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MINIREVIEWS

Sublingual immunotherapy for pediatric allergic rhinitis: The clinical evidence

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Abstract

Allergic rhinitis is estimated to affect 10%-20% of pediatric population and it is caused by the IgE-sensitization to environmental allergens, most importantly grass pollens and house dust mites. Allergic rhinitis can influence patient's daily activity severely and may precede the development of asthma, especially if it is not diagnosed and treated correctly. In addition to subcutaneous immunotherapy, sublingual immunotherapy (SLIT) represents the only treatment being potentially able to cure allergic respiratory diseases, by modulating the immune system activity. This review clearly summarizes and analyzes the available randomized, double-blinded, placebo-controlled trials, which aimed at evaluating the effectiveness and the safety of grass pollen and house dust mite SLIT for the specific treatment of pediatric allergic rhinitis. Our analysis demonstrates the good evidence supporting the efficacy of SLIT for allergic rhinitis to grass pollens in children, whereas trials regarding pediatric allergic rhinitis to house dust mites present lower quality, although several studies supported its usefulness.

Key words: Allergic rhinitis; Grass pollen allergy; House dust mite allergy; Sublingual immunotherapy

Core tip: This manuscript aims at describing objectively the current evidences of sublingual immunotherapy (SLIT) for the treatment of pollen and house dust mite allergic rhinitis in children, based upon the available randomized, double-blinded, placebo-controlled trials. All these studies have been directly analyzed by the authors and have been summarized in this manuscript, in order to be readily available to the reader. We concluded that there is a good evidence of efficacy for grass pollen SLIT, while the benefit seems to be weaker for house dust mite SLIT, in the specific setting of pediatric allergic rhinitis.

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BACKGROUND

Rhinitis is the term indicating the inflammatory disease of nasal mucosa and, clinically, is defined by the onset of two or more of the following symptoms: Nasal discharge, sneezing, nasal itching and congestion.

If these symptoms last longer than 10 d, the rhinitis is defined as chronic. Chronic rhinitis can persist weeks and even months or can have a recurrent trend. While acute rhinitis are usually caused by transient viral illnesses, infectious agents are not the main etiology of chronic rhinitis and, when it is so, these are due to an overlapping bacterial infection, leading to rhino-sinusitis, characterized by purulent nasal discharge, persistent fever, headache, facial pain and cough.

Actually, chronic rhinitis can recognize several etiologies (vasomotor, occupational, hormonal, atrophic, iatrogenic, idiopathic), but the most consistent group is represented by allergic rhinitis, which is estimated to affect 10%-20% of pediatric population worldwide.

Allergic rhinitis is caused by an IgE-mediated sensitization to environmental allergens, such as dust, pollens, domestic animals and moulds. Depending upon the specific pattern of sensitization, allergic rhinitis can be intermittent or persistent and seasonal or perennial, although the distinction is not always obvious, as some people can be sensitized to several allergens. Therefore, the diagnosis of allergic rhinitis is correctly made whenever the nasal symptoms are associated to a profile of allergic sensitization (which must be documented by skin prick tests and/or the dosage of serum of allergen specific IgE), which is consistent with the clinical picture and its temporal pattern[1,2].

Once the diagnosis of allergic rhinitis is established, the general clinical management is constituted by the avoidance of allergen exposure, whether it is practicable, and by the control and/or the prevention of nasal symptoms by nasal or systemic anti-histamine drugs, intranasal steroids, leukotriene-receptor antagonists and, in a lesser extent, cromolyn sodium. Among those drugs, intranasal steroid have been demonstrated to be able to produce the greatest relief, being able to improve significantly the symptoms related to the nasal obstruction. Unfortunately, all these drugs control the symptoms, but cannot cure the allergic disease[3].

Allergic rhinitis has been considered for long time as being just a nuisance disorder. However, nasal symptoms can interfere with daily activities importantly and can disrupt or alter the sleep pattern, leading to negative consequences on patient's social life and intellectual performance. Moreover, according to the "allergic/atopic march" hypothesis and to the "united airways disease" concept, allergic rhinitis can be associated to lung function test abnormalities and/or anticipate the onset of asthma. Thus, the appropriate therapy of allergic rhinitis could help to prevent the progression to more serious respiratory diseases, in addition to ameliorating patient's life quality. Such a goal may be reached through the inclusion of specific immunotherapy (SIT) in the early treatment of allergic rhinitis, before it evolves to asthma: Indeed, SIT - unlike symptomatic drugs - aims at modulating the immune mechanisms underlying the allergic disease and, currently, it is the only available treatment which modifies the disease process[4].

SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC RHINITIS

Basically, SIT consists in the administration of increasing doses of specific allergens up to a maintenance dose, which can be repeated according to different schedules depending on the allergic disease and its pattern of sensitization.

SIT can be mainly administered by two ways: Subcutaneously (SCIT) or sublingually (SLIT). Although in many European countries SCIT is still the most common way to administer allergy immunotherapy, actually sublingual immunotherapy (SLIT) is getting growing success, especially in the pediatric population: It is usually preferred because it is easier to be administrated and it hasn't been associated to systemic and life-threatening adverse reactions[5,6].

SLIT should result in the progressive acquisition of the immune tolerance against a specific allergen. Several cellular and humoral immune mechanisms have been proposed. The main immunological modifications related to the SLIT desensitization process can be summarized briefly, as it follows: Emergence of regulatory T cells (Treg), shifting of T helper polarization toward Th1 cells, increased production of interleukin (IL)-10 and transforming growth factor-β, immunoglobulin class-switching from specific IgE to IgA and IgG4 isotypes (which would compete with IgE reducing allergen-mediated release of inflammatory molecules)[7].

