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REVIEW ARTICLE

Sublingual immunotherapy (SLIT) – indications, mechanism, and efficacy

Position paper prepared by the Section of Immunotherapy, Polish Society of Allergy

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Abstract

SLIT (*sublingual immunotherapy,*) induces allergen-specific immune tolerance by sublingual administration of a gradually increasing dose of an allergen. The mechanism of SLIT is comparable to those during SCIT (subcutaneous immunotherapy), with the exception of local oral dendritic cells, pre-programmed to elicit tolerance. In the SLIT dose, to achieve the same efficacy as in SCIT, it should be 50–100 times higher with better safety profile. The highest quality evidence supporting the efficacy of SLIT lasting 1 – 3 years has been provided by the large scale double-blind, placebo-controlled (DBPC) trials for grass pollen extracts, both in children and adults with allergic rhinitis. Current indications for SLIT are allergic rhinitis (and conjunctivitis) in both children and adults sensitized to pollen allergens (trees, grass, *Parietaria*), house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae),* cat fur, as well as mild to moderate controlled atopic asthma in children sensitized to house dust mites. There are positive findings for both asthma and new sensitization prevention. Severe adverse events, including anaphylaxis, are very rare, and no fatalities have been reported. Local adverse reactions develop in up to 70 – 80% of patients. Risk factors for SLIT adverse events have not been clearly identified. Risk factors of non-adherence to treatment might be dependent on the patient, disease treatment, physician-patient relationship, and variables in the health care system organization.

Key words

child, adult, desensitization, immunologic/methods, allergen/therapeutic use

INTRODUCTION AND OBJECTIVE

SLIT (*sublingual immunotherapy,*) is a method of inducing allergen-specific immune tolerance by sublingual administration of a gradually increasing dose of an allergen. [1]. SLIT appears to involve some of the pathways that have been identified in subcutaneous immunotherapy (SCIT) [2]. Considering the favourable safety profile and absence of anxiety-provoking injections, SLIT may be preferred in children [3, 4]. The aim of this study is to assess the evidence supporting the use of SLIT.

The first reports on the use of SLIT appeared in the early 1970s, hence, experience with SLIT in the treatment of allergic diseases is less extensive compared to SCIT [5, 6]. Since that time, tremendous progress has been made in the methodology of assessing SLIT efficacy, especially with respect to the following:

1) randomized double-blind placebo-controlled (DBPC) trials – starting from 2004;
2) studies evaluating SLIT efficacy following completion of a 3-year cycle of vaccinations with a 2-year follow-up [7, 8];
3) meta-analyses and comprehensive reviews spanning the period starting from 2004 and ending with the most recently published reports on efficacy of treating diverse allergic diseases, and on prevention of sensitization to various allergens in diverse age groups [7, 9, 10, 11, 12, 13, 14];
4) studies performed in children, dating back from 1997 to the present day [15, 16, 17];
5) practice recommendations on SLIT published in the form of national position papers [18, 19].

In most SLIT regimens the allergen preparation is kept under the tongue for a few minutes and then swallowed. The minority of regimens when the allergen preparation is then spat out, will not be considered here. The most commonly employed form of vaccine used in SLIT continues to be a standardized aqueous allergen solution. In 1998, vaccines in the form of sublingual soluble tablets were introduced to the

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market. Both forms are currently available. The characteristics of extracts for sublingual allergen immunotherapy available in Poland are presented in Table 1 [20].

Table 1. Characteristics of allergen extracts for SLIT available in Poland [20]

Form	Dose
Sublingual aqueous allergen extracts (SLIT-drops) – STALORAL 300 (Stallergenes, France)	IR standardized allergen extract (solvent 50% glycerine solution). Standard extracts: house dust mites (D. pter. 50%, D. farinae 50%), 5 grass pollens (*Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pretense*), birch pollen 100%, tree pollens (birch 35%, alder 30%, hazel 35%), *Artemisia vulgaris* 100%. Individual extracts compounds are available. Initial dose: STALORAL 300 10 IR/ml (1 vial/10 ml) (start 1 dose on day 1 up to 10 doses on day 6), followed by STALORAL 300 100 IR/ml (2 vials/10 ml), 1 dose on day 7, up to 8 doses on day 11. Maintenance dose: STALORAL 300 100 IR/ml (2 vials/10 ml), 8 doses 3 days per week, or 4 doses every day. Should be kept under the tongue for 2 minutes after application, before being swallowed. Recommended treatment: continuation for 3–5 years.
Sublingual allergen tablets (SLIT-tablet) – GRAZAX (ALK/ Abello, Denmark)	Standardized allergen extract of grass pollen from *Phleum pratense* 75,000 SQ-T oral lyophilisate a 30, 60, 90 doses. Should be kept under the tongue for 1 minute after application, no food or drink up to 5 minutes after swallowing. Recommended initiation of treatment: at least 4 months before pollen season.
Sublingual allergen tablets (SLIT-tablet) ORALAIR (Stallergenes, France)	IR standardized 5 grass pollen allergen extract from *Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pretense.* 100 IR &300 IR– initial dose. 300 IR – maintenance dose. Initial dose: Oralair 1 tablet/100 IR on day 1, 2 tablets/100 IR on day 2, followed by Oralair 1 tablet/300 IR on days 3 to 30 (small blister 3 tablets/100 IR, large blister 28 tablets/300 IR). Maintenance dose: Oralair 1 tablet/300 IR every day (blisters/30 tablets). Should be kept under the tongue for at least 1 minute (to be completely dissolved) after application. Recommended initiation of treatment: at least 4 months before pollen season.

SLIT – sublingual immunotherapy; SQ-T – Standardized Quality units Tablet; IR – Index of Reactivity

Novel forms of treatment – grass monomeric allergoid and mite monomeric allergoid in sublingual immunotherapy – are under investigation [21, 22] The updated recommendations addressing SLIT have been published both by research groups in Europe and worldwide [1, 5, 23]. Since 2001, subsequent editions of the ARIA guidelines have been updating the position on SLIT [24, 25, 26]. Numerous reports emphasize the need for a methodological control of research projects in order to increase their objectivity [7, 27, 28, 29]. The investigations are recommended as being prospective, based on double-blind placebo-controlled randomization, and their results should be presented in accordance with the *Consolidated Standards of Reporting Trials* (CONSORT) [30].

