

Sublingual immunotherapy for house dust mite allergy in Southeast Asian children

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Summary

Objective: To determine the use and efficacy of sublingual immunotherapy (SLIT) for house dust mite (HDM) allergies in Southeast Asian children.

Data sources: A literature search was performed in Pubmed and the Asian Pacific Journal of Allergy and Immunology. We also evaluated the literature for similar studies performed in Asia.

Study selections: Clinical trials involving children that assess SLIT for HDM allergies in Southeast Asia and Asia.

Results: There are no published studies on the use of SLIT for HDM allergies in Southeast Asian children. However, there are seven studies from Asia which show that there are discrepancies over the benefits of SLIT for HDM allergies in Asian children. Limitations in these studies include small sample sizes and short study periods.

Conclusions: We cannot say with certainty what the impact of SLIT is on HDM allergies in Southeast Asian children due to the lack of data. The available studies performed in Asia have their limitations but are suggestive of the potential of SLIT for HDM allergies in Southeast Asian children. This review highlights that good quality clinical research in this area in the Southeast Asian setting is warranted. (*Asian Pac J Allergy Immunol* 2013;31:190-7)

Key words: epigenetics, DNA methylation, asthma, allergy

Introduction

In a large number of studies, such as The International Study of Asthma and Allergies in Childhood (ISAAC), it has been demonstrated that the prevalence of childhood allergic diseases, such as asthma, allergic rhinoconjunctivitis and eczema, has been increasing worldwide during the last three decades.¹ This is particularly the case in children living in industrialized countries.¹ However, it appears that during recent years a plateau phase has been reached in many countries, especially for asthma and rhinitis.²⁻⁴

A variety of different allergens are responsible for the development of allergic disease, however, house dust mites (HDM) remain a major implicating factor.⁵⁻⁷ The most frequently responsible mites are *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df) which produce 22 defined mite allergens.⁸ However, there are some differences in the profile of HDM species that sensitize patients in Southeast Asia, with the storage mite *Blomia tropicalis* being recognised as an important domestic species in the tropics.⁹⁻¹¹ Studies involving Singaporean children have also shown that different manifestations of allergic disease are associated with different sensitization profiles to HDM.^{12,13}

Whilst there is scant epidemiological data specifically on the prevalence of HDM allergy in the Southeast Asian paediatric population, the rising trend in the prevalence of allergic disease has also been evident in the region.¹⁴⁻¹⁶ There are a few studies whereby skin prick tests (SPT) have been performed to quantify the prevalence of HDM sensitization in children.¹⁴⁻¹⁶ These studies suggest that HDM sensitization is the most common cause of allergic disease in Southeast Asian children. For example, 98% of Singaporean and 70% Malaysian children with allergic rhinitis (AR) are sensitized to dust mite.^{15,16} There also appears to be demographic and socioeconomic factors influencing the prevalence and severity of allergic disorders. In a study assessing the epidemiology of allergic disease

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in Singaporean children, a higher prevalence of symptoms was reported in subjects of higher socioeconomic status.¹⁷ Given that socioeconomic status is improving in the region, we can anticipate that HDM allergy will become the mainstay of patients presenting with allergic disease in Southeast Asia.¹⁸

In addition to being a common chronic paediatric disorder, allergic disease also has significant impact on quality of life of the affected child and their family. In addition to the discomfort caused by symptoms, functional impairment caused by allergic disease includes restriction of activities, interrupted sleep, disturbed routines, increased stress and poor concentration and school performance. Poorly controlled disease can also be associated with growth retardation and can also impair a child's confidence and self-esteem. The burden of allergic disease in childhood can therefore have lasting impact in adulthood. AR, eczema and asthma may also occur in combination, along with other comorbidities such as sinusitis, conjunctivitis, otitis media and Eustachian tube dysfunction.¹⁹⁻²¹ Allergic disease in childhood, particularly HDM allergy, therefore remains an important area in paediatric medicine that requires addressing.

In this review, we will discuss the management options for HDM allergy; in particular, the use of sublingual immunotherapy (SLIT). As HDM allergy is a common chronic paediatric disorder in the Southeast Asian region, immunotherapy may play an important role in the management of HDM allergy in this population. Therefore, we will also evaluate the available literature for clinical trials to assess the use and efficacy of SLIT for HDM allergies in Southeast Asian children.

