Curr Otorhinolaryngol Rep (2015) 3:155–161
DOI 10.1007/s40136-015-0087-8

Sublingual Immunotherapy in Children

David J. Mener[1] · **Sandra Y. Lin**[1]

Published online: 24 June 2015

Abstract Allergic rhinitis and food allergies are two of the most prevalent chronic medical diseases affecting children. Poorly controlled allergic rhinitis symptoms may impact quality of life and missed school days. Recent clinical trials have demonstrated that sublingual immunotherapy is effective in decreasing hypersensitivity to allergens such as dust mite, pollens, and cockroach. Research evaluating efficacy of sublingual immunotherapy for peanuts is promising; however, sublingual immunotherapy for food allergy should only be performed in a research setting until further evidence demonstrates consistent safety. Sublingual immunotherapy is an effective and safe alternative to more traditional subcutaneous immunotherapy, is well tolerated, and has good compliance among pediatric patients. The majority of adverse events with sublingual immunotherapy are reported as minor and have a lower systemic complication rate compared to subcutaneous immunotherapy, an important consideration among children.

Keywords Allergic rhinitis · Asthma · Allergen-specific immunotherapy · Sublingual immunotherapy · Food allergy

Abbreviations

SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
FEV-1	Forced end vital capacity at 1 s
ASI	Allergen-specific immunotherapy

This article is part of the Topical Collection on *Otolaryngic Allergy*.

✉ Sandra Y. Lin
slin30@jhmi.edu

[1] Department of Otolaryngology-Head & Neck Surgery, Johns Hopkins School of Medicine, Johns Hopkins University, 601 N. Caroline Street, 6th Floor, Baltimore, MD 21287, USA

Introduction

Allergic rhinitis (AR), one of the most prevalent chronic medical diseases affecting nearly 9 % of children [1], has become increasingly more prevalent in recent years. The prevalence of AR has nearly doubled since 1970 [2] and is estimated to cost more than 2 billion dollars annually [3]. Allergic rhinitis symptoms may impact quality of life and contribute to missed school days with subsequent decrease in school productivity.

AR consists of symptoms consistent with an allergic cause such as clear rhinorrhea, nasal congestion, pale nasal mucosa, and red/watery eyes in response to inhaled allergens [4]. Allergic rhinitis symptoms caused by increased sensitivities to house dust mites and pollens usually require treatment to ameliorate symptoms satisfactorily. Specific immunotherapy is recommended for children with uncontrolled asthma and allergic rhinitis symptoms who cannot be adequately controlled with maximal medical therapy or allergen avoidance alone. Medications classically prescribed to control symptoms of allergic rhinitis include antihistamines and intranasal corticosteroids. Allergen-specific immunotherapy is the only treatment available that can alter the natural course of allergic diseases and provide sustained long-term effects. Subcutaneous immunotherapy has traditionally been considered the administration route for therapy; however, sublingual immunotherapy (SLIT) has recently become a novel alternative.

SLIT has previously been shown to be safe, effective, and well tolerated as an alternative means of receiving immunotherapy treatment [5]. SLIT involves placement of allergen extract under the tongue for several minutes for local absorption and then is ultimately swallowed or spit

out. This method of administration is especially advantageous immunologically since the oral mucosa has proportionally fewer inflammatory cells but is rich in tolerogenic myeloid dendritic cells, suggesting potentially high efficacy with low likelihood of adverse events [6]. Systematic titration of allergen extracts are used to desensitize children, usually over a period of months to years, which may be performed at home. SLIT may be considered as a more appealing alternative in the pediatric population compared to traditional subcutaneous immunotherapy due to convenience of administering the majority of therapy outside of the clinician's office, avoidance of potentially painful subcutaneous injections, and improved safety profile.

Background

Allergy-specific immunotherapy (ASI) should be strongly considered in children with allergic rhinitis who desire to avoid long-term pharmacotherapy, and those who seek to improve allergen provoked asthma symptoms, bronchial hyper-responsiveness, and pulmonary function. ASI may be considered in children with food allergies who hope to prevent life-threatening anaphylaxis to accidental exposure. With ASI, allergens are given to patients and titrated to doses necessary to promote immune tolerance [7]. The mechanism of action of allergen-specific immunotherapy is likely the result of a switch from TH2- to TH1-mediated immunity. Clinicians should consider children with AR for immunotherapy who have had an inadequate reduction in symptoms with standard pharmacotherapy and avoidance according to current practice guidelines [4].