In 2013, the European Academy of Allergy and Clinical Immunology (EAACI) edited an important position paper on pediatric rhinitis, providing several evidence-based insights on diagnostic and therapeutic aspects. In this document, SLIT is confirmed as an effective treatment for grass pollens and house dust mite allergic rhinitis and this concept is labeled through a force of this statement of grade A, according to the system for grading clinical recommendation in evidence-based guidelines[1,8].

Such a recommendation was reached through the evaluation of available studies, considering the results of several reviews and meta-analysis. However, most clinical trials regarded mainly the adult population and specific pediatric studies are much fewer. For instance, the important systematic review of the literature made by Radulovic *et al*[9] concluded that SLIT is an effective and safe therapy for allergic rhinitis. Although this analysis considered randomized, double-blind, placebo-controlled (RDBPC) clinical trials, actually it included

patients of any age, both children and adults, affected with allergic rhinitis (with or without allergic asthma)[9].

Similarly, the World Allergy Organization (WAO) Position Paper also stated that the indication to SLIT in the treatment of IgE-mediated allergic respiratory diseases is well established in children, provided the diagnostic work-up has been appropriate[10]. Moreover, several systematic reviews supported the specific use of SLIT in the treatment of allergic rhinitis in children. In 2006, Penagos *et al*[11] made a pivotal meta-analysis of randomized controlled trials (RCTs) of SLIT in the treatment of allergic rhinitis in pediatric patients, concluding that SLIT with standardized extract is an effective therapy in this field. More recently, Kim *et al*[5] and Larenas Linnemann *et al*[12], in their reviews, reinforced the evidence supporting the efficacy and the safety of SLIT for the treatment of allergic respiratory diseases.

However, in the medical literature, the RCTs concerning specifically the role of SLIT in pediatric allergic rhinitis are, actually, fewer than expected. We performed a specific search through PUBMED (search terms: Allergic rhinitis, children, SLIT) and it returned 201 references: Almost all (195) were published after the year 2000. Among those, we found 56 reviews and/or meta-analysis; in the remaining part, considering only english-written papers, we found 35 RCTs and 11 retrospective and/or observational studies regarding pediatric allergic rhinitis (associated to grass pollen and house dust mite sensitization). Moreover, many of these RCTs were small trials, including less than 100 patients.

In this practical review, we attempt to highlight and comment the major evidences on the use of grass pollen and dust mite SLIT against allergic rhinitis in children, deriving from available RCTs being strictly oriented to allergic rhinitis and limited to pediatric population.

SLIT FOR GRASS POLLEN ALLERGIC RHINITIS IN CHILDREN: RCTS

In our search, the first randomized, double-blind, placebo-controlled (RDBPC) study on SLIT in children (n = 22) affected with seasonal allergic rhinitis was written by Wüthrich *et al*[13] in 2003: After 2 years of treatment, authors detected a statistically significant reduction ($P < 0.05$) in the drug consumption in the SLIT group and such an effect resulted to be more relevant in the second year of therapy.

In 2004, Bufe *et al*[14] published a multicenter RDBPC study, including 161 children with seasonal rhino-conjunctivitis: The authors were able to find a significant ($P = 0.046$) benefit of SLIT after 3 years of treatment, but such a positive result was limited to the group of children with severe symptoms. Similarly, Rolinck-Werninghaus *et al*[15] enrolled 97 children (3-14 years) with allergic rhinoconjunctivitis to grass pollen: They treated the active group by a 5-grass mixture SLIT (3 times/wk), documenting a positive effect in term of reduction of both multiple symptoms-medication score ($P < 0.05$) and medication score ($P = 0.0025$) rather than isolated symptom score.

Again in 2004, the multicenter study by Novembre *et al*[16], including 113 children (5-14 years) supported the beneficial effect ($P < 0.05$) of 3 years' coseasonal SLIT based upon the medication score. Another important value of this work was the demonstration that SLIT could reduce the incidence of asthma in children with grass pollen rhino-conjunctivitis. Indeed, they calculated a 3.8 relative risk of development of asthma in the control group, which was not related to differences in sex, presence of household pets, family allergic background or exposure to passive smoking[16].

A large perspective study was performed by Röder *et al*[17] in a primary care setting: 204 patients (aged 6-18 years), coming from general practitioners' office (not from allergy referral centers), were randomized to receive SLIT (five grasses pollen extract) or placebo, based on a diagnosis of allergic rhino-conjunctivitis. However, in this clinical setting, SLIT did not result to be effective in ameliorating the allergic symptoms nor in reducing the need of medications[17].

In 2009, Wahn *et al*[18] published the largest multi-national RDBPC study (n = 278 children, aged 5-17 years), by using five-grass pollen tablet (300 IR, Index of reactivity) according to a pre-co-seasonal scheme. SLIT treated patients showed a highly significant improvement compared to placebo, both in term of symptoms score ($P = 0.001$) and in term of use of medications ($P = 0.0064$). The clinical benefit was evident also considering each symptom individually, including nasal congestion and conjunctivitis. Interestingly, this study covered a period as long as 8 mo, which means that the clinical improvement became evident in a relatively short period of time, compared to previous studies encompassing 2-3 years' follow-up. Moreover, this study included also poly-sensitized children, showing a comparable improvement as well as mono-sensitized patients: that reinforced the concept that the multi-sensitization is not an absolute limit to the access to SLIT, provided that the allergy evaluation is appropriate[18].

In the same year, Bufe *et al*[19] carried out a similar research by the use of a different SLIT product, namely 75.000 Units SQ-standardized grass allergen tablets, which contain approximately 15 μg Phl p5 (Phleum pratense major allergen 5), whereas a dose of 300 IR five grasses extract corresponds to 20 μg Phl p5. A total of 253 children (aged 5-16 years) were randomized and treated according to a pre-co-seasonal scheme. SLIT group showed a significant 24% reduction of symptom score ($P = 0.0195$) and 34% reduction of medication score ($P = 0.0156$) compared to placebo group, considering the entire grass pollen season[19].