Management options for HDM allergy

Management options for HDM allergy is varied depending whether the allergy manifests as rhinoconjunctivitis, atopic dermatitis or asthma. However, HDM avoidance along with pharmacotherapy is the mainstay of treatment for HDM allergy.^{7,20,22}

HDM avoidance is often promoted as part of an overall therapeutic strategy to alleviate symptoms of HDM sensitization. However, life-long effective mite avoidance is very difficult to achieve or maintain.⁷

The arsenal of pharmacotherapy for treatment of allergy includes antihistamines and corticosteroids, in addition to the myriad of medications for specific manifestations of allergic disease.^{20,22} Unfortunately, these measures provide symptomatic relief at best

and do nothing to alter the natural history of the condition. Pharmacotherapy also comes with adverse effects which can be problematic. For example, intranasal corticosteroids for AR can cause throat irritation, dry nose, epistaxis and mucosal crusting.²⁰ Parents also have lingering concerns over the systemic effects and growth reduction associated with corticosteroid use thus resulting in suboptimal compliance.²³

Immunotherapy still remains the only option for the long term management of AR and allergic asthma, including disease due to HDM allergy.^{24,25} It is currently administered via the subcutaneous (SCIT) and sublingual (SLIT) routes.²⁶ Unlike other pharmacological treatment options, immunotherapy acts on symptoms as well as alters the natural course of the disease. For example, immunotherapy can prevent the development of asthma in patients with AR and the onset of new sensitizations.^{22,26,27} Much is yet to be learned about the complex mechanisms that cause immune tolerance in sensitized individuals. However, it is known that immunotherapy reduces the allergic inflammatory reaction by addressing the imbalanced T cell response that is seen in allergic disease.²⁷ An example includes generation of regulatory T cells secreting interleukin-10 and transforming growth factor- β and inducing a shift from Th2 to Th1 type response in T cells in the periphery and mucosa.^{25,26,28,29}

The safety profile and efficacy of SCIT use in the paediatric population is still questionable, with reports of severe asthma, angioedema, generalized urticaria and anaphylaxis.^{30,31} SLIT, however, has been shown to have greater promise for the treatment of paediatric patients, with efficacy and safety being established in a number of studies, including for HDM allergy.^{28,32,33} The long term efficacy of SLIT is demonstrated in a 10-year prospective study of 60 children suffering from AR and asthma due to HDM. Results indicate that SLIT maintains its clinical efficacy for 4 to 5 years after discontinuation.³⁴ The oral mucosa is also a natural site for immune tolerance due to its sophisticated immune network comprising of Langerhans cells, epithelial cells and monocytes; thus forming an ideal site for which immunotherapy can be administered.³⁵ SLIT is currently indicated for patients with mono-sensitized rhinitis and/or mild to moderate asthma due to HDM and grass, weed or tree pollens.²⁸ SLIT requires the daily sublingual administration of incremental amounts of purified allergen in the form of drops, oral spray or rapidly dissolving tablet. The

maintenance dose is achieved in approximately 4 weeks, after which it is continued daily or on alternate days for 3 to 4 years. SLIT has the added convenience of being performed at home, is painless and has been shown to be safe for treating children under 5.^{28,36} Although SLIT appears to be better tolerated than SCIT, adverse reactions may still occur. The majority of these are mild and appear during the beginning of treatment and most commonly include oral mucosal reactions as well as gastrointestinal symptoms, rhinoconjunctivitis, urticaria or a combination of these symptoms. Few cases of non-fatal SLIT-related anaphylaxis have been reported.²⁵