CURRENT STATE OF KNOWLEDGE

The mechanism of SLIT. The site of allergen application plays an important role in the mechanism of tolerance induced in the course of SLIT, i.e. oral mucosa, which is considered to be 'immuno-priviledged'[31, 32, 33, 34]. Oral mucosa is the 'entrance gate' to the gastrointestinal tract, where numerous environmental allergens (predominantly originating from nutritional proteins, physiological bacterial flora and pathogenic microorganisms) come into contact with the immune system. Thanks to the potent tolerogenic mechanisms of the oral mucosa, inflammatory reactions are rare. Various mechanisms of local tolerance have been described within the oral mucosa: the absence of MALT (mucosa-associated lymphoid tissue) and a small number of cells participating in inflammatory reaction (eosinophils, mast cells), the presence of *lamina propria*, which ensures limited absorption of antigen macromolecules and contact with inflammatory cells situated in the submucosal layer [35], the phenomenon of immune exclusion via secretory IgA, which restricts antigen penetration [36], the presence of IFN-g-producing Th1 lymphocytes [37] and regulatory T lymphocytes, which affect immunosupression via intercellular mechanisms through cytokine release (IL-10), and the induction of anergy or depletion of T lymphocytes [38, 39, 40].

Antigen-presenting cells (APCs), mainly dendritic cells (DCs), which are densely distributed in the epithelium, lamina propria and submucosal layer of the oral mucosa, are crucial for immunotolerance in SLIT. DCs capture antigens that reach the oral epithelium (within 15–30 minutes), migrate to regional lymph nodes (within the subsequent 12 – 24 hours) and at the same time transform (by proteolytic degradation) antigen proteins into fragments that can be presented to T lymphocytes [35, 41]. DCs residing within the oral mucosa differ by origin and phenotype:

1) myeloid dendritic cells (mDCs) with the phenotype CD11b+/CD11c- and CD11b+/CD11c+ situated in the lamina propria and submucosal layer;
2) oral Langerhans cells (oLCs) that express CD1a, CD11b, C-type lectin langerin (CD207), receptors for IgE (FcεRI), IgG (FcγR)I, FcγRII, FcγRIII and Toll-like receptors (TLR)4 – the most numerous in the epithelium and playing the key role in antigen capture;
3) plasmocytoid DCs (pDCs) – the least numerous and situated in the submucosal layer [42].

For all the DCs subpopulations, in healthy individuals as well as in patients undergoing SLIT, there have been documented numerous tolerogenic (through the release of IL-10 and IL-12) and regulatory functions (through induction of differentiation of naive or Th0 lymphocytes into the population with the phenotype Th1/Treg [43, 44].

Of critical importance in activating the tolerogenic function of DCs and thus SLIT efficacy are:

1) the duration of allergen contact with antigen-presenting cells in the oral mucosa;
2) the dose and frequency of allergen contact (application);
3) oral mucosa micro-environment;
4) the effects of adjuvant factors that increase tolerogenic abilities and induce a Th1-type response (e.g. MPL – a TLR-4 agonist) [31, 45].

Indications for SLIT. Indications for SLIT are aligned with general indications for allergen immunotherapy (AIT) [46]. Particular indications for SLIT depend on the type of hypersensitivity reaction and symptoms, as well as age of the patient and clinical condition at the time the therapy is initiated.

Qualification for SLIT should be based on assessment of clinical, laboratory (immunological) and pharmacological

indications [1, 4, 46]. At all times – and in particular in the case of children – the individual profile of the patient and the family should be evaluate. The assessment needs to consider such factors as risks involved in the very disease and the employed therapy, abilities and willingness to adhere to the therapy, and psychological determinants.

Immunological indications:
- Documented IgE-dependent hypersensitivity (as IgE presence confirmed in *in vivo* or *in vitro* tests) to pollen allergens (trees, grass, *Parietaria*), house dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae)* or cat fur [8, 16, 47, 48].
- It is necessary to confirm the significant clinical importance of the above – immunization (see below).

Clinical indications:
- Significant disease symptoms resulting from exposure to the above-mentioned allergens.
- Disease entities:
  1. Allergic rhinitis (and conjunctivitis); anticipated effects: alleviation of symptoms, prevention of asthma development.
  2. Controlled atopic asthma with mild to moderate course; anticipated effects: alleviation of asthma symptoms, decreased bronchial hypersensitivity.

SLIT is a very good alternative if the patient or the family cannot accept injection immunotherapy.

Indications associated with assessment of pharmacological efficacy:
1. Lack of anticipated effect,
2. Lack of acceptance of pharmacotherapy on the part of the patient or his family (children),
3. Adverse effects after treatment.

NOTE. There are no age-associated indications, yet there is limited evidence of efficacy in children below 5 years of age [49, 50], only monovalent vaccines have been used in controlled studies.

Further studies are necessary to assess SLIT efficacy in atopic dermatitis, food allergy and allergy to latex and insect venom; current data are not sufficient to recommend SLIT in those conditions [51, 52, 53, 54].

Contraindications to SLIT [1, 46]. There are no studies focusing on the safety of SLIT when SIT is contraindicated. According to expert opinion, it seems reasonable to maintain the same contraindications.
- *Absolute:*
  1. Severe immune systemic disorders, severe circulatory system disorders, neoplastic diseases, chronic inflammations.
  2. Severe asthma – FEV1 less than 70% of the predicted normal value in spite of the patient undergoing treatment.
  2. β–blocker treatment.
  3. Poor adherence and severe mental disturbances.
- *Relative:* pregnancy (pre-conception initiated, hitherto uncomplicated immunotherapy may possibly be continued; initiation of immunotherapy is not recommended).
- *Temporary:* inflammatory processes involving gastrointestinal tract mucosa, acute infections, tooth extraction, surgery intervention in mouth. Note: a 7-day interval prior to and following preventive vaccinations must be observed.

Precautions – It is recommended that the first dose of SLIT is administered under the supervision of a physician, and if tolerated well, followed by home dosing. The patient should be educated about the principles of SLIT and the requirement of strict adherence to recommendations, and be provided with a clear written emergency treatment plan in case of adverse effects [2].

Efficacy of SLIT in atopic diseases – criteria of efficacy. Based on the position of the European Medicines Agency (EMA) Guidelines 2008 (CHMP/EWP/18504/2006), the following criteria of efficacy have been adopted for allergen-specific immunotherapy.
1. A decrease or resolution of allergy symptoms in the first season following initiation of AIT. Stable clinical effect in the course of AIT (2nd – 3rd year of treatment).
2. Long-term clinical effects maintained after completion of treatment and beneficial effects on the natural course of the disease.
3. Curing the patient of allergy (symptoms absent for many years following treatment, optimally throughout the patient's life).

