



House dust mite sublingual immunotherapy in allergic rhinitis

Sung-Woo Cho¹, Doo Hee Han², Jeong-Whun Kim¹, Dong-Young Kim² & Chae-Seo Rhee^{*,1,3,4}

¹Department of Otorhinolaryngology-Head & Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea

²Department of Otorhinolaryngology-Head & Neck Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul 03080, Korea

³Research Center for Sensory Organs, Seoul National University Medical Research Center, Seoul 03080, Korea

⁴Institute of Allergy & Clinical Immunology, Seoul National University Medical Research Center, Seoul 03080, Korea

*Author for correspondence: Tel.: +82 31 787 6074; Fax: +82 31 787 4057; csrhee@snu.ac.kr

Allergen immunotherapy has been shown to be effective in treatment of allergic rhinitis (AR). Sublingual immunotherapy (SLIT) is generally recommended for treating seasonal AR in adults and children; however, questions remain in regard to AR treatment in relation to house dust mite (HDM). Due to heterogeneous formulations, different outcome reporting systems, and the lack of a standardized dose, HDM SLITs have not been standardized in published studies. Nevertheless, studies continuously report positive effects of HDM SLIT in AR, and HDM SLIT remains a treatment option for patients with HDM-induced allergic asthma that frequently co-exists with AR. Therefore, it is likely that HDM SLIT usage will increase. This review will focus on HDM SLIT in AR exclusively.

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Allergic rhinitis (AR) is one of the most common allergic diseases, and its incidence continues to increase worldwide [1]. It is associated with other comorbidities, such as allergic asthma in children, and is considered as a significant risk factor for developing future allergic asthma [2]. Among available treatment options, allergen immunotherapy (AIT) is the only therapy that can possibly modify the natural course of the disease [3].

In AIT, the two most commonly used routes of administration are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In general, the efficacy of SCIT and SLIT are both effective in reducing symptom and medication scores; however, when there is a safety issue such as severe systemic reactions, SLIT's safety is significantly higher [4]. In preventing the natural course of the disease, which is important in children, safer treatment would be beneficial. SLIT's superiority in relation to safety and near equal efficacy to that of SCIT have led to extensive use worldwide.

In general, SLIT can be recommended for the treatment of seasonal AR in adults and children and is known to provide symptom improvement during and after treatment in patients with moderate-to-severe disease despite pharmacotherapy. However, to date evidence of the outcomes for AR in relation to the house dust mite (HDM) have been less convincing [5]. Nevertheless, studies continue to report a positive effect of HDM SLIT in AR.

This review focuses on HDM SLIT in AR exclusively, regarding its formulation heterogeneity, clinical efficacy and biomarkers.

Distinct characteristics of HDM

There are several reasons why an HDM allergy is clinically important. The HDM is widespread in human living environments, and constitutes the major source of indoor allergens, and is a significant factor for underlying AR and asthma [6]. Moreover, immunotherapy is important as sensitization to the mite allergen in the first 3 years of

life significantly affects lung function in the pediatric population with wheezing, and is associated with long-term poor clinical outcomes [7].

Unlike other allergens, the allergenic effects of HDM allergens are considered to derive from two main routes: through CD4⁺ Th2 cells and IgE-dependent; and through the innate immune system [8]. Some of the HDM allergens, such as Der p1, Der f1, Der p2 or Der f2, have been known to directly affect the host immune system. Der p1 and Der f1 are associated with protease activities that can potentially destroy the epithelial tight junctions and are considered to be recognized by Toll-like receptors, and to mimic pathogen-associated molecular pattern activation [9]. Der p2 and Der f2 are considered to mimic the action of Toll-like receptor 4 and its co-receptor myeloid differentiation factor 2 (MD-2). The action of these allergens, particularly Der p1 and Der f1, has the capacity to distort the immune response.

Various HDM SLIT formulations

The AR and its impact on asthma noted that studies on SLIT are substantially heterogeneous and that each product is required to be evaluated separately [10].

Allergen extracts are manufactured through an aqueous extraction of the allergenic source from natural raw materials, which are inherently variable in composition. Therefore, various control measures using references are extremely important and include using a combination of laboratory techniques to obtain uniform compositions regarding the extract complexity, allergen content and IgE binding potency. Different manufacturers use differing raw materials, production processes and standardization procedures, which have therefore resulted in diverse compositions of allergen products. An analysis of SLIT products from various manufacturers has revealed approximately 7- to 200-fold differences in major allergen concentrations [11]. Therefore, it is not easy to extrapolate from these clinical results, even in compositions that are derived from products of a single allergen.