In 2010, Halken *et al*[20] published another multinational RDBPC study, which included 267 pediatric patients (aged 5-17 years). Patients were treated according to a pre-co-seasonal schedule for one year and the SLIT group received five-grass pollen 300 IR tablet daily. As previously

reported, the benefit of SLIT was confirmed even in the first pollen season: The relative mean improvement of symptom score was around 28% compared to placebo group ($P < 0.001$) and the relative mean improvement of medication score was almost 50% ($P = 0.01$)[20].

In 2011, the first RDBPC trial performed in North America has been published. Blaiss *et al*[21] randomized 345 pediatric subjects to receive 75000 SQ tablets or placebo. Study population was made by children and adolescents affected with grass pollen induced rhino-conjunctivitis and some presented asthmatic co-morbidity too; moreover, 85% patients were multi-sensitized. Patients were treated according to pre-co-seasonal scheme before and during the 2009 grass pollen season and all efficacy parameters (symptom score, medication score, total combined score) improved significantly in the treated group compared to controls (in the extent of 25%, 81% and 26%, respectively)[21].

Recently, in 2012, a small RDBPC trial by Ahmadiafshar *et al*[22] published the only english-written study performed outside western countries. It included 24 children (5-18 years) and patients were treated for 6 mo with five-grass pollen 300 IR extract: As well as previous trials, the benefit of SLIT was confirmed and was reported as being evident after 4 mo of therapy[22]. In the same year, Wahn *et al*[23] published another multicentric RDBPC trial including 207 children affected with rhinitis/rhinoconjunctivitis with/without asthma, where the outcome was evaluated by the comparison of the area under the curve (AUC) of the symptom-medication score before and after the treatment. Patients experienced a clear improvement thank to the SLIT and the efficacy resulted to be statistically significant, even considering separately the symptoms score and the medication score[23].

SLIT FOR POLLEN-INDUCED PEDIATRIC ALLERGIC RHINITIS: GLOBAL CLINICAL EVIDENCE

A summary of pediatric RDBPC trials reported in the previous paragraph is made in Table 1. It is evident that almost all the aforementioned studies supported the efficacy of grass pollen SLIT in order to improve the burden of symptoms and medications of allergic rhinitis in children. Among those, many are well-conducted trials and some are multicentric studies being large enough to draw consistent conclusions on the efficacy of SLIT in this setting as well as its good safety.

The only trial where a clear benefit of SLIT was not evident is the one performed by Röder *et al*[17], but it seems important to underline actually the fact that the study population was not made of patients evaluated at allergy referral centers[19]. This aspect could have affected the results for several reasons. Patients managed in the primary care setting could show greater variability in the severity of allergic rhinitis; moreover, many patients included in this study resulted to be sensitized to several environmental allergens and a good correlation between symptoms and sensitization, which can require some specific allergy expertise, has been stressed as being a main aspect for the correct indication and efficacy of SLIT. Indeed, the large multicentric trials performed in North America, which included mostly multisensitized patients (85% of study population), provided results consistent with a clear benefit of SLIT in grass-pollen induced rhino-conjuctivitis[21].

Therefore, in our opinion, these experiences together demonstrate how the multi-sensitization is not a limit for the use of SLIT in children affected with grass-pollen allergic rhinitis, provided that an accurate selection of allergic patients, that SLIT is offered to, can be made. According to the EAACI position paper, a clear relationship between the occurrence of nasal symptoms and the exposure to grass pollen, especially in multi-sensitized patients, should be ascertained before prescribing SLIT, in order to obtain a good efficacy from this expensive treatment[1].

Moreover, also the severity of allergic rhinitis can impact on the evidence of a clinical improvement after the treatment with SLIT. Indeed, in order to get a study population as more homogeneous as possible, the inclusion criteria of RCTs performed at allergy referral centers are often more restrictive than those used in the daily allergy practice; however, recent observational and multi-centric studies supported the effectiveness of SLIT in real life practice[24,25].

Finally, in the measurement of the effectiveness of therapies against grass pollen allergy, allergen exposure must be considered too, as it is different over several seasons and regions. Such an aspect is thought to have even a greater impact on the analysis of grass pollen SLIT than on the evaluation of other drugs used to treat allergy symptoms acutely. Indeed, in seasonal allergy trials with grass pollen SLIT, the treatment effect resulted to be greater in presence of higher pollen exposure[26]. This aspect must be considered in the individual clinical trials and this effect can be overcome through multi-centric studies and through meta-analysis pooling data from several RCTs. Recently, several post-hoc analysis have been published by using pooled data from some randomized, placebo-controlled and double-blind North American trials on timothy grass SLIT against allergic rhinitis and/or rhinoconjunctivitis in children and adolescents. This research confirmed that grass pollen SLIT administered daily, pre-seasonally and during the grass pollen season, is clinically effective and safe in children older than 5 years[27].