SLIT was first introduced in 1986 as an alternative to the traditional subcutaneous route of administration [8]. The development of SLIT was an important advancement, with reduction in systemic side effects from subcutaneous immunotherapy and improved tolerance in pediatric patients [9]. There are currently 2 modality types of SLIT available in the United States: SLIT tablets and aqueous SLIT. The United States Food and Drug Administration (US FDA) has approved of three different types of SLIT tablets consisting of extracts of ragweed (trade name Ragwitek), timothy grass (Oralair), and grass mix (Grastek). However, Ragwitek is approved for use only in adult patients aged 18–65, and only Oralair and Ragwitek are approved for use in children. In respect to pediatric patients, Oralair and Grastek were approved in 2014 for children and adults aged 5–64 and 10–65, respectively, for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis after appropriate confirmatory testing. Initiation of therapy is recommended for at least 12 (Oralair)–16 (Grastek) weeks prior to start of pollen season and throughout the entire season for maximal efficacy. Patients should be observed in the office for at least 30 min after the initial physician prescribed dose to monitor for signs and symptoms of anaphylaxis, prescribed an auto-injectable epinephrine pen, and is contraindicated in children with severe asthma, eosinophilic esophagitis, or individuals taking beta blockers.

Data supporting the efficacy of timothy grass immunotherapy tablets are strong; among 345 children aged 5–17 years randomized to sublingual immunotherapy starting 16 weeks prior to the 2009 grass pollen season, daily symptom score improved by 25 %, daily medication score improved by 81 %, and rhinoconjunctivitis quality of life score improved by 18 %. Not un-expectantly, serum-specific IgG4- and IgE-blocking levels were significantly higher after immunotherapy treatment, an indication that AIT had a stimulating effect on the immune system. The most common adverse event was oral pruritus occurring in 38.9 % of children, with only one participant experiencing a systemic reaction which included angioedema [10]. Regarding the efficacy of 5-grass pollen sublingual immunotherapy tablets, a multinational randomized double-blind placebo-controlled trial of 278 children aged 5–17 years, who started treatment 4 months prior to pollen season, found that the rhinoconjunctivitis total symptom score improved by 28 %. No serious adverse events attributed to the immunotherapy were reported; however, the most frequently reported minor adverse event was oral pruritus [11] (32.4 %).

However, the United States Food and Drug Administration has not approved the use of aqueous SLIT in adults or children for treatment of allergic rhinitis and allergic asthma. As a result, aqueous SLIT when administered to children is used off label by clinicians; aqueous SLIT is derived from allergen extracts approved for subcutaneous immunotherapy. These extracts are then placed in the sublingual space. Only approved allergen extracts for subcutaneous immunotherapy to treat allergic rhinitis and allergic asthma. The use of similar extracts for SLIT is currently used in an off-label fashion in the United States; however, SLIT has become more commonplace in Europe over the past few years.

The Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology Immunotherapy practice parameters justify the use of using a representative allergen for immunotherapy treatment within a subgroup of allergens as adequate efficacy against an entire similar group of allergens. Numerous allergens including house dust mite, grasses, and ragweed can be targeted in monosensitizied and polysensitized children with SLIT [12].

SLIT has been studied extensively, with many recent clinical trials evaluating efficacy (Table 1). A recent

systematic review evaluating 34 randomized controlled trials of children aged 4–18 with allergic asthma or rhinoconjunctivitis treated with subcutaneous immunotherapy (920 children) or sublingual therapy (1583 children) found high strength of evidence and low bias that SLIT improves asthma symptoms, and moderate strength of evidence that SLIT improves rhinitis and conjunctivitis symptoms [13••] (Table 2). Likewise, a case–control study involving 140 children aged 5–14 undergoing 3 years of SLIT demonstrated significant improvement in rhinitis symptom scores, asthma symptoms scores, and force expiratory volume at 1 s (FEV-1). Specifically, only 20 % versus 37 % of children undergoing SLIT compared to control participants had persistent rhinitis at the end of the trial period. In addition, only 4.3 versus 25.7 % of children undergoing immunotherapy compared to control participants had mild persistent asthma after completion of therapy [14].