One option to address this issue is through standardizing the allergen content according to each commercially available HDM SLIT product. Recently, the Japanese Society of Allergology assigned nominal strengths to HDM tablets using Japanese allergen units [12]. Through standardizing the allergen content, study results can be compared. However, the different composition ratio between Der 1 and Der 2 in each tablet should also be considered.

SLIT medication is prepared in two forms, namely, droplets and tablets. One recent meta-analysis compared the efficacy of HDM SLIT tablets and SLIT droplets [13]. Overall, both forms of medication resulted in a significant decrease in symptom scores. Most studies on SLIT tablets have shown significantly reduced symptoms; however, results from the SLIT droplet studies have varied, with some studies reporting unsatisfactory results. No investigation has been undertaken to compare the efficacy of SLIT droplets and tablets; however, in droplet formulations, there are issues regarding the reliability of the dosage because the drop volume is known to vary significantly depending on several other related factors [14].

HDM SLIT tablets have been developed and designed to meet the regulatory requirements for authorization in Europe and by the US FDA. Currently, SLIT tablets are the best-documented immunotherapy products available, and the only products that meet current standards for clinical documentation [15]. On the other hand, SLIT droplets are used off-label in the USA and have not been standardized; therefore, they may not be as effective as tablets. Meanwhile, in Europe, SLIT droplets are standardized, and some studies have shown them to be effective at appropriate doses [16]. Therefore, SLIT products with documented evidence of clinical efficacy should be used [5].

Basic mechanism of SLIT

Pharmacokinetics & mechanism of immune tolerance

The target organ in the SLIT is the local sublingual immune system. SLIT products are administered under the tongue and are held there for a few minutes until swallowed or expelled. During SLIT, systemic absorption does not occur in the oral mucosa [17], and even if swallowed, allergens continue to be broken down in the GI tract [18]. Additionally, allergens can persist in the mouth for up to 3 h [19].

Therefore, allergen concentrations in the oral mucosa, and the mucosal contact time, are the two main parameters that determine the extent of interaction between allergens and the sublingual mucosa. In this regard, the solubility of tablet-formed allergens may be a further factor challenging or affecting drug efficacy [20].

SLIT operates and acts in the sublingual mucosa. A substantial amount of administered allergens adhere to epithelial cells within minutes and are then absorbed through the sublingual mucosa within 15–30 min. Allergens are absorbed via local dendritic cells or oral Langerhans cells. The current understanding of AIT, including SLIT, can be described as an APC-mediated shift in the balance between Th2 cells and Treg cells [21]. Sublingual dendritic

and oral Langerhans cells can produce IL-10 and TGF- β , contributing to the maintenance of tolerance [22,23]. Due to these features, the oral immune system elicits tolerance. Dendritic cells presenting with allergen-driven peptides on their surface migrate to the cervical lymph node within 12–24 h, where they interact with naive CD4 T cells and induce Treg cells. Treg cells can mediate immune tolerance through: the suppression of APCs supporting the effector T-cell generation; direct suppression of Th2 cells; modulation of B cells, reduction of allergen-specific IgE production, and induction of IgG4; reducing the activity of mast cells, basophils and eosinophils; and interaction between resident tissue cells and remodeling [24]. These CD4⁺ T cells subsequently migrated into the blood and tissues, resulting in clinical tolerance [25]. Upon allergen exposure, the serum levels of allergen-specific IgE and IgG change. In addition, SLIT also appears to elicit mucosal IgA response, which may contribute to tolerance [26].

Clinical efficacy of HDM SLIT

AIT is indicated only in the presence of symptoms strongly suggested of AR. Therefore before initiation of HDM SLIT, history of perennial allergic symptoms as well as evidence of allergen-specific IgE sensitization (positive skin prick test or serum specific IgE test) should be identified.