General Issues with SLIT

SLIT has been available for over 20 years; therefore, there are still several general issues with SLIT that require addressing. The available meta-analyses on double-blind placebo-controlled randomised controlled trials (DBPC-RCT) involving SLIT in paediatric patients with AR or allergic asthma provide only suggestive evidence of the positive results due to the large heterogeneity of the studies.^{25,37} One meta-analysis revealed the promising efficacy for SLIT in HDM sensitized adults and children with allergic asthma and AR [38]. However, another meta-analysis has shown that there are non-concordant results for the efficacy of SLIT in children with HDM allergy.³⁹ Therefore, there is a need for the assessment of the magnitude of the efficacy of SLIT for HDM allergy in larger and longer multicentre studies, particularly in the paediatric population. Other important issues include the standardization of allergen products and schedules for therapy; determination of optimal dose; assessment of the efficacy of SLIT in patients with multiple sensitizations; assessing the role of SLIT in secondary prevention of asthma and allergy; exploring the benefits of SLIT in conditions other than respiratory allergy; determining the indications of SLIT and further safety issues and the investigation of the exact mechanisms of action.^{25,32,40}

SLIT in Southeast Asia and Asia

As discussed above, HDM sensitization is the most prevalent cause for allergic disease in Southeast Asian children. Therefore, SLIT presents as an important management option for the treatment of HDM allergy in the region. To determine the use of SLIT for HDM allergy in Southeast Asian children, we analysed all the available literature published up until December

2012. Firstly, an advanced search in PubMed, in all fields, was conducted using the keywords sublingual immunotherapy, SLIT and house dust mite. The search results were then combined with each of the following key words: Southeast Asia, Singapore, Philippines, Indonesia, Brunei, Malaysia, Vietnam, Thailand, Myanmar, Burma, Laos and Cambodia. We also searched in all categories in the Asia Pacific Journal of Allergy and Immunology for SLIT and HDM. The above search strategies were unable to locate any published literature, even without limiting the search to children under 18 years old.

Out of interest, we also broadened our search strategy in PubMed to include studies from Asia. We combined search results derived from the above key word search, using sublingual immunotherapy and house dust mite, with Asia. This strategy yielded six results, one of which was a study performed in Turkey³³ and another in China⁴¹ which was not in English; therefore these have been excluded from our review. As the remaining studies were conducted in Korea^{42,43} and Taiwan,^{44,45} we also combined results of the key word search, using sublingual immunotherapy and house dust mite, with Korea and Taiwan. This search resulted in an additional four studies, three Korean⁴⁶⁻⁴⁸ and one Taiwanese,⁴⁹ that were cohort studies or clinical trials. For all the studies that were retrieved, we were only interested in studies that included children under 18 years old, even if adults also participated in the study. Therefore, we excluded the Korean study by Mun and colleagues as it was not clear if children were included in their study.⁴⁶ To summarize, a review of the available literature on the effects of SLIT on HDM allergy in Asia have yielded a total of seven studies, shown in Table 1.^{42-45,47-49} Whilst we cannot say with certainty what the impact of SLIT is on HDM allergies in Southeast Asian children due to the lack of data, these few studies that have been performed on Asian children show insightful results.

In 2006, two studies performed in Taiwan became Asia's first multicentre DBPC-RCT of SLIT for dust mite allergy.^{45,49} In a multicentre DBPC-RCT by Niu and colleagues, 97 Taiwanese children with mild to moderate asthma, mono-sensitized to HDM, were recruited to assess the efficacy of high dose SLIT with standardized HDM extract. The children were aged between six to twelve years and



Table 1. Pubmed search results on the use of sublingual immunotherapy for house dust mite allergies in Asia