However, despite sometimes significant improvement in allergic symptoms following therapy, a systematic review reported there was low strength of evidence demonstrating that SLIT decreases combined nasal, eye, bronchial symptoms, and pharmacotherapy use in children with asthma and allergic rhinitis [13••]. In addition, there was

Table 1 Recent trials evaluating sublingual immunotherapy in pediatric patients

Study	Study characteristics	Number (age, years)	Conclusions
De Castro et al. [14]	Case control study evaluating effect of SLIT on rhinitis and asthma symptoms	140 (6–14)	Children undergoing SLIT had a significant improvement in rhinitis and symptom scores.
Holt et al. [19]	Randomized controlled pilot trial evaluating dust mite, cat, and timothy grass SLIT	50 (1.5–2.5)	No differences in allergen-specific IgE/IgG antibodies and associated Th-cell responses were observed.
Dust mite SLIT			
Tosca et al. [20]	Retrospective study evaluating self-perceived dust mite SLIT efficacy	31 (mean 12.5)	Children with serum-specific IgE > 10kU/l perceived greater SLIT efficacy than those with IgE < 10kU/l.
Yukselen et al. [16•]	Randomized double-blind controlled trial comparing dust mite SCIT and SLIT	30 (mean 11.65)	Children receiving 24 months of SLIT showed 28 % median reduction in rhinitis and asthma symptoms compared to 12 months of SCIT
Corzo et al. [17]	Randomized double-blind phase 1 trial evaluating dust mite SLIT	72 (5–14)	No changes in FEV1. Increase in specific IgE to dust mite. Over 1/3 of children experienced mild adverse events.
Rienzo et al. [18•]	Randomized open parallel-group evaluating dust mite SLIT	NA (5–18)	After 72 weeks, reduction in atopic dermatitis scores in SLIT children
Aydogan et al. [15]	Randomized double-blind placebo-controlled trial evaluating clinical efficacy of dust mite SLIT	22 (5–10)	After 12 months, SLIT did not significantly improve total rhinitis symptoms/medication scores. Skin reactivity was reduced in SLIT participants.
Peanut SLIT			
Fleischer et al. [26••]	Randomized double-blind placebo-controlled multicenter trial evaluating peanut SLIT	40 (12–37, median 15)	After 44 weeks of immunotherapy, 70 % of participants responded, with median successfully consumed dose increasing from 3.5 mg to 496 mg. After 68 weeks of therapy, median successfully consumed dose increased to 996 mg.
Chin et al. [27]	Retrospective study comparing oral and SLIT peanut immunotherapy	27 (2–11, median 6.3)	Oral immunotherapy proved superior to SLIT. Higher median peanut-specific IgG4/IgE were observed with oral immunotherapy. Oral immunotherapy children were 3 times more likely to be desensitized after 12 months.
Cockroach SLIT			
Wood et al. [22••]	Randomized double-blind trial evaluating high and low-dose cockroach SLIT	99 (5–17)	40 % of Children undergoing rapid escalation of cockroach SLIT showed nearly threefold increase in allergen-specific IgE levels.
Pollen SLIT			
Maloney et al. [23••]	Randomized double-blind trial evaluating grass SLIT	238 (5–18)	32 % reduction in total rhinoconjunctivitis score in children receiving SLIT.

Table 2 Summary of systematic review

Study	Study characteristics	Number (Age)	Conclusions	Years studied
Kim et al. [13••]	34 Randomized controlled trials studying children with allergic asthma and rhinoconjunctivitis	1583 (4–18)	High strength of evidence: SLIT improves asthma symptoms Moderate strength of evidence: SLIT improves rhinitis and conjunctivitis symptoms Low strength of evidence to support SCIT over SLIT	Inception-2012

insufficient evidence evaluating the impact of SLIT on disease-specific quality of life [13••]. Despite these conclusions, subcutaneous immunotherapy was not found to be superior to SLIT; the review suggested that there is low evidence that subcutaneous immunotherapy results in a more significant decrease in asthma symptoms, rhinitis symptoms, or pharmacotherapy use compared to SLIT [13••]. Although the challenges in having children correctly maintain SLIT extracts under the tongue, compliance is generally acceptable, with reports ranging from 34 to 58 % [13••] up to as high as 88 % with SLIT over several years of observation [14].