Overall, sublingual therapy is effective, therefore SLIT is recommended by the World Allergy Organization and by the European Academy of Allergy and Clinical Immunology (EAACI) [4,5]. However, studies are comprised of various allergens other than HDM, and subgroup analysis for seasonal and perennial allergens may provide controversial results. As such, HDM SLIT should be considered separately. Numerous studies have shown the effectiveness of HDM SLIT. However, until recently, there have been few meta-analyses on HDM SLIT [13,27–28]. In addition, due to the high degree of statistical heterogeneity, the validity of the meta-analyses remains limited [29]. Moreover, the symptom and medication scores are generally effective; however, efficacy on pediatric patients is somewhat controversial, and studies have shown insignificant effects on the symptom or medication scores [13,27,30]. Most previously conducted studies have not included children aged <5 years old, and the evidence of SLIT efficacy on these children is therefore limited. A lack of evidence, an anticipated poor adherence to therapy and safety issues in children may be limitations to enrolling preschool children in further studies. The recent EAACI guideline has stated that there is no clear evidence to support the use of HDM SLIT with aqueous solutions in children [5]; however, two recent studies have been conducted involving adolescents (aged >12 years) using standardized quality (SQ) SLIT tablets and these studies demonstrated positive outcomes [31,32]. A pooled analysis of these studies also confirmed the effectiveness of SQ SLIT in adolescents (aged 12–17 years) with HDM AR [33]. It is known that the safety of SLIT does not differ from children below the age of 5 years and older ones [34], and therefore, further studies may be performed for younger children to clear out the controversy regarding the efficacy in children.

Meanwhile, a subgroup analysis on the use of HDM SLIT in pediatric allergic asthmatic patients (aged <18 years) has been shown to be effective, and another recent systematic review has concluded that HDM SLIT in asthmatic children was effective in reducing asthma symptoms [28].

Some trials have reported a marked decrease in the symptom score within the placebo group, and these studies should also be considered and interpreted carefully [35,36]. The placebo effect is usually relevant in immunotherapy trials, even though SLIT appears to show fewer placebo effects than SCIT [37,38]. Therefore, World Allergy Organization has suggested that a 20% or higher relative difference between the placebo and SLIT can be considered as having a clinically relevant effect.

The lack of consensus on efficacy parameters, such as treatment dose and duration, and the different outcome measures in various studies, should also be considered. Therefore, EAACI produced a position paper to standardize outcome measures and provide a guide for SLIT [39].

Studies that had evaluated the efficacy of HDM SLIT are summarized in [Table 1](#).

Effects in polysensitized patients

Polysensitization is more prevalent than monosensitization in the general population and approximately 50–80% of patients seeking treatment are polysensitized [42]. HDM SLIT for polysensitized patients is based on two assumptions. One assumption is that polysensitized patients may not be polyallergic. Some polysensitization may have resulted from the cross-reactivity of the allergen during diagnosis or may have only been sensitized rather than having an allergic disease.

In polysensitized patients, symptom intensity, duration and the amount of environmental exposure to causative allergens provide useful historical information when determining which allergen to treat. However, despite being known as a perennial allergen, HDM also has a seasonal variation [43,44] and may depend on geographical char-

Table 1. Clinical efficacy of house dust mite sublingual immunotherapy.

Product name	Study country	Dose	Form	Study type	Age	Duration	Summary	Ref.
Staroral®	Turkey	300 IR/ml	Drops	Double-blind placebo-controlled study	5–10 years	1 year (44,500 IR)	No significant difference in change rhinitis symptom score	[30]
Staroral	Poland	300 IR/ml	Drops	Double-blind placebo-controlled study	60–75 years	3 years (421,200 IR)	Significant improvement in rhinitis symptoms score	[40]
SLIT®	UK	1000 STU/ml	Drops	Open-label randomized controlled trial	5–10 years	1 year (295.5 µg/295.5 µg for Derp1, Der f1) (73,876.8 STU)	Significant improvements in symptom score and medication score	[41]
*SQ®-HDM SLIT	Japan	10,000 JAU (65Q) 20,000 JAU (125Q)	Tablet	Double-blind placebo-controlled study	12–64 years	1 year (3,650,000 JAU; 7,300,000 JAU)	Significant reduction in total combined rhinitis symptom score	[32]
SQ-HDM SLIT	North America	12 SQ	Tablet	Double-blind placebo-controlled study	≥ 12 years	1 year (4380 SQ)	Significant reduction in total combined rhinitis score	[31]
ACTAIR®	Japan	300 IR 500 IR	Tablet	Double-blind placebo-controlled study	12–64 years	1 year (109,200 IR; 180,500 IR)	Significant reduction in average adjusted symptom score	*[35]

SQ®-HDM SLIT is currently registered as ACARIZAX® (Europe), ODACTRA™ (USA), and MITICURE® (Japan).