Another aspect to be discussed is that physicians could have the impression that SLIT is less effective than it is actually or compared to the other classes of drugs for allergic rhinitis, despite all the evidences we reported. Although that is not specific for pediatric age, a huge meta-analysis by Devillier *et al*[28] deserves to be reported, as it provided an indirect comparison between SLIT and pharmacotherapy: The administration of pollen SLIT tablets resulted in a relative clinical impact (RCI) *vs* placebo greater than that observed with second-

Table 1 Randomized double-blinded placebo controlled trials on grass pollen sublingual Immunotherapy for the treatment of allergic rhinits in children

Ref.	Year	Age	No. of patients	Product	Efficacy parameters	Duration	Statistical significance	Other observation
Wüthrich *et al*[13]	2003	4-11	22	ALK-Abello'	Medication score	2 yr	$P = 0.05$	A difference in drug consumption has been shown only in the second year
Bufe *et al*[14]	2004	6-12	161	Sublivac BEST, HAL-allergy	Clinical Index (combining symptom and medication score)	3 yr	$P = 0.046$	A significant difference was shown in patients with severe symptoms
Rolinck-Werninghaus[15]	2004	3-14	97	Pangramin-SLIT ALK-SCHERAX	Multiple symptom – medication score	32 mo	$P = 0.498$	Symptom score did not reveal significant difference; medication score improve significantly ($P = 0.0025$)
Novembre *et al*[16]	2004	5-14	113	ALK-Abello'	Medication score	3 yr	$P < 0.05$	Significant improvement was shown after the second year; symptom score did not improve significantly
Röder *et al*[17]	2007	6-18	204	Oralgen Grass Pollen, Artu Biologicals	Medication and symptom score	2 yr	NS	Study population was enrolled from general practices
Wahn *et al*[18]	2009	5-17	278	5-grass tablets 300IR,	Rhinoconjunctivitis total symptom score	6 mo	$P = 0.001$	SLIT was started 4 mo before before the pollen season; both symptom score and medication score improved singularly too
Bufe *et al*[19]	2009	5-16	253	Stallergenes SQ-standardized grass allergen tablet (Grazax)	Medication and symptom score	4-6 mo	$P < 0.02$	SLIT was started 8 to 23 wk before the estimated pollen season in 2007
Halken *et al*[20]	2010	5-17	267	5-grass tablets 300IR,	Medication and symptom score	6 mo	$P < 0.01$	SLIT was started 4 mo before the estimated pollen season
Stelmach *et al*[29]	2011	6-18	60	Stallergenes Staloral 300IR, Stallergenes	Combined symptom and medication score	2 yr	$P < 0.01$	Both pre-coseasonal and continuous regimen were efficacious in the same extent
Blaiss *et al*[21]	2011	5-17	345	SQ-standardized grass allergen tablet (Grazax)	Medication and symptom score	6 mo	$P < 0.01$	SLIT started 8 wk before the pollen 2009 season; 89% patients were multi-sensitized
Wahn *et al*[23]	2012	4-12	207	6-grass pollen aqueous extract (AllerSlit, Allergopharma)	Area under the curve of symptom-medication score	6-8 mo	$P = 0.004$	Patients were treated with a pre-coseasonal regimen; after this first phase, unblinding was made and all patients were treated
Ahmadiafshar *et al*[22]	2012	5-18	24	Staloral 300IR, Stallergenes	Medication and symptom score	6 mo	$P < 0.05$	SLIT was started 8-10 wk before pollen season

SLIT: Sublingual Immunotherapy; NS: Not significant.

generation H1-antihystamines and montelukast, and it was comparable to nasal corticosteroids[28]. Most recent RCTs demonstrated that SLIT is beneficial even since the first year of treatment, provided that an appropriated scheme of treatment is instituted before the pollen season. Previously, in the study by Stelmach *et al*[29], where the pre-co-seasonal and the continuous schedule were compared after a 2-years perspective RDBPC trial, both protocols resulted to be associated to a significant improvement in the total symptom and medication scores and there was no significant difference between them. Actually, the pre-co-seasonal group showed a lower improvement for nasal symptoms than the continuous schedule[29]. Similarly, the results emerging from an open randomized controlled study by Pajno *et al*[30] observed that the continuous protocol performed in a better way than the pre-co-seasonal schedule in the first pollen season, whereas in the following years both were rather equivalent.

Therefore, based upon most recent studies, a good efficacy of a pre-co-seasonal treatment beginning around 4 mo before the pollen season has been showed. Differences in both the efficacy endpoint - in the research setting - and the clinical results - in the daily allergy practice - could be due not only to the variable scheme of vaccine administration, but also to different allergen formulation and product standardization, whose discussion overcomes the purpose of the present analysis.

Finally, it must be underlined the optimal profile of safety of grass pollen SLIT, which is confirmed by all RCTs and systematic revisions regarding children and adolescents affected with allergic rhinitis. No death or life-threatening events resulted to be associated to the treatment. Treatment related adverse events have been limited to mild to moderate local symptoms, such as oral pruritus, ear pruritus and throat irritation, reported in 15%-30% of subjects.

In conclusion, available pediatric RDBPC trials as well as reviews/meta-analysis clearly demonstrated the effectiveness and the safety of five-grass pollen

SLIT administered with the appropriate scheme and formulation (*e.g.*, 300 IR drops, 300 IR tablets, 75000 SQ-standardized tablets). Particularly, the pre-co-seasonal schedule is the most used and it is beneficial even in the first year of treatment, if it is started appropriately (3-4 mo before the supposed beginning of the pollen season).

Of course, despite these good evidences supporting grass pollen SLIT in the treatment of allergic rhinitis, some issues need consideration and further research, such as the use of different vaccines, the variable follow-up in the aforementioned studies and the lack of SLIT *vs* SLIT and SLIT *vs* SCIT trials. However, current evidences can be considered strong enough to support prescription of grass pollen SLIT to all pediatric patients suffering from grass pollen allergic rhinitis, after an appropriate diagnostic assessment by an allergy specialist, who will plan a correct schedule for SLIT administration and will provide an adequate follow-up.

