middle-aged people.[76] Perhaps due to its high prevalence and as a disease unique to Japan, large number of Japanese studies have focused on SLIT for JC pollinosis. Cedar forests cover nearly 12–18%[70] of the total land area of Japan, and produce a large amount of pollen every year, which when dispersed is far-reaching and affects major cities. The pollen seasons of cedar and cypress combined amount to exposure to allergens for nearly 3 months of the year.[77] AIT in general and SCIT specifically has not been widely used in Japan due to safety concerns.[15,77]

South Korea

In South Korea, AR and asthma are the main diseases AIT is prescribed for,[78] and HDM is the most common culprit allergen.[79] In a survey on Korean allergists, Hur *et al.* found AIT to be prescribed by 69% of respondents, and only 20% among this group prescribed SLIT.[78] The main reasons cited was its relatively new introduction in Korea and lack of familiarity with this therapeutic modality.[78] With increase in experience with AIT, SLIT is expected to be rise in popularity in the future.[80]

Southeast Asia

Southeast Asia is a diverse region with many developing countries. One major difference in allergic disease is the higher prevalence of allergic disease due to the storage mite, *Blomia tropicalis*.[49,81] Overall, data is lacking in Southeast Asia, with no major randomized clinical trials on SLIT, possibly representing the under-utilization of immunotherapy overall. As socioeconomic conditions improve, however, HDM sensitization is expected to become the mainstay of patients presenting with allergic disease in Southeast Asia.[49,81]

Research needs and perspectives

- Prospective randomized, double-blind, placebo-controlled trials in South and Southeast Asian populations
- Comparative trials on single-allergen versus multi-allergen SLIT may shed more light on the clinical significance of the bystander effect.
- Prospective randomized, double-blind, double-dummy, placebo-controlled trials comparing SCIT and SLIT.
- Longitudinal data on long term clinical outcomes of SLIT in Asia, especially on paediatric population, with follow up period of more than 1 year after completion of SLIT.
- More prospective placebo-controlled trials to study effect of SLIT in prevention of new sensitization and halting of progression of allergic disease.
- Characterization of poor responders to SLIT and predictors towards response.
- Standardization of SLIT dosage and potency measurements allowing for direct comparison of efficacy across countries.
- Effects of socioeconomic disparities on relative utilization of SLIT by healthcare providers within countries and across the region.
- Cost-benefit analysis on SLIT in treatment of allergic disease in Asia.

Summary

Current available evidence suggests that sublingual immunotherapy has significant efficacy on Asian populations in AR and asthma. However, a significant amount of evidence is derived from non-placebo controlled studies with methodological limitations. A majority of trials originate from China and Japan, likely representing a severe asymmetry of access to SLIT within the region related to socioeconomic development. More data is needed in South and Southeast Asian populations. Future efforts may be directed towards improving access to SLIT in developing countries, standardization of SLIT dosage, and evaluating long term clinical outcomes.

Conflict of interest

The authors have no conflict of interest to declare.

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