IR: Index of reactivity; JAU: Japanese allergy unit; SLIT: Sublingual immunotherapy; SQ: Standardized quality; STU: Standardized unit.

Table 2. Effects in polysensitized patients.

Study (year)	Country	Study type	Age	Form	Treatment duration (cumulative dose)	Summary
Lee <i>et al.</i> (2011) [48]	Korea	Open label, nonrandomized, observational study	4–53 years	Droplet	1 year (73,876.8 STU)	Equivalent as monosensitized patients
Li <i>et al.</i> (2014) [49]	China	Open-label, randomized study	4–13 years	Droplet	1 year(N/A)	Equivalent as monosensitized patients

STU: Standardized unit.

acteristics. Patients with AR due to HDM may suffer worse symptoms in early spring or in the fall [45]. Even in patients previously co-sensitized with pollen, HDM and having a seasonal symptom variation, HDM may remain the allergen that is clinically relevant. To decrease the possibility of cross-reactivity among allergens, more precise diagnostics such as the component-resolved diagnostic test may be necessary. Also in order to prove that HDM as the relevant allergen causing AR, nasal provocation test (NPT) may be necessary. In fact, only about 70–80% of patients with proven to be sensitized to HDM had a positive NPT result [46,47]. However, as far as we know, no study had demonstrated that the NPT and component resolved diagnosis may actually increase the efficacy of HDM SLIT and therefore further studies regarding this seem to be necessary.

The second assumption is that even after polysensitization, HDM SLIT may induce tolerance toward other allergens likely to have been mediated by Treg cells. Treg cells reduce the activity of basophils and eosinophils, and interact with the resident tissue cells and remodeling cells, which are processes beyond allergen sensitization [24].

One of our previous studies compared the efficacy of HDM SLIT in 70 HDM monosensitized and 64 polysensitized (simultaneously sensitized to HDM and other allergens) patients and reported that HDM SLIT was equally effective in improving total nasal symptoms and rescue medication scores following 1 year of treatment [48]. A similar result has also been demonstrated among children aged 4–13 years treated with HDM SLIT for 52 weeks [49]. The open-label usage and the lack of a control group are likely to have decreased the level of evidence in these studies; therefore, more studies are required. Aforementioned studies are summarized in Table 2.

Prevention of new sensitization

Preventing new sensitization may be important, especially in children, as polysensitization in early childhood is associated with an increased risk of developing asthma at 6 years of age [50]. In adults, the prevalence of asthma is

Table 3. Preventive effect of house dust mite sublingual immunotherapy.

Study (year)	Country	Study type	Age	Form	Treatment duration (cumulative dose)	Summary
Szépfalusi <i>et al.</i> (2011) [53]	Austria	Double-blind, placebo-controlled study	2–5 years	Droplet	1 year 2 years (N/A)	Does not decrease the rate of new sensitization
Lim <i>et al.</i> (2017) [55]	Korea	Open label, nonrandomized, observational study	4–15 years	Droplet	3 years(221,630.4 STU)	Does not increase the rate of new sensitization Does not affect negative conversion of bronchial hyper-responsiveness
Marogna <i>et al.</i> (2008) [56]	Italy	Open-label, randomized controlled study	5–17 years	Droplet	3 years(1440 µg of Der p1, Der p2)	Decrease the rate of new sensitization Lower occurrence of persistent asthma compared with controls

STU: Standardized unit.

known to increase with a rising number of sensitized allergens [51]. Polysensitization is also known to be associated with severe symptoms associated with allergic disease [52]. Therefore, prevention of new sensitization may play a role in the prevention of asthma and in improving patient outcomes. This so-called bystander effect appears to be related to the increased secretion of IL-10 and TGF- β [53]. Hypothetically, Treg cells induce local allergen tolerance through the secretion of tolerogenic cytokines, such as IL-10 and TGF- β . One study demonstrated that mice, which had been tolerized with ovalbumin, showed significantly reduced asthma symptoms when both ovalbumin and allergen had been challenged. However, when challenging with the allergen only, the allergic symptom was again observed [54]. Tolerance was mediated through the CD25⁺ Treg cells, via CTLA-4 and ICOS signaling, which can be generated through continuously stimulating the Treg cells with the causative allergen. Based on this perspective, HDM SLIT can possibly obtain the highest bystander effect in places where HDM is the most common aeroallergen.