SLIT FOR HOUSE DUST-MITE ALLERGIC RHINITIS IN CHILDREN: RCTS

Available RCTs concerning the efficacy of dust mite SLIT on pediatric allergic rhinitis are relatively poor and most have been made in the last few years. Indeed, the first multicenter RDBPC trial was produced by Tseng *et al*[31] in 2008. This study included 59 children (aged 6-18 years) from Taiwan and the treatment group received a standardized extract of Dermatophagoides pteronyssinus (D.p.) and Dermatophagoides farinae (D.f) up to 20 drops of a 300 IR/mL formulation, as a 5 mo' maintenance dose, which was reached in a period of 3-4 wk. Here, the authors were not able to demonstrate a significant benefit in either symptoms or medication score after 6 mo of SLIT. However, they described a significant serological response in patients treated with SLIT, in term of increase of specific IgG4 to D.f-D.p. ($P < 0.001$) and specific IgG4/IgE ratio ($P = 0.01$), which is reputed to be one mechanism of the potential efficacy of SLIT in allergic diseases[31].

Previously, we were able to find one retrospective analysis by Nuhoglu *et al*[32] in 2007, regarding 39 children affected with dust mite allergic rhinitis, which reported a positive impact of SLIT on nasal symptoms, in addition to a significant decrease of asthma attacks[32]. Moreover, in 2003 Marcucci *et al*[33] performed a 3 years' partially double-blind case-control clinical study including 24 children (aged 4-15 years) complaining dust mite allergic rhinitis for at least 2 years. In the first year of follow-up, patients were randomized to receive dust mite SLIT or placebo; subsequently, also children in the placebo group were switched to the SLIT treatment until the end of the study. The first double-blind placebo-controlled phase was not able to demonstrate a significant amelioration of symptoms and drug scores for rhinitis; however, intra-group comparison of the effect of SLIT in term of cumulative yearly nasal symptoms score revealed a significant reduction in the second ($P = 0.01$) and, even more, in the third year ($P < 0.001$) of SLIT treatment compared to first year[33,34].

All these studies suggested the potential role of SLIT on dust mite pediatric allergic rhinitis, but none satisfied the standard quality parameters needed to draft strong evidence-based conclusions.

The first small RDBPC trial supporting the safety and the effectiveness of SLIT in house dust mite allergic rhinitis in children (aged 7-15 years) was published in 2010 by Yonekura *et al*[35]. They randomized 31 subjects and used a dust mite extract (containing 5 μg/mL of Der f 1 allergen) for 40 wk. The authors were able to find a significant reduction of symptom scores between the active group and the placebo group after 32 wk of treatment ($P < 0.05$); furthermore, whereas the placebo group reported no significant benefit at the 40th week (compared to the beginning of the study), in term of symptom scores, the active group showed a significant intra-group amelioration after SLIT treatment ($P = 0.03$). Indeed, at the end of the trial, 33% patients reported a clear improvement of symptoms, whereas placebo patients showed no more than a slight amelioration; moreover, the authors reported that half children, showing an important reduction of nasal symptom scores at the end of the treatment, had a beneficial effect persisting up to one year later. However, this study was not able to document a parallel improvement on medication score and the response to SLIT was quite variable among all the patients[35].

The paper written by de Bot *et al*[36] in 2012 investigated the results of SLIT for house dust mite allergic rhinitis in a population of children recruited in primary care settings rather than in referral centers for allergy. They included 251 patients, aged from 6 to 18 years, and performed a 2 years' RDBPC trial, being the greatest RCTs so far. Unfortunately, this study found no significant improvement in allergic children treated with dust mite SLIT compared to placebo. However, the authors themselves hypothesized some probable limitations of the present study, such as the relative low cumulative dose of allergen they used to treat the patients or a lower clinical severity of symptoms presented by patients followed in a primary care setting, compared to a referral center[36].

In the same year, we can find two more studies on dust mite pediatric allergic rhinitis, which showed some points of interest, in our opinion, despite their numerical and/or design limitations. Han *et al*[37] treated with SLIT 54 youngsters (aged 6-18 years) in parallel to 22 adults, showing a similar tendency to the amelioration of symptom and medication scores in both age groups after one year of treatment[37]. Barberi *et al*[38] performed a 2 years' small case-control study, treating 30 children with dust mite respiratory allergy with symptomatic drugs alone or with SLIT and drugs on demand. They observed a significant amelioration of symptoms and of drug utilization in patients treated with SLIT, in addition to the evidence of the induction of a condition of allergenic hypo-reactivity through the measurement of serum IL-10

Table 2 Randomized double-blinded placebo controlled trials on house dust mite sublingual Immunotherapy for the treatment of allergic rhinitis in children

Ref.	Year	Mean age (yr)	No. of patients	Product	Efficacy parameters	Duration	Statistical significance	Other observation
Marcucci *et al*[33,34]	2005	4-15	24	Aqueous solution (ALK-Abello')	Symptoms score	1 yr	NS	A significant difference was recorded in the last trimester of the year; the study was carried on after the first year in open way
Tseng *et al*[31]	2008	6-18	59	Staloral (Stallergenes)	Symptoms score	6 mo	NS	In treated group a slight improvement was recorded. Specific IgG4 and IgG4/IgE significantly increased in SLIT group
Yonekura *et al*[35]	2010	7-15	31	Extract of house dust mite (Torii Pharmaceutical)	Symptom score	40 wk	$P < 0.05$	The improvement in SLIT group increased progressively according to the duration of the therapy
de Bot *et al*[36]	2012	6-18	251	Oralgen House Dust Mite (Oralgen Mijten)	Symptom score	2 yr	NS	Study population was recruited in primary care setting
Aydogan *et al*[41]	2013	5-10	22	Staloral (Stallergenes)	Medication and symptom score	12 mo	NS	-

SLIT: Sublingual Immunotherapy; NS: Not significant.

and Th2-dependent cytokines[38].