Dust Mite Sublingual Immunotherapy

Atopic dermatitis and allergic disease are increasing in prevalence. Children with atopic dermatitis may later develop other allergic diseases such as allergic rhinitis and asthma, otherwise known as the allergic march. House dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farina) are common indoor allergens, and may confer an increased risk for developing asthma [4]. Recently, a double-blind placebo-controlled randomized clinical trial consisting of 22 children monosensitized to house dust mites with isolated allergic rhinitis/conjunctivitis symptoms found no significant differences on total rhinitis symptoms (sneezing, nasal itching, nasal blockage, and rhinorrhea) and medication scores among those receiving SLIT compared to placebo. However, a reduction in baseline nasal sensitivity was observed after 12 months of immunotherapy treatment, and skin reactivity was significantly reduced in children undergoing immunotherapy compared to participants taking placebo. Interestingly, children taking placebo were over three times more likely to experience non-specific bronchial hyper-reactivity symptoms compared to baseline [15].

In contrast, a separate double-blind randomized controlled clinical trial consisting of 30 children monosensitized to house dust mite demonstrated that those receiving SLIT showed reduction of clinical symptoms (rhinitis and asthma), need for pharmacotherapy, sputum eosinophil, and bronchial hyper-reactivity. However, this benefit was only achieved after 2 years of sublingual therapy with a 28 % median improvement in rhinitis symptoms, increase in FEV-1, and improvement in nasal provocation with house dust mite allergens compared to only 1 year of treatment in children receiving subcutaneous immunotherapy [16•]. However, improvement in FEV-1 has not been consistently demonstrated [17]. Interestingly, children receiving subcutaneous immunotherapy may have a greater reduction in asthma symptoms and associated increase in serum IgG4 compared to those receiving SLIT [16•].

Recently, Denmark has produced a new orodispersible house dust mite SLIT tablet. In a double-blind randomized controlled phase 1 trial that consisted of 72 children aged 5–14 years, serum-specific IgE to house dust mite increased significantly from baseline with doses above 4 DU [17], indicating stimulation of the immune system. Additional benefits of SLIT to house dust mite may include clinical improvement in systemic allergy symptoms, such as atopic dermatitis. For example, in a randomized open parallel-group design study evaluating dust mite SLIT in children between the ages of 5–18 with atopic dermatitis, treatment for 72 weeks resulted in a significant decrease in atopic dermatitis scores compared to children receiving standard therapy [18•].

Whether SLIT prevents the development of allergy sensitization warrants further exploration. The allergen hypothesis consists of theories that early exposure to allergens may reduce future atopy. This theory was explored in more depth through a small randomized controlled pilot trial evaluating 50 high-risk children aged 18–30 months with an atopic family history who were given SLIT consisting of house dust mite, cat, and timothy grass extracts for 12 months. Serum sampling performed at 3 and 6 months failed to demonstrate differences in allergen-specific IgE/IgG antibodies and Th-cell responses among participants undergoing immunotherapy versus placebo patients [19]. However, children with serum allergen-specific IgE to house dust mite > 10 kU/L were more likely to perceive SLIT efficacy after 3 years by

visual analog scale compared to children with serum allergen-specific IgE < 10 kU/L. In addition, visual analog scores and asthma control tests were significantly improved in children with serum-specific IgE to house dust mite > 10 kU/L [20]. While these results may suggest that the perceived clinical effectiveness of SLIT may partially depend on baseline clinical severity of disease, this conclusion has not been consistently demonstrated. Alternatively, there may be an identifiable sub-population, such as children, that simply perceives overall greater benefit with immunotherapy.