Author,[ref] Year	Country	Age	Article Type	Patients enrolled initially	Duration	Manufacturer	Main Results
Park, ⁴² 2012	Korea	6m- 15 years	Cohort study, non randomised, closed, without placebo	112 patients with AR, sensitized to <i>Dpand/</i> or <i>Df</i>	12m	Stallergenes	Decrease nasal and non nasal symptom scores, total medication score at 6m after treatment ($p < 0.05$) No change in serologic tests ($p < 0.05$) 34.1% of patients reported adverse effects. Nil life threatening
Han, ⁴⁷ 2012	Korea	6-53 years	Retrospective study	76 patients with AR, sensitized to <i>Dpand/</i> or <i>Df</i> ; treated with SLIT for at least one year (54 children, 22 adults)	12m	ALK-Abelló	Improved total symptom score ($p < 0.05$), comparable change in both groups ($p = 0.538$) Decrease in allergic medication scores in both groups Nil serious adverse effects
Lee, ⁴⁸ 2011 Lee, ⁴⁸ 2011	Korea	4-53 years	Prospective study	A total of 134 patients with AR, treated with SLIT for HDM for at least 1 year (73.6% of patients who were enrolled initially) (70 monosensitized to <i>Dpand/</i> or <i>Df</i> only; 64 polysensitized to other allergens in addition to HDM)	12m	ALK-Abelló	Improved total nasal symptom scores ($p < 0.05$) and medication scores ($p < 0.05$) in both groups Nil serious adverse effects
Kim, ⁴³ 2011	Korea	5-53 years	Cohort study, non-randomised, closed, without placebo	58 patients with AR, sensitized to <i>Dpand/</i> or <i>Df</i> only	12m	ALK-Abelló	Decrease in total symptom ($p < 0.001$) and medication scores ($p = 0.001$) in 62% of patients Decrease in peripheral blood eosinophils counts ($p = 0.025$) and ECP ($p = 0.048$). Increase in specific IgE for <i>Df</i> ($p = 0.019$) whereas no statistically significant change in specific IgE for <i>Dp</i> and total IgE No serious adverse effects reported

Table 2. (continued)

Author,[ref] Year	Country	Age	Article Type	Patients enrolled initially	Duration	Manufacturer	Main Results
Tseng, ⁴⁴ 2008 Tseng, ⁴⁴ 2008	Taiwan	6-18 years	DBPC-RCT	63 patients with at least a 2 year history of AR, sensitized to Dpand/ or Df only (30 SLIT; 33 placebo)	24 weeks	Stallergenes	No statistically significant differences in skin sensitivity, total nasal symptom scores and medication consumption Increase in specific IgG4 Dp ($p < 0.001$) and Df ($p = 0.002$) in SLIT group Increase in IgG4/IgE to Dp ($p = 0.119$) and Df ($p = 0.001$) in SLIT group Increase in specific IgE in both groups ($p < 0.10$), but no difference between groups SLIT well tolerated
Lue, ⁴⁹ 2006	Taiwan	6-12 years	DBPC-RCT	20 patients with mild to moderate asthma, sensitized to Dpand/ or Df only (10 SLIT, 10 placebo)	6m	Stallergenes	Improvement in day/nighttime asthma symptom scores, medication scores and total IgE, specific IgG4, eosinophil counts, FEV1 and mean evening PEF in SLIT group ($p < 0.05$)
Niu, ⁴⁵ 2006 Niu, ⁴⁵ 2006 (continued)	Taiwan	6 -12 years	DBPC-RCT	110 patients with at least one year history of mildly persistent to moderately persistent asthma, allergic to Dpand/ or Df only (56 SLIT; 54 placebo)	24 weeks	Stallergenes	Improvement of asthma symptoms ($p < 0.10$), FVC ($p = 0.042$), FEV1 ($p = 0.048$) and PEF ($p = 0.001$) Reduced use of rescue medications in SLIT group (not statistically significant) No differences in SPT, total serum IgE ($p = 0.063$) and specific IgE to Dp and Df SLIT tolerable to most patients

the study was conducted over a period of 24 weeks. Patients received a starting dose of one drop of 10 Units/ml and increasing to 10 drops on day seven. Drops were kept sublingually for two minutes then swallowed. Patients started one drop of 100IR/ml on day eight and the dose was increased to 20 drops on day 14. On day 15, patients were given seven drops of 300IR/ml and this was increased to 20 drops on day 19. After this, 20 drops of 300 Units/ml was the maintenance dose, daily for the next 21 weeks. Symptom and medication scores, lung function tests, SPT, total serum IgE and specific IgE to *Dp* and *Df* were compared between the treatment and placebo groups after the 24 weeks study period. Results indicated that patients receiving SLIT had a reduction in symptoms and medication use and improved lung function. No changes in the other parameters were reported. The study also reported good tolerance with high dose SLIT with few minor adverse events.⁴⁵ Overall, this study is suggestive of the potential benefits of high dose SLIT for HDM sensitized Taiwanese children with mild to moderate asthma. These potential benefits were mirrored in another DBPC-RCT conducted in Taiwan by Lue and colleagues.⁴⁹