In 2013, Wang *et al*[39] obtained a significant result supporting the efficacy of SLIT in dust mite allergic rhinitis in a multicenter RDBPC trial, including 120 patients (aged 4-60 years). A similar output was previously described also by another RDBPC study (by Lee *et al*[40]), which enrolled 134 patients (aged 4-53 years). They showed that both mono-sensitized and poly-allergic patients, recruited in allergy referral centers, had achieved a comparable and significant improvement of nasal symptom and medication scores, after at least 1 year of treatment with house dust mite SLIT[40]. Unfortunately, both trials included a small proportion of children and an age-specific analysis was not made.

In the same year, Aydogan *et al*[41] published a small RDBPC trial with 22 children (aged 5-10 years), but they were not able to demonstrate the superiority of SLIT to placebo after 12 mo of treatment.

However, very recently, Shao *et al*[42] published the results of a large (n = 264) randomized and placebo-controlled, but open-label trial, including children (aged 3-13 years) affected with dust mite allergic rhinitis. They were able to demonstrate a significant ($P < 0.01$) reduction of nasal symptoms and medication scores, starting from 6-7 mo of treatment. Moreover, as the study included even 133 children aged 3-5 years, they reported also that, in the SLIT group, the therapeutic response was comparable in children older and younger than 5 years[42].

SLIT FOR HOUSE DUST-MITE PEDIATRIC ALLERGIC RHINITIS: GLOBAL CLINICAL EVIDENCE

Our brief analysis showed that the clinical research, addressed to evaluate specifically the effectiveness of SLIT against house dust mite allergic rhinitis in children, is quite poor (Table 2). We were not able to find randomized double-blind placebo controlled trial showing clearly and conclusively the improvement of children affected with house dust mite allergic rhinitis through SLIT. Thus, evidences supporting the effectiveness of SLIT on dust mite rhinitis in children are largely derived from studies on adults and from trials where actually patients were affected by asthma and the nose disease represented more a co-morbidity than a primary end-point of the research[6]. Actually, the only multicenter RDBPC trial assessing the specific effect of SLIT on pediatric rhinitis was not able to show a significant clinical improvement: Maybe a six month's period of study was too short in order to achieve a positive conclusion, as actually several immunological changes, proposed as inducing tolerance in the setting of allergy, have been described in patients receiving dust mite SLIT[30].

Environmental pollutants might affect the outcome of SLIT, worsening the nasal inflammation due to house dust mite allergy. However, as regards pediatric allergic rhinitis, we found very few studies addressing this topic. Interestingly, Marogna *et al*[43] conducted a prospective study showing that the exposure to passive smoke significantly reduced the clinical response to SLIT in children affected with allergic rhinitis due to house dust mite.

However, as a final remark, it deserves to be told that the usefulness of HDM-SLIT must be sought in some indirect beneficial effects, as the prevention of asthma development, through the potential modification of the natural history of the respiratory allergic disease, and the reduction of respiratory infections too. As regards the latter aspect, allergic children are known to have more frequent and more severe respiratory infection than non-allergic controls. Indeed, the persistent mucosal inflammation in the nose of house dust mite allergic people compromises the mechanical barrier against

external infectious agents and can constitute a favorable environment for microbial proliferation; moreover, the defective production of anti-viral cytokines and the over-expression of some epithelial adhesion molecules in patients with allergic rhinitis increase the susceptibility to viral infections. Recent evidences supported that HDM-SLIT can reduce the burden of recurrent respiratory infections in allergic children and some observational studies suggested that SLIT-treated children significantly developed fewer respiratory infections compared to controls and also the use of antibiotics was reduced[44,45].

CONCLUSION

As well as the EAACI position paper on pediatric rhinitis, several reviews and meta-analysis concluded for a general efficacy and safety of AIT for pediatric rhinitis and rhino-conjunctivitis. Recently, Kim *et al*[5], trough their systematic review, inferred a moderate-strength and general evidence that SLIT improves pediatric allergic rhinitis and conjunctivitis through a reduction of symptoms and/or a decrease of drug consumption. Similarly, Pleskovic *et al*[46] concluded that SLIT is a good option for the treatment of children with grass pollen and dust-mite allergic rhino-conjunctivitis.

Similarly, our brief and practical review supports the global effectiveness of SLIT intended to treat grass pollen and house dust mite allergic rhinitis in children, but some differences must be made, in our opinion, based on current clinical evidences.

As concerns grass pollen SLIT, several RDBPC trials of good standard quality are available and almost all produced clinical data showing a positive effect of SLIT in the control of allergic symptoms and/or drug request and also in the prevention of the development of asthma.

However, the evidence of the clinical efficacy of house dust mite SLIT on pediatric allergic rhinitis is milder. Indeed, RCTs and good standard quality studies exploring this aspect are less abundant and smaller; therefore, in our opinion, more trials are needed to consolidate the recommendation for dust mite SLIT in pediatric allergic rhinitis.

These conclusions are comparable to the evidences emerging from the analysis performed recently by Larenas Linnermann *et al*[12] These authors concluded that the evidence is strong for grass pollen SLIT efficacy in the treatment of pediatric allergic rhinitis, whereas the evidence for house dust mite SLIT effectiveness is still considered "of moderate-low quality".

Finally, we think that it should be stressed the concept that SLIT for pediatric allergic rhinitis seems to be more efficacious if the prescription of SLIT derives from an experienced diagnostic pathway and if an appropriated follow-up is planned.