However, the bystander effect remains controversial. In one double-blinded study, asymptomatic sensitized children aged between 2 and 5 years old were treated with either HDM ($n = 12$) or grass pollen ($n = 3$) SLIT, according to the sensitization profile, and were compared with a placebo. Following 12 and 24 months of immunotherapy, the rate of new sensitization did not differ [53]. Our recent study has also indicated that 3 years of HDM SLIT in droplet form did not have a preventive effect on new sensitization [55]. Among HDM monosensitized patients (children aged from 4 to 15 years), 54.5% developed new sensitization in the SLIT group, while 39.2% developed new sensitization in the non-SLIT group. However, in another open randomized controlled study, AR children aged between 5 and 17 years were treated with SLIT, and 98 of 216 children were treated with HDM. In this study, new sensitization was observed in 34.8% of the controls and in 3.1% of the SLIT patients [56].

Furthermore, to the best of our knowledge, the significance of new sensitization in HDM-sensitized children has not been clarified. Previous birth cohort studies have revealed that, as a natural course with patients aging, the number of monosensitized patients decreased and they became polysensitized patients [57]. However, this does not mean that polysensitization increases the risk of further allergic diseases. One study demonstrated that early polysensitized children seemed to be at a significantly higher risk of developing asthma than those polysensitized in late childhood [58]. It appears that prevention of polysensitization should be implemented in early childhood, most likely at an age <5 years; however, initiation of immunotherapy is difficult at this age given the lack of evidence involved in treating these young children. Some of the aforementioned studies are summarized in [Table 3](#).

Prevention of asthma development

Herein, we are focusing on the prevention of asthma development in patients with established AR. Allergic asthma, the most common phenotype of asthma, may present at any age. However, allergic asthma has been known to develop at a younger age than nonallergic asthma [59], with mean age of onset at 15.8 years [60]; therefore, HDM SLIT should be established before this age if it is to successfully prevent the onset of asthma. One prospective randomized study involved children aged from 5 to 17 years. Of 144 patients who received SLIT, 98 received HDM SLIT. A total of 3 years after SLIT, the prevalence of mild persistent asthma significantly decreased in the

patients treated with SLIT compared with those in the control group who had been treated with conventional drug therapy only [56].

A recent meta-analysis demonstrated a significant reduction in asthma development after AIT in general (relative risk: 0.40; 95% CI: 0.3–0.54). However, whether the preventive effect lasted for a longer period was unclear. In a subgroup analysis, both SLIT and SCIT, patients aged <18 years old, and treatment with a pollen AIT showed a significant reduction, whereas treatment with HDM AIT did not (relative risk: 0.20; 95% CI: 0.01–3.94) [61]. Therefore, HDM SLIT may not have a definitive effect on asthma prevention in patients with established HDM-induced AR. Further studies are warranted to determine an adequate conclusion.

Bronchial hyper-responsiveness is a strong risk factor for future development of asthma [62]. One of our recent studies analyzed the negative conversion rate of bronchial hyper-responsiveness after 3 years of HDM SLIT, which was defined when the provocative concentration was <16 mg/ml, causing a 20% decrease in the forced expiratory volume in 1 s. We analyzed children with HDM-induced AR aged between 4 and 15 years. After 3 years of HDM SLIT, 10 of 16 patients who were initially hyper-responsive had reversed bronchial hyper-responsiveness. However, in the control group (HDM-induced AR without SLIT), 13 of 31 patients initially having positive hyper-responsiveness became negative after 3 years of conventional treatment without SLIT. The 3-year HDM SLIT affected the negative conversion of bronchial hyper-responsiveness but this effect was not significant [55]. Aforementioned studies are summarized in Table 3.

While HDM SLIT may not be significant as a preventive measure, HDM SLITs have shown positive effects in asthma symptom improvement and reduction in inhaled corticosteroid use [63–65] and HDM SLIT tablets had been approved for the treatment of allergic asthma in Europe. As such, controlling and preventing asthma may require similar but not identical mechanisms.