ALLERGIC RHINITIS

Placebo-controlled clinical trials confirmed significant alleviation of clinical symptoms compared to the placebo group [9, 55, 56, 57]. Comparing the efficacy of SLIT and SCIT is difficult due to an extremely small number of studies that would directly compare these two immunotherapy forms [58, 59, 60, 61]. Of importance are marked differences between particular trials, which may also result from the type of allergen employed. Based on the available trials, it may be surmised that the highest effect of SLIT is demonstrated by vaccines containing grass and birch pollen allergens [9, 62].

The normal effect of SCIT is a long-term clinical effect maintained after discontinuation of therapy. There are only few studies regarding SLIT and to long-term clinical effect (after 3 – 5 years of SLIT with grass and house dust mites extracts) lasting 1 and 8 years; more will probably be published [57, 63]. Three years of treatment with the SQ-T (Standardized Quality units Tablet) grass allergy immunotherapy resulted in a clinical improvement that was sustained 1 year after treatment [57]. SLIT with mites extract induced a clinical benefit that persisted for 8 years [63]. There are results which confirm disease modification by SQ-T grass allergy immunotherapy in addition to effective symptomatic treatment of allergic rhinoconjunctivitis [9]. The DBPC studies in patients with allergic rhinitis showed the impact of SLIT on the natural course of the disease, including a decrease in the number of new sensitizations, and decreased risk of asthma development

Of particular interest is the efficacy of SLIT in paediatric patients. Meta-analyses are available that confirm SLIT efficacy [9, 64, 65]; however, depending on the methodology employed, some authors caution that no final conclusions can be drawn at this time [10].

Considering the total effect and standardized mean difference (SMD), SLIT with house dust mite appears to be more effective than SLIT with *Parietaria*, trees and grass pollen. However, the majority of these trials were small, with 5 out of 9 trials involving fewer than 20 participants, and were highly heterogenous. When comparing the results of studies on children with those on adults, standardized medication difference (SMD) was statistically significantly reduced only in adults [9].

	Studies	(n) active	(n) placebo	SMD	p
Adults	26	1,168	1,067	-0.4	<0.00001
Children	12	569	575	-0.16	0.06

Conclusion: SLIT is recommended in the treatment of allergic rhinitis in children and adults. SLIT efficacy depends on allergen type, maintenance and cumulative dose.

ASTHMA

Assessment of treatment efficacy includes alleviation of clinical symptoms, a decreased need for pharmacotherapy and improved pulmonary ventilation indices.

In 13 randomized placebo-controlled trials where SLIT efficacy in allergic rhinitis and asthma was investigated, the duration of treatment was 6 months to 2 years [66]. Eleven studies demonstrated alleviation of asthma symptoms, while only 2 showed improved spirometry indices (FEV1) and decreased bronchial hyperreactivity [66]. An important argument for using SLIT in treating patients with asthma is the comparison of the SLIT results with the results achieved by other methods of asthma treatment. None of the studies indicated a decrease in demands for medications employed in asthma therapy. Significant improvement was also demonstrated in functional pulmonary parameters in SLIT-treated vs. budesonide-treated patients in the 5th year of treatment [67]. Longitudinal studies on the clinical and immunological efficacy of SLIT and natural course of asthma are lacking.

A critical assessment was made of 5 meta-analyses, emphasizing their drawbacks that might result in over-interpretation of therapeutic results. These meta-analyses were found not to provide sufficiently firm evidence to support the use of SLIT in routine asthma therapy [68].

The drawbacks of the studies carried out to-date are as follows:
- considerable heterogeneity of results;
- the small number of studies performed in large groups of patients;
- little data on the effect of SLIT on pulmonary function.

The recently published meta-analyses that separately addressed patients allergic to house dust mites and grass pollen indicated clinical improvement only in the patients allergic to HDM [13, 14].

CONCLUSION

Even though the findings are promising, the results of SLIT still show little effect in meta-analysis; hence, they do not provide justification for recommending SLIT in treating all asthma patients [66].

ATOPIC DERMATITIS (AD)

At present, there are at our disposal too few studies performed on small groups of patients, and the results of these investigations are ambiguous. The study carried out by Pajno et al. showed an improvement in the SCORAD index solely in individuals allergic to house dust mites who suffered from a mild form of AD [69]. In AD patients with mono-sensitization to house dust mites, SLIT may be considered [70]. The authors of the review emphasize that the efficacy of immunotherapy in patients with atopic eczema has been poorly investigated in the past 5 years, mostly with small, heterogeneous groups, and short duration of study. [53]

Conclusion: Based on the currently available evidence, there is no proof of the efficacy of SLIT in patients with AD [53].

FOOD ALLERGY

Promising results have been achieved in children allergic to cows' milk and peanuts [51, 52, 71]. The most recent and highest quality evidence comes from a randomized, double-blind, placebo-controlled multicenter trial, in which 40 subjects, aged 12 – 37 years (median, 15 years), were randomized 1:1 across 5 sites to daily peanut or placebo SLIT. After 44 weeks of SLIT, 14 (70%) of 20 subjects receiving peanut SLIT were responders, compared with 3 (15%) of 20 subjects receiving placebo (p <.001). In this rigorous study, peanut SLIT safely induced a modest level of desensitization in the majority of subjects compared with placebo [71].

CONCLUSION

SLIT in the treatment of food allergy continues to be in the clinical trial phase – allergen dose vs. efficacy of desensitization. A meta-analysis of studies assessing the dependence between SLIT efficacy and allergen dosage failed to allow for formulating practical conclusions on the recommended allergen content in allergy vaccine and optimal desensitization protocols [72]. The data for clear dose-dependent effect to the immune modulation have been published for sublingual monomeric carbamylated mite allergoid [22].

Mode of treatment – continuous and co-seasonal regimen. Sustained efficacy of 2- and 4-month pre- and co-seasonal treatment with the 300 IR tablet during 3 pollen seasons was demonstrated, with reduction in symptoms and rescue medication use [73]. In children allergic to grass pollen, both protocols were effective compared with placebo, and showed similar decreases for combined symptoms/medication score and all secondary endpoints, with the exception of nasal symptoms that were lower in the pre-co-seasonal group [74]. Similar data have been published in a study comparing 3-year-lasting perennial with co-seasonal grass pollen SLIT (drops). The authors showed that the continuous regimen performed better than the co-seasonal in the first season, whereas in the subsequent years, the two regimens are nearly equivalent [75].