Cockroach Sublingual Immunotherapy

Exposure of children, especially those living in urban dwellings, to cockroach may be an important risk factor to worsening respiratory symptoms in those with suffering from asthma [21]. The use of SLIT for children with increased allergic sensitivity towards cockroach allergen is less well studied. Several pilot clinical trials were recently performed evaluating the safety of cockroach SLIT in children including a randomized double-blind biomarker study evaluating 2 doses (low and high) of cockroach extract. A total of 190 children were studied between the ages of 5–17 and given a 1-day rapid 8 dose escalation to achieve maintenance dosing, which was then continued for 14 days; results showed that nearly 40 % of children receiving high- and low-dose immunotherapy showed a threefold increase in serum-specific IgE levels compared to those receiving placebo. Increase in allergen-specific IgG4 was only observed for high-dose SLIT. However, this study was limited since clinical response to treatment was not an evaluated endpoint [22••].

Grass Sublingual Immunotherapy

Nearly 50–70 % of children with allergic rhinitis are sensitized to grass allergens, which include common grasses such as timothy grass, orchard grass, and kentucky bluegrass [23••]. The largest randomized clinical trial to date was recently conducted in adults and children aged 5–18 over approximately 34 weeks, evaluating the efficacy and safety of MK-7242, a grass SLIT tablet. Results showed that among 283 children treated with MK-7243, there was a 32 % reduction in total combined rhinoconjunctivitis score and a dose of 2800 BAU was well tolerated. Interestingly, adults and children were treated with identical sublingual doses without noticeable effect differences thus advocating that doses should not be adjusted for age or weight [23••].

Safety of Sublingual Immunotherapy in Children

Due to a series of fatal outcomes in the 1980s with subcutaneous immunotherapy, the use of SLIT has been viewed by clinicians and the public as possibly a safer alternative even in patients under the age of 5 years [24]. Systemic and local reactions have been commonly reported in children taking SLIT for environmental allergens. Common symptoms that have been reported with use of sublingual therapy in general include gastrointestinal [15], ocular, respiratory, or cutaneous reactions to immunotherapy. This is in contrast to subcutaneous immunotherapy where systematic reactions, while rare, have been reported, including anaphylaxis. However, to date, there have been no fatal anaphylaxis occurrences from SLIT reported in the literature; [13••] the predicted anaphylaxis rate is likely on the order of 1:100 million administration doses compared to 1:1 million administration doses with subcutaneous immunotherapy. [25].

During a 3-year observation period of SLIT in children, no systemic adverse events were reported, and the vast majority of adverse events were considered mild, with only 5.7 % of children complaining of oral burning or itching, 2.9 % of children complaining of urticaria, and 1.4 % complaining of gastrointestinal effects such as abdominal pain or nausea [14]. In children undergoing SLIT to house dust mite, over one third were reported to have adverse events such as aphthous tongue ulcerations, edema, erythema, with 96 % considered mild, and 4 % considered moderate in severity [17]. In children undergoing rapid escalation SLIT with cockroach allergen, oral pruritus was noted in 11 %, and nasal congestion, nasal pruritus, or hives were reported in 16 % of participants [22••].

Estimates for local side effects affecting the oral mucosa have been reported as high as 30 % though; however, in reality this is likely comparable to local site reactions from subcutaneous immunotherapy [24]. Administration error or giving excessively high dose of antigens may anecdotally be partially responsible for exceedingly rare severe systemic reactions [24]. Overall, this suggests especially in children that SLIT may be safer than the subcutaneous route; however, it is impossible to completely eliminate the possibility of a future life-threatening reaction.

In contrast to environmental allergen SLIT, most of the adverse events reported to peanut SLIT were found to be unrelated to the peanut extract, with 86 % of adverse events considered mild [26••]. Most local reactions involved only the oropharyngeal mucosa, with less than 3 % of participants necessitating treatment with antihistamines; however, one participant in a trial did develop erythema, pruritus, and oral symptoms classified as grade 1 anaphylaxis requiring diphenhydramine and epinephrine without additional squeal [26••].