A more recent six-month, multicentre DBPC-RCT of 59 Taiwanese children with AR mono-sensitized to mites reported conflicting results. SLIT was well tolerated but did not significantly improve clinical manifestations of AR when used for 6 months; despite utilising the same treatment protocol as the above Taiwanese study by Niu and colleagues.⁴⁵ However, there were significant increases in mite-specific IgG4 and IgG4/IgE antibodies in Taiwanese children with AR. The authors have proposed that these serologic changes to treatment indicate that there are real changes occurring and that it remains to be seen if this will translate into a clinically effective means of treating children with AR.⁴⁴ Other studies have also found no consistent benefit of SLIT compared to placebo, however these were not conducted in Asia.^{50,51} Important limitations to the studies performed in Taiwan were the short study period of six months and small sample size; thus, larger and longer studies are required to confirm these results.

In Korea, Park and colleagues recruited 112 patients less than 15 years of age who had AR to HDM and treated them with SLIT using a standardized HDM extract consisting of an even mixture of allergenic extracts of *Dp* and *Df*. The treatment regimen was performed according to the

manufacturer's instructions. This consisted of 11 days of a build-up phase using a single starting dose of 10IR/ml. This dose was gradually increased to ten doses of 10IR/ml over the first six days, then patients took increasing doses daily of one to eight doses of 300IR/ml for the remaining five days of the build-up phase. This was then followed by a maintenance phase whereby patients took four doses every day. The patients were then followed up over 12 months and assessed for changes in nasal and non-nasal symptoms, quality of life, medication use, adverse events and compliance. Serological tests were also performed to evaluate the immunologic changes after SLIT. Results of the study indicated that SLIT reduced symptoms, significantly improved quality of life and reduced medication use. Minor adverse effects were reported, but there were no systemic reactions. The dropout rate was 21%; due to reports of adverse effects, lack of efficacy, inconvenient application and no time to visit the clinic. There were no significant changes in serological tests, which included total IgE, IgG, IgG1, IgG4, white blood cell differential counts and eosinophilic cationic protein level.⁴² Overall, this study revealed the beneficial effects of SLIT for the management of Korean children with HDM sensitized AR.

Another 12 month study involving 58 Korean patients also reported improvement of symptoms and medication scores in patients with AR who were mono-sensitized to HDM. However, the study was not limited to paediatric patients and there were differences in the treatment protocol.⁴³

Conclusions

There are still discrepancies over the benefits of SLIT for HDM allergy in Asian children. As discussed above, there exists large heterogeneity for allergen dose, duration and patients' selection in current studies.²⁵ Limitations which need to be addressed in future studies include recruiting larger number of patients to allow adequate statistical power, designing studies with improved or different outcomes and assessing efficacy of SLIT over longer periods of time, particularly when the World Health Organization guidelines recommend patients complete between three to five years of treatment.³¹ SLIT efficacy is dose-dependent and sufficient duration of treatment is essential to elicit the immunologic changes underlying its clinical effectiveness.⁵² An ideal trial period should therefore be performed over at least three years to

fully assess the potential of SLIT. With respect to the use of SLIT in children, the optimal dose and dosing frequency, as well as the duration of treatment, is another aspect that requires further research. We still need to determine the efficacy of SLIT in patients who are unresponsive to pharmacotherapy and whether there are any differences in giving SLIT in drop or tablet form. It would also be vital to conduct more studies on the long term efficacy and preventive capacity of SLIT, as well as its use in preschool children.²⁵

SLIT for HDM allergy in children promises to be an effective long term solution in providing symptomatic relief and modifying the natural history of allergic disease. However, there are still gaps in our knowledge of SLIT and further research on its use, particularly in the paediatric population, is warranted. A large proportion of studies on SLIT use in children have been conducted in Europe. Therefore it would be interesting to determine how Southeast Asian children respond to SLIT. Given that there is high prevalence of HDM allergy in Southeast Asian children, good quality studies involving children from the region is essential so that findings will be externally valid. This is especially when there are documented differences in HDM fauna and their impact on allergic disease in children living in the tropics.

Finally, we must appreciate that we have only scratched the surface of our understanding of allergic diseases and that further research should be encouraged in this complex field. In doing so, we can open up opportunities for further intervention in allergic children.

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