SLIT in polysensitized patients. Most of the studies dedicated to SLIT concern monosensitized patients. The real life study (POLISMAIL) was designed to evaluate current practices in prescribing SLIT in polysensitized patients, as well as to evaluate the clinical outcome and QoL. Both the severity grade of allergic rhinitis and the QoL were significantly improved by 2-year SLIT, indicating that SLIT with 1–2 allergen extracts achieves a significant improvement in polysensitized patients [76]. In another study in polysensitized allergic rhinitis patients, SLIT for *D. pteronyssinus* and/or *D. farinae* produced improvements in both nasal symptoms and rescue medication scores comparable to those in monosensitized patients, regardless of other positive allergens [77].

SLIT in children. In paediatric sublingual immunotherapy efficacy evidence analysis 2009–2012, from 56 articles, 29 met an inclusion criteria. New evidence is robust for the pre-, co-seasonal tablet and drop grass pollen SLIT efficacy in allergic rhinitis, and scarce for seasonal asthma. Some evidence for *Alternaria* SLIT efficacy has been published [78]. For house dust mite (HDM) SLIT in asthma, there is high-quality evidence for medication reduction while maintaining symptom control; evidence for HDM SLIT efficacy in allergic rhinitis is of moderate-low quality. There is moderate evidence for the efficacy of dual grass pollen-HDM SLIT after 12 months of treatment and 1 year after discontinuation. Specific provocation test results (nasal, skin) improved with grass pollen and HDM SLIT, while nonspecific bronchial provocation results remained unchanged.

Food oral immunotherapy is more promising than food SLIT. No anaphylaxis was found among 2469 treated children [17] (Tab. 2). Three years of SLIT seems to be an adequate duration for the treatment of childhood asthma associated with HDM allergy, as 2 further years of SLIT added no clinical benefit [79]. Some studies indicate that SLIT in house dust mite allergic children should be carried out under the supervision of an allergist, as it does not seem to be effective in primary care [80].

Table 2. Data of evidence-based studies in children [17]

Duration	No. of studies
≤ 6m	6
≤ 12 m	11
12–24m	11
Maintenance dose	
<5 ug	4
5–25 ug	8
>25 ug	7
undefined	9
Formulation	
Drops	24
Tablets	4
GRADE tool	
0	2
1	4
2	6
3	7
4	9
Study participants (n)	
< 30	7
30–100	13
over 100	9
SLIT allergens	
Grass	11
Tree	3
House dust mites	9
Peanut, milk, mixed	3
Indication, disease	
Asthma	5
Rhinitis, rhinoconjunctivitis	22
Food allergy	2

Safety of SLIT. Reports, meta-analyses and review papers indicate a superior safety profile of SLIT, as well as a high tolerance of the employed allergen preparations [1, 29, 81, 82, 83]. Some studies demonstrate that SLIT is safe in children under 5 years of age, with a lower limit of 3 years [49, 50] and pregnant women [84].

Frequency of SLIT-induced adverse reactions (AE). A review of articles on SLIT indicates that severe AE, including anaphylaxis, are very rare, and no fatalities have been reported to-date. Nevertheless, with increasing numbers of patients undergoing treatment, isolated cases of anaphylaxis, including anaphylactic shock, generalized urticaria, or asthma exacerbation, have been reported [85, 86, 87, 88, 89], some of them, however, being questioned [90]. In contrast to systemic allergic reactions, local adverse reactions, such as pruritus/swelling of mouth, tongue or lips, throat irritation, nausea, abdominal pain, vomitus, diarrhea, heartburn or uvular oedema, develop frequently in up to 70 – 80% of patients [3, 82], the most frequent being oral pruritus (17%), throat irritation (14%) and ear pruritus (10%) [91]. Local AEs can be early (< 30 minutes) or delayed. Symptoms are graded from mild (grade 1) to moderate (grade 2), severe (grade 3), and of unknown severity. Several grades of local AEs indicate the necessity for discontinuation of the treatment.

Speaking the same language in grading local side-effects due to SLIT is important for make comparisons between the results of different studies [92]. Local allergic symptoms usually persist for a short time only, resolve spontaneously, and only in sporadic cases require treatment. They rarely lead to discontinuation of therapy; more frequently, they may affect its regularity. The adverse effects occur predominantly in the initial period of treatment, when allergen doses are increased [28]. Risk factors for SLIT AE have not been clearly established. From the safety aspect, that SLIT does not induce any IgE neosensitization to allergens contained in the vaccine, was documented in a cohort of 509 patients followed over a 2-year period [93].

Comparison of SLIT *vs.* SCIT. While comparing sublingual and subcutaneous immunotherapy, generalized reactions are noted, occurring more frequently in SCIT and local reactions in SLIT. Nevertheless, only scarce papers evaluate both therapeutic methods together [9, 94]. Pilot randomized double-blind, placebo-controlled studies (RDBPC) that compared both immunotherapy forms suggest that SCIT

is superior to SLIT in decreasing symptoms of asthma and allergic rhinitis and lower respiratory tract inflammation, based on provocation tests, whereas both methods have comparable effects on immune parameters (sIgE, IL-10) and upper respiratory tract inflammation [58]. Promising results have been demonstrated in initial trials combining the 2 immunotherapy methods, with SCIT as an initial dose (a prompt beginning and high potential effect) and SLIT as continuation of therapy as a maintenance dose (safety and comfort of employment) [95]. The comparison of SLIT vs. SCIT in view of available evidence is presented in Table 3 [96, 97, 98].

Table 3. Comparison of SCIT and SLIT: the available evidence [72, 96, 97, 98]

Treatment	SCIT	SLIT
Dose-effect relationship	Studied for various allergens: multiple mixed, ragweed, HDM, cat, dog, grass, honey bee, wasp, hornet	Studied for various allergens: grass, pollen mix, birch, alder, hazel, ragweed
Definition of optimal dose	Documented in one DBPC trial of HDM allergens	Documented in one DBPC trial of a grass pollen tablet
Efficacy after 1 year of treatment	Determined for multiple allergens in DBPC trials, some on a large scale	Determined in large scale DBPC trials for grass pollen extracts
Efficacy after 2 and 3 years of treatment	Shown in trials of various allergens	Shown in large scale DBPC trials of grass pollen extracts
Sustained therapeutic benefit	Shown in multiple trials, most of which were controlled	Shown in trials of adequate size, for grass pollen extracts for adults
Efficacy for allergic asthma	Shown for various allergens	Small effect in meta-analysis
Asthma prevention	No DBPC trials, positive findings in controlled trials	No DBPC trials, positive findings
Prevention of new sensitization	Shown in controlled trials of individual allergens	No DBPC trials, positive findings
Calculation of effect strength in meta-analysis SMD (95%CI)		
symptoms	-0.73 (-0.97 to -0.5)	-0.49 (-0.64 to -0.34)
medication	-0.57 (-0.82 to -0.33)	-0.32 (-0.43 to -0.21)