Peanut Sublingual Immunotherapy

SLIT has traditionally been given to children suffering from allergic rhinitis and asthma with allergen sensitivities to dust mite, and pollen from grasses, trees, and weeds. The safety profile of administering SLIT to children with food allergies has been studied less. Traditionally, administering sublingual food extract allergens has been thought to be less safe by potentially inducing anaphylaxis in susceptible children. However, there is immunologic evidence that SLIT for food allergy may decrease toll-like receptor induced IL-6 secretion by myeloid dendritic cells, thereby decreasing TH2 cytokine secretion immune response and restoring TH1/TH2 balance [6]. Specifically, immunologic changes noted after peanut SLIT included increases in peanut-specific IgE levels, peanut-specific IgG4 levels, and decreases in %CD63+ levels [26••].

In respect to peanut allergies, a randomized double-blind placebo-controlled multicenter trial of 40 participants, where the vast majority were children (interquartile range 13–18), demonstrated that peanut SLIT induced a modest level of desensitization in the majority of participants. After 44 weeks of immunotherapy, 70 % of participants receiving immunotherapy responded compared to 15 % of participants receiving placebo, with successful participants tolerating a median increase of peanut extract from 3.5 to 496 mg. After 68 weeks of immunotherapy, successful participants were able to tolerate a median peanut extract of 996 mg. Excluding local oral/pharyngeal symptoms in successful participants, over 95 % of immunotherapy participants, was symptom free after peanut allergen exposure. Interestingly, although most participants were considered responders, none of the participants treated with lower dose peanut extract were able to ingest 5 g of peanut powder without symptoms, suggesting that 44 weeks of immunotherapy may provide statistically significant protection rather that clinically significant protection [26••].

Additional evidence supporting the efficacy of peanut SLIT includes a recent retrospective study. This study consisted of 27 children evaluating sublingual versus oral immunotherapy for peanut allergic participants for 24 months. Findings included higher median peanut-specific serum IgE levels in children treated with oral immunotherapy compared to SLIT (204.5 versus 66.7 kU/L) at 12 months; however, after 24 months of immunotherapy treatment, levels were not significantly different. Peanut-specific IgG4 was significantly higher in children treated with oral immunotherapy at 12 (20.1 versus 3.1 mg/L) and 24 (20.3 versus 7.9 mg/L) months, and median peanut-specific IgE/IgG4 ratios and CD63+ basophils were significantly lower in children receiving oral immunotherapy. Overall, children undergoing SLIT were more likely to react to peanut challenges at lower doses, with children on oral immunotherapy over three times more likely to be desensitized after 12 months of treatment, even though baseline-specific IgA, peanut-specific IgG, and CD4 were not significantly different among treatment groups [27]. While results for sublingual immunotherapy for food allergens is promising, the most recent American Academy of Allergy, Asthma, and Immunology guidelines state that food allergy immunotherapy should not be implemented into clinic practice at the present time due to insufficient evidence and potential risk for serious adverse events [28].

Conclusions

These studies have highlighted important recent developments in SLIT in children with allergic rhinitis and food allergies. SLIT is very effective in improving tolerance towards suspected allergens responsible for causing debilitating allergies and food sensitivities. SLIT has significant advantages over traditional subcutaneous immunotherapy, especially in the pediatric population where frequent physician visits, and potentially painful subcutaneous injections over long periods of time is a less appealing alternative. Efficacy and safety of immunotherapy is of paramount importance, especially in the pediatric population. Despite potential limitations in the effectiveness of SLIT compared to more traditional subcutaneous efficacy, the safety profile of serious life-threatening adverse events with SLIT is more reassuring. However, SLIT unfortunately has constraints due to the volume that can be held in the sublingual space by children in addition to extract potency limitations in creating sublingual formulations.