REFERENCES

1 **Roberts G**, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, Papadopoulos NG, Rotiroti G, Scadding G, Timmermans F, Valovirta E. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013; **68**: 1102-1116 [PMID: 23952296 DOI: 10.1111/all.12235]

2 **Dykewicz MS**, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2010; **125**: S103-S115 [PMID: 20176255 DOI: 10.1016/j.jaci.2009.12.989]

3 **Benninger M**, Farrar JR, Blaiss M, Chipps B, Ferguson B, Krouse J, Marple B, Storms W, Kaliner M. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol* 2010; **104**: 13-29 [PMID: 20143641 DOI: 10.1016/j.anai.2009.11.020]

4 **Morjaria JB**, Caruso M, Rosalia E, Russo C, Polosa R. Preventing progression of allergic rhinitis to asthma. *Curr Allergy Asthma Rep* 2014; **14**: 412 [PMID: 24408536 DOI: 10.1007/s11882-013-0412-6]

5 **Kim JM**, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, Erekosima N. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013; **131**: 1155-1167 [PMID: 23650298 DOI: 10.1542/peds.2013-0343]

6 **Marseglia GL**, Incorvaia C, La Rosa M, Frati F, Marcucci F. Sublingual immunotherapy in children: facts and needs. *Ital J Pediatr* 2009; **35**: 31 [PMID: 19852795 DOI: 10.1186/1824-7288-35-31]

7 **Burks AW**, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, Nelson H, Akdis CA. Update on allergy immunotherapy: American Academy of Allergy, Asthma & amp; Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 2013; **131**: 1288-1296.e3 [PMID: 23498595 DOI: 10.1016/j.jaci.2013.01.049]

8 **Harbour R**, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; **323**: 334-336 [PMID: 11498496 DOI: 10.1136/bmj.323.7308.334]

9 **Radulovic S**, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; **66**: 740-752 [PMID: 21443635 DOI: 10.1111/j.1398-9995.2011.02583.x]

10 **Passalacqua G**, Compalati E, Canonica GW. Sublingual Immunotherapy: Clinical Indications in the WAO-SLIT Position Paper. *World Allergy Organ J* 2010; **3**: 216-219 [PMID: 23282652 DOI: 10.1097/WOX.0b013e3181e8d19c]

11 **Penagos M**, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, Canonica GW. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; **97**: 141-148 [PMID: 16937742 DOI: 10.1016/S1081-1206(10)60004-X]

12 **Larenas Linnemann D**, Compalati E, Blaiss M, Van Bever HP, Baena-Cagnani CE. Author response. *Ann Allergy Asthma Immunol* 2013; **111**: 306-307 [PMID: 24054373 DOI: 10.1016/j.anai.2013.07.032]

13 **Wüthrich B**, Bucher Ch, Jörg W, Bircher A, Eng P, Schneider Y, Schnyder F, Eigenmann P, Senti G. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003; **13**: 145-148 [PMID: 14635462]

14 **Bufe A**, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, Braun W. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; **59**: 498-504 [PMID: 15080830 DOI: 10.1111/j.1398-9995.2004.00457.x]

15 **Rolinck-Werninghaus C**, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, Hammermann J, Leupold W, Bartels P, Gruebl A, Bauer CP, Schnitker J, Wahn U, Niggemann B. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004; **59**: 1285-1293 [PMID: 15507097 DOI: 10.1111/