SCIT – subcutaneous immunotherapy; SLIT – sublingual immunotherapy; DBPC – double blind placebo-controlled; SMD – standardized mean difference; CI – confidence interval; HDM – house dust mites

Non-adherence to treatment. In view of the necessity of daily administration of the vaccine over a prolonged time, some reports point to possible non-adherence/non-compliance of the patients in daily practice. They might be [99, 100, 101, 102]:

1. *Patient dependent:* presence of physical disorders, cognitive difficulties and psychiatric comorbidities, age (children, adolescents and elderly present high risk of non-adherence), social and family support.
2. *Disease dependent:* chronicity, symptoms stability or absence.
3. *Treatment dependent:* high number of daily doses taken, presence of side-effects, complexity of therapeutic regimes, ease of use.
4. *Physician-patient relation dependent:* poor relationship, behavioural inappropriateness by the doctor or patient, inadequate patient's involvement
5. *Health care system organization dependent:* difficult access to health service, high medication costs.

In a trial designed to investigate the adherence aspects of SLIT, the adherence rates varied from 75% to more than 95%. This has been attributed to ease of use, convenience and good safety profile [100, 102]. However, data based on sales profiles from allergen extracts manufacturers indicated that over 50% of patients discontinued SLIT during the first year of treatment. The adherence seems to be significantly affected by the frequency of following visits, the perception of efficacy, and the cost. More detailed education of patients and strict follow-up seems to improve the adherence results [100].

CONCLUSIONS AND SUMMARY

SLIT is presently commonly employed in Europe, although differences between particular countries are considerable. In Poland, aqueous allergen extract and 2 types of sublingual allergen tablets (standardized allergen extract of *Phleum pretense,* and 5 grass pollen allergen extract from *Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pretense)* are available. SLIT, although available in Poland, is recommended by physicians to a limited extent, which may be associated with the relatively high out-of-pocket cost of the therapy for the patients. It should be emphasized, however, that pharmaco-economic studies carried out in various European countries have demonstrated that both SCIT and SLIT may be cost-effective when compared with standard treatment over a period of approximately 6 years [103]. In the western European countries, SLIT with *Phleum pretense* sublingual tablets is a cost-effective strategy compared with standard management in the patients with rhinoconjunctivitis and co-existing asthma [104].

Current meta-analyses, regardless of the great heterogeneity of the studies, are in favour of SLIT in rhinitis in adults and asthma and rhinitis in children, although differences exist among allergens, with the best results for house dust mites and grass pollens [105]; there are also differences in results between countries [91]. The clinical efficacy and dose dependency have been demonstrated for rhinoconjunctivitis due to grass pollen. Reported SLIT allergen dose is a 2.4-fold – 92-fold multiplication in comparison to the SCIT dose [2]. Safety and efficacy are associated with daily administration of an appropriate dose of the medication for a period spanning, usually, 2 – 4 years. SLIT appears to be better tolerated than SCIT, and systemic side-effects are extremely rare, in contrast to frequent local oral side- effects. Although safe, SLIT should only be prescribed by an allergy-trained physician. SLIT is effective in children aged ≥ 5 years, but may be safe in children aged ≥ 3 years of age. The clinical effects of SLIT may persist for up to 5 years after discontinuation. National and international reports indicate the necessity for conducting further clinical trials, especially including a direct comparison between SCIT and SLIT with respect to efficacy and safety [106, 107, 108, 109, 110].

REFERENCES

1. Canonica GW, Bousquet J, Casale T, Lockey RF, Baenna-Cagniani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. Allergy 2009; 6(suppl.91): 1–59.
2. Calderon MA, Simons FER, Malling H-J, Lockey RF, Moingeon P, Demoly P. Sublingual immunotherapy: mode of action and its relationship, with the safety profile. Allergy 2012; 67: 302–11.