Duration of treatment

Some studies have indicated that for those undergoing HDM SLIT, the rhinitis symptom score changed significantly within 8–12 weeks following initiation of therapy, and this change remained up until the end of treatment [32,35]. Improvement in the symptom scores has been reported to sustain throughout 3 years of therapy [66,67].

Long-term efficacy refers to having a clinical benefit to the patient for at least 1 year after cessation of treatment [68]. One study has shown that in patients receiving HDM SLIT over a 3-year period, long-term effect lasted 7 years, and in those receiving immunotherapy for 4 or 5 years, long-term effect lasted 8 years [69]. This study also showed that even when the long-term efficacy had decreased, reinitiation of SLIT was more rapidly effective than during the first course. Although this was an open-labeled study, it clearly demonstrated that a longer duration of treatment was warranted. Another study which was a double-blind placebo-controlled study on elderly patients has also shown long-term efficacy of HDM SLIT [40]. The EAACI guideline recommends a minimum of 3 years of HDM SLIT to achieve long-term efficacy and to sustain clinical efficacy after discontinuation of immunotherapy (especially in adults; however, in children more data are required) [5]. Moreover, considering the cost-effectiveness of AIT [70], a longer duration of treatment appears reasonable. Details of aforementioned studies are summarized in Table 4.

Biomarkers

From our experience, approximately 40% of patients adhered to the 3-year HDM SLIT treatment protocol that required frequent visits. Throughout the 3 years of treatment, between 56 and 79% of the patients showed an effective response, depending on the treatment duration [66]. During treatment, some of the patients dropped out, or their symptoms did not improve, incurring substantial medical costs without any significant benefit. It is important to identify those patients likely to respond effectively to therapy, to determine those who need to maintain or discontinue HDM SLIT. Biomarkers should represent clinical and immunological responses during treatment and assist with patient selection to identify those responsive to therapy and to exclude those unresponsive to therapy. Serum-specific IgE (sIgE) and IgG4 (sIgG4) have been extensively evaluated. Some of the double-blinded placebo-controlled studies have shown a noteworthy increase in sIgE during treatment [71–73]; however, other studies have not shown this [74,75]. Nevertheless, most studies on sIgE have not shown clinical significance. However, one retrospective study demonstrated that the initial ratio of sIgE/total IgE [76] significantly correlated with a clinical response after 4 years of immunotherapy. This was the first study that showed the possibility of initial serum IgE concentration as a marker of good responders. However, another randomized open-label study could not demonstrate a similar conclusion [41].

Table 4. Onset and maintenance of efficacy during sublingual immunotherapy, and long-term efficacy after cessation of treatment.

Study (year)	Country	Study type	Age	Form	Treatment duration (cumulative dose)	Summary
Okubo et al.(2017) [32]	Japan	Double-blind, placebo-controlled study	12–64 years	Tablet	1 year (3,650,000 JAU; 7,300,000 JAU)	Significant decreased rhinitis symptom score being evident from 12 weeks of treatment onward
Okamoto et al. (2017) [35]	Japan	Double-blind, placebo-controlled study	12–64 years	Tablet	1 year (109,200 IR; 180,500 IR)	Symptom score being evident from 8–10 weeks from treatment onward
Karakoc-Aydiner et al.(2015) [67]	Turkey	Open label, randomized controlled study	5–10 years	Drops	3 years (221,630.4 STU)	Significant reduction in rhinitis symptom score and medication score up to 3 years
Kim et al.(2015) [66]	Korea	Retrospective cohort study	5–59 years	Drops	3 years (221,630.4 STU)	Significant reduction in rhinitis symptom score and medication score up to 3 years
Marogna et al. (2010) [69]	Italy, Canada	Prospective open controlled study	18–65 years	Drops	3, 4, 5 years (390 µg of Der p 1/Der f 2 per year)	Long-term efficacy* lasted for 7 years for those treated for 3 years, and 8 years for those treated for 4 or 5 years.
Bozek et al.(2017) [40]	Poland	Double-blind, placebo-controlled study	Mean age: 65.78 ± 4.89 years	Drops	3 years (421,200 IR)	During 3 years of observation off SLIT, symptom scores remained at a significantly low level

*Long-term efficacy refers to having a clinical benefit to the patient for at least 1 year after session of treatment.
 IR: Index of reactivity; JAU: Japanese allergy unit; SLIT: Sublingual immunotherapy; STU: Standardized unit.