Compliance with Ethics Guidelines

Conflict of Interest David J Mener and Sandra Y Lin declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Dl Blackwell, Lucas JW, Clarke TC. Summary health statistics for US adults: national health interview survey. Vital Health Stat. 2014;260:1–161.
2. Koh YY, Kim CK. The development of asthma in patients with allergic rhinitis. Curr Opin Allergy Clin Immunol. 2003;3: 159–64.
3. Dykewicz M, Fineman S. Exectuvie summary of joint task force practice parameters on diagnosis and management of rhinitis. Ann Allergy Asthma Immunol. 1998;81:463–8.
4. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. Otolaryngology. 2015;152(1S):S1–43.
5. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol. 2005;15: 9–16.
6. Frischemeyer-Guerrerio PA, Keet CA, Guerrerio AL, et al. Modulation of dendritic cell innate and adaptive immune functions by oral and sublingual immunotherapy. Clin Immunol. 2014;155:47–9.
7. Akdis CA. Therapies for allergic inflammation: refining strategies to induce tolerance. Nat Med. 2012;18:736–49.
8. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis to house dust mite. Clin Allergy. 1986;16:483–91.
9. Fiocchi A, Fox AT. Preventing progression of allergic rhinitis: the role of specific immunotherapy. Arch Dis Child Educ Pract Ed. 2011;96:91–100.
10. Blaiss M, Maloney J, Nolte H. Efficacy and safety of timothy grass allergy immunotherapy tablets in north American children and adolescents. J Allergy Clin Immunol. 2011;127:64–71.
11. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009;123:160–6.
12. Linkov G, Toskala E. Sublingual immunotherapy: what we can learn from the European experience. Curr Opin Otolaryngol Head Neck Surg. 2014;22:208–10.
13. •• Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. Pediatrics. 2013;131:1155–67. *High strength of evidence that SLIT improves asthma symptoms. Moderate strength of evidence that SLIT improves rhinitis and conjunctivitis symptoms and low strength of evidence to support SCIT over SLIT as primary therapy.*
14. De Castro G, Zicari AM, Indinnimeo L, et al. Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life. Eur Rev Med Pharmacol Sci. 2013;17: 2225–31.
15. Aydogan M, Eifan AO, Keles S, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomized trial. Respir Med. 2013;107:1322–9.
16. • Yukselen A, Kendirli SG, Yilmaz M et al. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. Asian Pac J Allergy Immunol. 2013;31:233–41. *Children who received 24 months of SLIT showed a 28% median reduction in rhinitis and asthma symptoms compared to only 12 months of SCIT, implying that a longer duration of therapy with SLIT was necessary to achieve similar effect.*
17. Corzo JL, Carrillo T, Pedemonte C, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. J Investig Allergol Clin Immunol. 2014;24(3):154–61.
18. • Rienzo VD, Cadario G, Grieco T et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, open, parallel-group study. Ann Allergy Asthma Immunol. 2014;113:671–2. *After 72 weeks of SLIT, children were observed to have a reduction in atopic dermatitis scores.*
19. Holt PG, Sly PD, Sampson HA, et al. Prophylactic use of sublingual allergen immunotherapy in high-risk children: a pilot study. J Allergy Clin Immunol. 2013;132(4):991–4.
20. Tosca M, Silvestri M, Accogli A, Rossi GA, Ciprandi G. Serum-specific IgE and allergen and immunotherapy in allergic children. Immunotherapy. 2014;6(1):29–33.
21. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med. 1997;336:1356–63.
22. •• Wood RA, Togias A, Wildfire J, et al. Development of cockroach immunotherapy by the inner-city asthma consortium. J Allergy Clin Immunol. 2013;133(1): 846–52. *40 % of Children undergoing rapid escalation of cockroach SLIT showed nearly three-fold increase in allergen specific IgE levels.*
23. •• Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol. 2014;112:146-153. *Among children receiving SLIT, there was* a *32 % reduction in total rhinoconjunctivitis score.*
24. Frati F, Ridolo E, Fuiano N, et al. Safety of sublingual immunotherapy in children. Expert Opin Drug Saf. 2014;13(7): 947–53.
25. Calderon MA, Simons FER, Malling HJ, et al. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy. 2012;67:303–11.
26. •• Fleischer DM, Burks AW, Vickery BP et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119–27. *After 44 weeks of SLIT, 70 % of participants responded, with median successfully consumed peanut dose increasing from 3.5 mg to 496 mg. After 68 weeks of therapy, median successfully consumed peanut dose increased to 996 mg.*
27. Chin SJ, Bickery BP, Kulis MD, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol. 2013;132(2):476–8.
28. Sampson HA, Acevves S, Bock SA, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5): 1016–25.