j.1398-9995.2004.00627.x]
16 **Novembre E**, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, Burastero SE, Calori G, Benetti L, Bonazza P, Puccinelli P, Parmiani S, Bernardini R, Vierucci A. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; **114**: 851-857 [PMID: 15480326 DOI: 10.1016/j.jaci.2004.07.012]
17 **Röder E**, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007; **119**: 892-898 [PMID: 17321581 DOI: 10.1016/j.jaci.2006.12.651]
18 **Wahn U**, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, Le Gall M. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009; **123**: 160-166.e3 [PMID: 19046761 DOI: 10.1016/j.jaci.2008.10.009]
19 **Bufe A**, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, Knecht R, Stephan V, Tholstrup B, Weisshaar C, Kaiser F. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **123**: 167-173.e7 [PMID: 19130937 DOI: 10.1016/j.jaci.2008.10.044]
20 **Halken S**, Agertoft L, Seidenberg J, Bauer CP, Payot F, Martin-Muñoz MF, Bartkowiak-Emeryk M, Vereda A, Jean-Alphonse S, Melac M, Le Gall M, Wahn U. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol* 2010; **21**: 970-976 [PMID: 20718927 DOI: 10.1111/j.1399-3038.2010.01050.x]
21 **Blaiss M**, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011; **127**: 64-71, 71.e1-4 [PMID: 21211642]
22 **Ahmadiafshar A**, Maarefvand M, Taymourzade B, Mazloomzadeh S, Torabi Z. Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study. *Iran J Allergy Asthma Immunol* 2012; **11**: 175-181 [PMID: 22761191]
23 **Wahn U**, Klimek L, Ploszczuk A, Adelt T, Sandner B, Trebas-Pietras E, Eberle P, Bufe A. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2012; **130**: 886-893.e5 [PMID: 22939758 DOI: 10.1016/j.jaci.2012.06.047]
24 **Eberle P**, Brueck H, Gall R, Hadler M, Sieber J, Karagiannis E. An observational, real-life safety study of a 5-grass pollen sublingual tablet in children and adolescents. *Pediatr Allergy Immunol* 2014; **25**: 760-766 [PMID: 25378225 DOI: 10.1111/pai.12298]
25 **Garcia MA**, Antolin D, Valbuena T, Valls A, Garrido S, Blanco C. Fisrt season with five grass pollen tablets in allergic children/teenagers. A real-life disease impact in terms of symptoms and medication. SMILE study. *Allergy* 2014; **69** (suppl 99): 411-412
26 **Durham SR**, Nelson HS, Nolte H, Bernstein DI, Creticos PS, Li Z, Andersen JS. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. *Allergy* 2014; **69**: 617-623 [PMID: 24605984 DOI: 10.1111/all.12373]
27 **Hébert J**, Blaiss M, Waserman S, Kim H, Creticos P, Maloney J, Kaur A, Li Z, Nelson H, Nolte H. The efficacy and safety of the Timothy grass allergy sublingual immunotherapy tablet in Canadian adults and children. *Allergy Asthma Clin Immunol* 2014; **10**: 53 [PMID: 25685162 DOI: 10.1186/1710-1492-10-53]
28 **Devillier P**, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014; **12**: 71 [PMID: 24885894 DOI: 10.1186/1741-7015-12-71]
29 **Stelmach I**, Kaluzińska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy* 2012; **67**: 312-320 [PMID: 22142341 DOI: 10.1111/j.1398-9995.2011.02758.x]
30 **Pajno GB**, Caminiti L, Crisafulli G, Vita D, Valenzise M, De Luca R, Passalacqua G. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. *Pediatr Allergy Immunol* 2011; **22**: 803-807 [PMID: 21929600 DOI: 10.1111/j.1399-3038.2011.01196.x]
31 **Tseng SH**, Fu LS, Nong BR, Weng JD, Shyur SD. Changes in serum specific IgG4 and IgG4/ IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. *Asian Pac J Allergy Immunol* 2008; **26**: 105-112 [PMID: 19054928]
32 **Nuhoglu Y**, Ozumut SS, Ozdemir C, Ozdemir M, Nuhoglu C, Erguven M. Sublingual immunotherapy to house dust mite in pediatric patients with allergic rhinitis and asthma: a retrospective analysis of clinical course over a 3-year follow-up period. *J Investig Allergol Clin Immunol* 2007; **17**: 375-378 [PMID: 18088019]
33 **Marcucci F**, Sensi L, Di Cara G, Salvatori S, Bernini M, Pecora S, Burastero SE. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sublingual immunotherapy. *Pediatr Allergy Immunol* 2005; **16**: 519-526 [PMID: 16176400 DOI: 10.1111/j.1399-3038.2005.00301.x]
34 **Marcucci F**, Sensi L, Frati F, Bernardini R, Novembre E, Barbato A, Pecora S. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy* 2003; **58**: 657-662 [PMID: 12823127 DOI: 10.1034/j.1398-9995.2003.00193.x]
35 **Yonekura S**, Okamoto Y, Sakurai D, Horiguchi S, Hanazawa T, Nakano A, Kudou F, Nakamaru Y, Honda K, Hoshioka A, Shimojo N, Kohno Y. Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children. *Allergol Int* 2010; **59**: 381-388 [PMID: 20864799 DOI: 10.2332/allergolint.10-OA-0200]
36 **de Bot CM**, Moed H, Berger MY, Röder E, Hop WC, de Groot H, de Jongste JC, van Wijk RG, Bindels PJ, van der Wouden JC. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol* 2012; **23**: 150-158 [PMID: 22017365 DOI: 10.1111/j.1399-3038.2011.01219.x]
37 **Han DH**, Choi YS, Lee JE, Kim DY, Kim JW, Lee CH, Rhee CS. Clinical efficacy of sublingual immunotherapy in pediatric patients with allergic rhinitis sensitized to house dust mites: comparison to adult patients. *Acta Otolaryngol* 2012; **132** Suppl 1: S88-S93 [PMID: 22582789 DOI: 10.3109/00016489.2012.660732]
38 **Barberi S**, Villa MP, Pajno GB, La Penna F, Barreto M, Cardelli P, Amodeo R, Tabacco F, Caminiti L, Ciprandi G. Immune response to sublingual immunotherapy in children allergic to mites. *J Biol Regul Homeost Agents* 2011; **25**: 627-634 [PMID: 22217994]
39 **Wang DH**, Chen L, Cheng L, Li KN, Yuan H, Lu JH, Li H. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope* 2013; **123**: 1334-1340 [PMID: 23616386 DOI: 10.1002/lary.23935]
40 **Lee JE**, Choi YS, Kim MS, Han DH, Rhee CS, Lee CH, Kim DY. Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2011; **107**: 79-84 [PMID: 21704889 DOI: 10.1016/j.anai.2011.03.012]
41 **Aydogan M**, Eifan AO, Keles S, Akkoc T, Nursoy MA, Bahceciler NN, Barlan IB. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. *Respir Med* 2013; **107**: 1322-1329 [PMID: 23886432 DOI: 10.1016/j.rmed.2013.06.021]
42 **Shao J**, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, Li Q, Cao LF. Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis. *Am J Rhinol Allergy* 2014; **28**: 131-139 [PMID: 24717951 DOI: 10.2500/ajra.2014.28.4006]
43 **Marogna M**, Massolo A, Colombo F, Isella P, Bruno M, Falagiani P. Children passive smoking jeopardises the efficacy of standard anti-allergic pharmacological therapy, while sublingual immunotherapy

withstands. *Allergol Immunopathol* (Madr) 2011; **39**: 60-67 [PMID: 21216083 DOI: 10.1016/j.aller.2010.05.002]

44 **Occasi F**, De Castro G, Zicari AM, Indinnimeo L, Tancredi G, Duse M. Sublingual immunotherapy in children and its potential beneficial collateral effect on respiratory tract infections. *Curr Med Res Opin* 2015; **31**: 939-941 [PMID: 25753228 DOI: 10.1185/03007995.2015.1027182]

45 **Barberi S**, Ciprandi G, Verduci E, D'Auria E, Poli P, Pietra B, Incorvaia C, Buttafava S, Frati F, Riva E. Effect of high-dose sublingual immunotherapy on respiratory infections in children allergic to house dust mite. *Asia Pac Allergy* 2015; **5**: 163-169 [PMID: 26240793 DOI: 10.5415/apallergy.2015.5.3.163]

46 **Pleskovic N**, Bartholow A, Skoner DP. Sublingual immunotherapy in children: the recent experiences. *Curr Opin Allergy Clin Immunol* 2014; **14**: 582-590 [PMID: 25188717 DOI: 10.1097/ACI.0000000000000112]

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