In contrast to sIgE, consistently elevated results have been reported in most sIgG4 studies with HDM SLIT [77]. However, most of the studies could not identify any relationship with the clinical responses.

In our experience, patients with an initially high serum eosinophilic cationic protein (ECP) had a better response to HDM SLIT [78]. This could be explained through the consideration that a high level of serum ECP indicates a severe AR [79], and severely affected patients tend to have an increased treatment effect of AIT [80]. In addition, a high ECP level may indicate that those patients are prone to pure AR rather than mixed rhinitis, in other words, AR with non-AR components, as AR has been shown to demonstrate higher serum ECP levels compared with non-AR in Korea [81]. This may explain the positive response to HDM SLIT in patients with high serum ECP levels, as the response to AIT is known to be better in AR than in mixed rhinitis [82]. As far as we understand, no study has shown a significant correlation between serum ECP levels and clinical response or outcome, and further studies are required. Summary of aforementioned studies are described in Table 5.

The recent EAACI position paper indicated that, to date, validated and generally accepted candidate biomarkers have not yet been identified [77].

However, some future candidates for biomarkers are still being investigated. Recently, one double-blinded placebo-controlled study investigated the serum IL-5/IFN- γ , IL-13/IFN- γ and IL-4/IFN- γ ratios during HDM SLIT, and found that these ratios significantly decreased in patients who responded positively following 24 months of AIT [83].

Conclusion & future perspective

Even within HDM SLIT, studies and formulations of different products are considerably heterogeneous and lack a standardized dose. Therefore, a product-specific approach is recommended to obtain the most appropriate evidence.

Despite these complexities, efforts are being made to standardize not only the products but also the efficacy measurements, and studies on recent products have a lower risk of bias.

Table 5. Change in serum markers in house dust mite sublingual immunotherapy.

Study (year)	Country	Study type	Age	Form	Treatment duration (cumulative dose)	Summary
Karakoc-Aydiner et al. (2015) [67]	Turkey	Open label, placebo-controlled	5–10 years	Drops	3 years(221,630.4 STU)	No significant change in specific IgG4, total IgE, specific IgE
Nolte et al. (2016) [31]	North America	Double-blind, placebo-controlled	>12 years	Tablets	1 year(4380 SQ)	Increase in specific IgE, and IgG4 increase over time beginning from 4 weeks
Yukselen et al. (2012) [72]	Turkey	Double-blind, placebo-controlled	9.2 ± 3.4 years	Drops	1 year(173,733 TU)	Significant increase in specific IgE, no significant change in sIgG4
Kim et al. (2010) [78]	Korea	Case series	5–53 years	Drops	1 year(73,876.8 STU)	Significant increase in specific IgE (Df). No significant change in specific IgE (Dp), or total IgE Significant decrease in eosinophil count and ECP

SQ: Standardized quality; STU: Standardized unit, TU: Treatment unit.

Currently, many studies on HDM SLIT have reported positive results; therefore, the use of HDM SLIT treatment may significantly increase. Despite the proven efficacy regarding medication and symptom scores in adults, its efficacy in children and the prevention of new sensitization, and development of other allergic diseases such as asthma, remains unclear. Until now, no validated biomarker has been definitively verified. Therefore, further HDM SLIT studies are necessary to investigate the effects on children, in addition to prevention of new sensitization, progression of asthma, long-term effect and biomarkers.

Executive summary

- House dust mite (HDM) is the most common indoor allergen, and these allergens have unique properties that induce both an innate and an adaptive immune response to developing allergic diseases, resulting in a significant disease burden.
- There have been heterogeneities regarding HDM sublingual immunotherapy (SLIT) products, and significant bias exists. Therefore, a product-specific approach is recommended to obtain appropriate evidence.
- Studies on more recent products have a lower risk of bias and have presented positive results concerning symptom and medication scores. However, stronger evidence and more data are required, particularly concerning studies involving children.
- HDM SLIT may improve symptoms in polysensitized patients although the level of evidence is low. Prevention of new sensitization and asthma development has not yet been clearly demonstrated.
- Serum-specific IgE and IgG4 have been extensively evaluated as biomarkers in HDM SLIT. However, no single biomarkers have been definitively verified.

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