3. Marseglia GL, Incorvaia C, La Rosa M, Fratti R, Marcicci F. Sublingual immunotherapy in children: facts and needs. Ital J Pediatr. 2009; 35: 31–4.
4. Campbell DE. Sublingual immunotherapy for children: are we there yet? Defining its role in clinical practice. Paediatric Respir Rev. 2009; 10: 69–74.
5. Ring J, Gutermuth J. 100 years of hyposensitization: history of allergen-specific immunotherapy (ASIT). Allergy 2011; 66: 713–24.
6. Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011; 127: S1-S55.
7. Casale TB, Canonica W, Bousquet J, Cox L, Lockey R, Nelson HS, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. J Allergy Clin Immunol. 2009; 124: 665–70.
8. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012; 129: 117–25.
9. Radulović S, Wilson D, Calderon M, Durham S. Systemic reviews of sublingual immunotherapy (SLIT). Allergy 2011; 66: 740–52.
10. de Boot CM, Moed H, Berger MY, Roder E, van Wijk RG, van der Wouden JC. Sublingual immunotherapy in children with allergic rhinitis, quality of systemic reviews. J Allergy Immunol. 2011; 22: 548–58.
11. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev. 2011 CD007685.
12. Frati F, Incorvaia C, Scurati S, Sensi L, Marcucci F. Dose-dependence of sublingual immunotherapy shown by meta-analysis. J Allergy Clin Immunol. 2011; 127: 1076–7.
13. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systemic review and meta-analysis. J Allergy Clin Immunol. 2010; 126: 558–66.
14. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house-dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy 2009; 64: 1570–9.
15. Hirsch T, Sähn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol. 1997; 8: 21–7.
16. Aydogan M, Eifan AO, Keles S, Akkoc T, Nursoy MA, Bahceciler NN, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: A double-blind-placebo-controlled randomised trial. Respir Med. 2013 Jul 23. doi: pii: S0954–6111(13)00233–3. 10.1016/j.rmed.2013.06.021.
17. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009–2012. Ann Allergy Asthma Immunol. 2013; 110: 402–15.
18. Ortolani C, Agostinis F, Amoroso S, Ariano R, Barbato A, Bassi M, et al. Practice parameters for sublingual immunotherapy. Monaldi Arch Chest Dis. 2006; 65: 44–6.
19. Jutel M, Kuna P, Bocheńska-Marciniak M, Cichocka-Jarosz E, Bartkowiak-Emeryk M, Rogala B. et al. Position paper on sublingual immunotherapy prepared by experts of Polish Society of Allergy [in Polish]. Alergia Astma Immunol. 2007; 12: 181–3.
20. Rogala B, Gluck J. Sublingual immunotherapy. [in:] Allergen immunotherapy [in Polish]. Red. Kowalski ML, Rogala B. Oficyna wydawnicza Mediton, Łódź 2012.
21. Quercia O, Bruno ME, Compalati E, Falagiani P, Mistrello G, Stefanini GF. Efficacy and safety of sublingual immunotherapy with grass monomeric allergoid: comparison between two different treatment regimens. Eur Ann Allergy Clin Immunol. 2011; 43: 176–8.
22. Di Gioacchino M, Cavallucci E, Ballone E, Cervone M, Di Rocco P, Piunti E, et al. Dose-dependent clinical and immunological efficacy of sublingual immunotherapy with mite monomeric allergoid. Int J Immunopathol Pharmacol. 2012; 25: 671–9.
23. Calderon MA, van Wijk RG, Eichler I, Matricardi PM, Varga EM, Kopp MV, et al. Perspectives on allergen-specific immunotherapy in childhood: an EAACI position statement. Pediatr Allergy Immunol. 2012; 23: 300–6.
24. Bousquet J, van Cauvenberge P, Khaltaev N. ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001; 108(5 suppl): 147–334.
25. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A.et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization), GA(2)LEN and AllerGen). Allergy 2008; 63(suppl 86): 8–160.
26. Brożek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010; 126: 466–76.
27. Malling J-J. Sublingual immunotherapy: efficacy – methodology and outcome of clinical trials. Allergy 2006; 61(suppl 81): 24–8.
28. Sieber J. Necessity of product-specific assessments or restrictions of meta-analyses to well-designed and well-powered studies. J Allergy Clin Immunol. 2011; 127: 1075–6.
29. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Clin Immunol. 2011; 127: 30–8.
30. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012; 10: 28–55.
31. Shim BS, Choi Y, Cheon IS, Song MK. Sublingual delivery of vaccines for the induction of mucosal immunity. Immune Netw. 2013; 13: 81–5.
32. Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. Allergy 2011; 66: 725–32.
33. Scadding G, Durham S. Mechanisms of sublingual immunotherapy. J Asthma 2009; 46: 322–34.
34. Fujita H, Soyka MB, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. Clin Transl Allergy 2012; 2: 2.
35. Marcucci F, Sensi L, Incorvaia C, Di Cara G, Moingeon P, Frati F. Oral reactions to sublingual immunotherapy: a bioptic study. Allergy 2007; 62: 1475–147.
36. Brandtzaeg P. Mucosal immunity: induction, dissemination, and effector functions. Scand J Immunol. 2009; 70: 505–15.
37. Mascarell L, Lombardi V, Zimmer A, Louise A, Tourdot S, Van Overtvelt L, et al. Mapping of the lingual immune system reveals the presence of both regulatory and effector CD4+ T cells. Clin Exp Allergy 2009; 39: 1910–19.
38. Allam JP, Duan Y, Winter J, Stojanovski G, Fronhoffs F, Wenghoefer M, et al. Tolerogenic T cells, Th1/Th17 cytokines and TLR2/TLR4 expressing dendritic cells predominate the microenvironment within distinct oral mucosal sites. Allergy 2011; 66: 532–9.
39. Kelsall B. Recent progress in understanding the phenotype and function of intestinal dendritic cells and macrophages. Mucosal Immunol. 2008; 1: 460–9.
40. Jonuleit H, Schmitt E. The regulatory T cell family: distinct subsets and their interrelations. J Immunol. 2003; 171: 6323–7.
41. Allam JP, Novak N. Local immunological mechanisms of sublingual immunotherapy. Curr Opin Allergy Clin Immunol. 2011; 11: 571–8.
42. Novak N, Allam JP. Mucosal dendritic cells in allergy and immunotherapy. Allergy 2011; 66(Suppl 95): 22–4.
43. Zimmer A, Bouley J, Le Mignon M, Pliquet E, Horiot S, Turfkruyer M, et al. A regulatory dendritic cell signature correlates with the clinical efficacy of allergen-specific sublingual immunotherapy. J Allergy Clin Immunol. 2012; 129: 1020–30.
44. Angelini F, Pacciani V, Corrente S, Silenzi R, Di Pede A, Polito A, et al. Dendritic cells modification during sublingual immunotherapy in children with allergic symptoms to house dust mites. World J Pediatr. 2011; 7: 24–30.
45. Moingeon P, Mascarell L. Induction of tolerance via the sublingual route: mechanisms and applications. Clin Dev Immunol. 2012; 2012 623474.
46. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E; EAACI, Immunotherapy Task Force. Standards for practical allergen – specific immunotherapy. Allergy 2006; 61: suppl. 82:1–20.
47. Alvarez-Cuesta E, Berges-Gimeno P, González-Mancebo E, Fernández-Caldas E, Cuesta-Herranz J, Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. Allergy. 2007; 62: 810–7.
48. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010; 40: 922–32.
49. Di Rienzo VD, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy. 2005; 35: 560–4.
50. Fiocchi A, Pajno G, La Grutta S, Pezzuto F, Incorvaia C, Sensi L, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol. 2005; 95: 254–8.

51. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012; 129: 448–55.
52. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011; 127: 640–6.
53. Compalati E, Rogkakou A, Passalacqua G, Canonica GW. Evidences of efficacy of allergen immunotherapy in atopic dermatitis: an updated review. Curr Opin Allergy Clin Immunol. 2012; 12: 427–33.
54. Gastaminza G, Algorta J, Uriel O, Audicana MT, Fernandez E, Sanz ML, et al. Randomized, double-blind, placebo-controlled clinical trial of sublingual immunotherapy in natural rubber latex allergic patients. Trials. 2011; 12: 191.
55. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: Systematic review and metaanalysis. Allergy 2005; 60: 4–12.
56. Durham SR, Yang WH, Pedersen MR, Johansen R, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 117: 802–9.
57. Durham S, Emminger W, Kapp A, Colombo G, de Monchy JG, et al. Long-term clinical efficacy in grass pollen–induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol. 2010; 125: 131–8.
58. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol. 2012; 157: 288–98.
59. Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy 2004; 59: 45–53.
60. Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. Eur Ann Allergy Clin Immunol. 2007; 39: 119–22.
61. Antúnez C, Mayorga C, Corzo JL, Jurado A, Torres MJ. Two year follow-up of immunological response in mite-allergic children treated with sublingual immunotherapy. Comparison with subcutaneous administration. Pediatric Allergy Immunol. 2008; 19: 210–18.
62. Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy 2006; 61: 1177–83.
63. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study. J Allergy Clin Immunol. 2010; 126: 969–75.
64. Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, et al. 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: 141–8.
65. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006; 61: 1162–72.
66. Passalaqua G, Canonica GW. Specific immunotherapy in asthma: efficacy and safety. Clin Exp Allergy 2011; 41: 1247–53.
67. Marogna M, Spadolini I, Massolo A, Berra D, Zanon P, Chiodini E, et al. Long term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. Ann Allergy Asthma Immunol. 2009; 102: 69–75.
68. Nieto A, Mazon, A, Pamies R, Bruno L, Navarro M. Montanes A, et al. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. J Allergy Clin Immunol. 2009; 124: 157–61.
69. Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study. J Allergy Clin Immunol. 2007; 120: 164–70.
70. Mastrandrea F, Mirelli SG, Meinardi A, Starcia G, Corraduzza G, Parciani S. Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up for 35 consecutive patients. Allergol Immunopathol. 2000; 28: 54–62.
71. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Consortium of Food Allergy Research (CoFAR). Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013; 131: 119–27.
72. Calderón MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on dose–response relationship in allergen-specific immunotherapy. Allergy 2011; 66: 1345–59.
73. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol. 2011; 128: 559–66.
74. 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: 312–20.
75. Pajno GB, Caminiti L, Crisafulli G, Vita D, Valenzise M, De Luca R, et al. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. Pediatr Allergy Immunol. 2011; 22: 803–7.
76. Ciprandi G, Incorvaia C, Puccinelli P, Scurati S, Masieri S, Frati F. The POLISMAIL lesson: sublingual immunotherapy may be prescribed also in polysensitized patients. Int J Immunopathol Pharmacol. 2010; 23: 637–40.
77. Lee JE, Choi YS, Kim MS, Han DH, Rhee CS, Lee CH, et al. Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis. Ann Allergy Asthma Immunol. 2011; 107: 79–84.
78. Cortellini G, Spadolini I, Patella V, Fabbri E, Santucci A, Severino M, et al. Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial. Ann Allergy Asthma Immunol. 2010; 105: 382–6.
79. Stelmach I, Sobocińska A, Majak P, Smejda K, Jerzyńska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. Ann Allergy Asthma Immunol. 2012; 109: 274–8.
80. de Boot CM, Moed H, Berger MY, Röder E, Hop WC, de Groot H, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. Pediatr Allergy Immunol. 2012; 23: 150–8.
81. Wahn U, Klimek L, Ploszczuk A, Adelt T, Sandner B, Trebas-Pietras E, et al. 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; 13: 886–93.
82. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. SLIT Study Group.: Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009; 123: 160–6.
83. Radulovic S, Calderon MA, Wilson D, Durham S.: Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010: CD002893.
84. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. Allergy 2012; 67: 741–3.
85. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. Allergy 2006; 61: 1235.
86. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2007; 62: 567–8.
87. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy 2008; 63: 374.
88. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy 2009; 64: 963–4.
89. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. J Allergy Clin Immunol. 2009; 124: 378–9.
90. André C, Fadel R. Anaphylaxis caused by allergen sublingual immunotherapy? Allergy 2007; 62: 1220–1.
91. Murphy K, Gawchik S, Bernstein D, Andersen J, Pedersen MR. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. J Negat Results Biomed. 2013; 12: 10. Published online 2013 June 1. doi: 10.1186/1477–5751–12–10.
92. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. J Allergy Clin Immunol. 2013; 132: 93–8.
93. Baron-Bodo V, Batard T, Nguyen H, Fréreux M, Horiot S, Harwanegg C, et al. Absence of IgE neosensitization in house dust mite allergic patients following sublingual immunotherapy. Clin Exp Allergy. 2012; 42: 1510–8.

94. Saporta D.: Efficacy of Sublingual Immunotherapy versus Subcutaneous Injection Immunotherapy in Allergic Patients. J Environ Public Health 2012; 2012: 492405.
95. Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. J Allergy Clin Immunol. 2011; 128: 808–15.
96. Brehler R, Klimek L, Kopp VM, Virchow JC. Specific immunotherapy – indications and mode of action. Dtsch Arztebl Int. 2013; 110: 148–58.
97. Calderon MA, Eichel A, Makatsori M, Pfaar O. Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials. Curr Opin Allergy Clin Immunol. 2012; 12: 249–56.
98. Creticos PS. Norman PS, Feldweg AM. Sublingual and oral immunotherapy for allergic rhinitis. 2013 UpToDate.com
99. Hsu NM, Reisacher WR. A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. Int Forum Allergy Rhinol. 2012; 2: 280–4.
100. Savi E, Peveri S, Senna G, Passalacqua G. Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach. Allergy 2013; 68: 1193–5.
101. Pajno GB, Caminiti L, Crisafulli G, Barberi S, Landi M, Aversa T, et al. Adherence to sublingual immunotherapy in preschool children. Pediatr Allergy Immunol. 2012; 23: 688–9.
102. Bernaola G, Corzo JL, Dominguez-Ortega J, Lucas C, Ojeda I, Torres-Borrego J. Sublingual immunotherapy: factor influencing adherence. J Investig Allergol Clin Imunol. 2012; 22: 437–59.
103. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. Systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess. 2013; 17: 1–336.
104. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. 2008; 63: 1624–9.
105. Gentile DA. Sublingual immunotherapy improves symptoms of allergical rhinoconjunctivitis and asthma. Evid Based Med. 2014; 19: 34–5.
106. Samoliński B, Fronczak A, Kuna P, Akdis CA, Anto JM, Bialoszewski AZ, et al. Council on the European Union. Prevention and control of childhood asthma and allergy in the EU from the public health point of view: Polish Presidency of the European Union. Allergy 2012; 67: 726–31.
107. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V, et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. Clin Transl Allergy 2012; 2: 21.
108. Calderon MA, Demoly P, van Wijk GR, Bousquet J, Sheikh A, Frew A, et al. EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. Clin Transl Allergy 2012; 2: 20.
109. Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al; World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol. 2012; 130: 1049–62.
110. Cox L, Compalati E, Kundig T, Larche M. New directions in immunotherapy. Curr Allergy Asthma Rep 2013; 13: 178–95.

UP-DATING COMMENTARY

In view of the fact that the manuscript was accepted for publication in October 2013 and published in March 2016, the authors consider it necessary to add short comments and present the most important conclusions according to studies published in the interim.

1. Availability of allergen extracts: At the present time, two allergen extracts (Staloral 300 and Oralair manufactured by Stallergenes, France) for sublingual immunotherapy are unavailable in Europe.
2. SLIT to house dust mites: The III phase trial confirmed the efficacy and favourable safety profile of both 6 SQ-HDM and 12 SQ-HDM in adults with HDM-induced AR. The treatment effect was present from 14 weeks of treatment onward *[Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite–induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016; 137: 444–51].* HDM-sensitized asthmatic children treated for at least 3 years with either SCIT or SLIT showed sustained clinical improvement. *[Karakoc-Aydiner E, Eifan AO, Baris S, Gunay E, Akturk E, Akkoc T, Bahceciler NN, Barlan IB. Long-Term Effect of Sublingual and Subcutaneous Immunotherapy in Dust Mite-Allergic Children With Asthma/Rhinitis: A 3-Year Prospective Randomized Controlled Trial. J Investig Allergol Clin Immunol. 2015; 25: 334–42].*
3. SLIT in asthma: Lack of data for important outcomes, such as exacerbations and quality of life and use of different unvalidated symptom and medication scores, limits the ability to draw a clinically useful conclusion. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma; therefore, comment on the safety of SLIT for those with moderate or severe asthma is impossible. SLIT is associated with increased risk of all adverse events *[Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev. 2015 Aug 28;8:CD011293].*
4. SLIT in atopic dermatitis: The quality of the evidence was low mainly due to the differing results between studies, lack of blinding in some studies, and relatively few studies reporting participant-centred outcome measures. There is limited evidence that SIT may be an effective treatment for people with atopic eczema *[Cochrane Database Syst Rev. 2016 Feb 12;2:CD008774. Specific allergen immunotherapy for the treatment of atopic eczema. Tam H[1], Calderon MA, Manikam L, Nankervis H, García Núñez I, Williams HC, Durham S, Boyle RJ. [Epub ahead of print].*
5. SLIT in food allergy: In a long-term study, peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and had an excellent long-term safety profile. However, most patients discontinued therapy by the end of year 3, and only 10.8% of subjects achieved sustained unresponsiveness. At this time, SLIT for allergy is limited by the low maximum dose of food allergen than can be delivered as drops. In the future, SLIT for food allergy may be optimized by using an alternative delivery vehicle, e.g. dissolvable tablets as well as administration in the areas of higher density of Langerhans cells, such as vestibular and buccal mucosa compared with sublingual mucosa *[Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, Vickery BP, Liu AH, Henning AK, Lindblad R, Dawson P, Plaut M, Sampson HA; Consortium of Food Allergy Research. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. 2015; 135: 1240–8.e1–3].*
6. SLIT in HIV-positive patients: Preliminary data showed that SLIT therapy in viro-immunological controlled HAART (highly active antiretroviral therapy) treated HIV positive patients was efficacious, safe and well tolerated *[Iemoli E, Borgonovo L, Fusi A, Magni C, Ricci ED, Rizzardini G, Piconi S. Sublingual allergen immunotherapy in HIV-positive patients. Allergy. 2016; 71: 412–5].*
7. Quality of SLIT products: For more than half of the products, SLIT was not "high dose" as has originally been

recommended. When reviewing the low- and high-dose products with respect to efficacy in clinical trials included in a meta-analysis on SLIT, some low-dose extracts showed efficacy *[Larenas-Linnemann DE, Mösges R. Dosing of European sublingual immunotherapy maintenance solutions relative to monthly recommended dosing of subcutaneous immunotherapy. Allergy Asthma Proc. 2016; 37: 50–6.]*. Substantial variations regarding allergen content were found among 5 SLIT-HDM products. Therefore, it can be necessary to guarantee the quality of the SLIT-HDM products and to demonstrate their effectiveness before they are marketed *[Moreno Benítez F, Espinazo Romeu M, Letrán Camacho A, Mas S, García-Cózar FJ, Tabar AI. Variation in allergen content in sublingual allergen immunotherapy with house dust mites. Allergy. 2015; 70:1413–20]*.

8. Optimal dosage: The results of a multicentre trial of sublingual liquid birch pollen preparation indicate that, within the studied dose range, SB 40 000 AUN/ml is the most optimal effective and safe dose *[Pfaar O, van Twuijver E, Boot JD, Opstelten DJ, Klimek L, van Ree R, Diamant Z, Kuna P, Panzner P. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. Allergy. 2016; 71:99–107]*.
9. Simultaneous administration of more than one allergen extract: In a 4-week sequential SLIT-tablet dosing schedule followed by simultaneous intake of timothy grass and ragweed tablets was well tolerated *[Maloney J, Berman G, Gagnon R, Bernstein DI, Nelson HS, Kleine-Tebbe J, Kaur A, Li Q, Nolte H. Sequential Treatment Initiation with Timothy Grass and Ragweed Sublingual Immunotherapy Tablets Followed by Simultaneous Treatment Is Well Tolerated. J Allergy Clin Immunol Pract. 2016 Jan 2. pii: S2213–2198(15)00647–9. Epub ahead of print]*.
10. Comparability of SLIT vs SCIT: The comparisons for grass pollen immunotherapy products indicate comparable reductions in allergic rhinoconjunctivitis symptoms and supplemental medication use for SLIT tablets and SCIT in the first pollen season *[Nelson H, Cartier S, Allen-Ramey F, Lawton S, Calderon MA. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. J Allergy Clin Immunol Pract. 2015; 3: 256–266.e3, Larenas-Linnemann D. Patient selection for subcutaneous versus sublingual immunotherapy. Curr Opin Allergy Clin Immunol. 2015; 15: 588–95]*.
11. Side effects and safety aspects: Eosinophilic esophagitis as a potential side effect due to SLIT was reported in case reports *[Miehlke S, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. Case Rep Gastroenterol. 2013; 7: 363–8]*. In-seasonal initiation or switchover of immunotherapy with tablet sublingual immunotherapy could potentially induce serious adverse reactions, including anaphylaxis *[Hsiao KC, Smart J. Anaphylaxis caused by in-season switchover of sublingual immunotherapy formulation. Pediatr Allergy Immunol. 2014; 25: 714–5]*.
12. A new position paper on sublingual immunotherapy was published *[Canonica GW[1], Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, Bousquet J, Calderón M, Compalati E, Durham SR, van Wijk RG, Larenas-Linnemann D, Nelson H, Passalacqua G, Pfaar O, Rosário N, Ryan D, Rosenwasser L, Schmid-Grendelmeier P, Senna G, Valovirta E, Van Bever H, Vichyanond P, Wahn U, Yusuf O. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014; 7: 6]*.