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Subcutaneous versus sublingual immunotherapy for allergic rhinitis and/or asthma

Subcutaneous allergen-specific immunotherapy has long been used in allergic rhinitis and/or asthma and has been recognized to be efficacious. However, owing to the inconvenience of injection and the risk of serious side effects, alternative concepts inspiring the search for effective noninjective routes, namely sublingual administration of allergens, have emerged. Sublingual immunotherapy (SLIT) appears to be associated with a lower incidence of systemic reactions. The clinical efficacy of subcutaneous immunotherapy (SCIT) is well established for both rhinitis and asthma. Meta-analyses relating to its efficacy on asthma and rhinitis are available. SLIT has also been validated in this respect. Comparative clinical studies of SLIT versus SCIT are scarce demonstrating both routes to be clinically efficient. Knowledge of the exact mechanism of action of SLIT has been increasing in the last decade. In addition, recent studies have proved similarities of the immunological changes with the treatment of both routes. Further comparative clinical and immunological studies of SLIT versus SCIT are needed to confirm the long-term efficacy and to complete the knowledge of immunological mechanisms of both routes. Moreover, better understanding of the interaction of allergen and oral mucosal dendritic cells during SLIT may allow improved targeting of SLIT vaccines.

KEYWORDS: allergic rhinitis ■ asthma ■ subcutaneous immunotherapy
■ sublingual immunotherapy

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The prevalence of allergic diseases, including asthma, rhinitis and eczema, has been increasing for the last two decades in developed and developing countries and its burden is substantial [1,2]. The mainstay treatments are patient education, allergen avoidance where feasible, pharmacotherapy for symptom relief and, when appropriate, allergen-specific immunotherapy [3].

Specific allergen immunotherapy is the only treatment modality with the capacity of changing the natural course of allergic disease, hence preventing its exacerbation [3], and might halt progression from rhinitis to asthma [4].

Since its discovery, specific immunotherapy (SIT) has been commonly performed by the subcutaneous route. However, in early studies, subcutaneous immunotherapy (SCIT) was associated with uncommon, but severe or even fatal, systemic reactions [5]. As a consequence, the interest in alternative routes increased, inspiring the search for more effective noninjection routes of administration of specific allergen immunotherapy. Therefore, delivery of allergens through the mucosal route have been proposed, and it has been suggested that the natural mechanisms underlying the induction of oral tolerance at mucosal surfaces may be an effective therapeutic strategy for suppression of ongoing pathological immune responses in allergic diseases [6]. Various

mucosal routes of administration were proposed and investigated during the last decades, involving local oral, nasal, bronchial and sublingual routes. Controlled trials failed to demonstrate clinical efficacy of oral and bronchial routes, therefore those routes have been abandoned. Although local nasal immunotherapy proved to be effective in a number of controlled trials [7–11], owing to the high incidence of reported side effects and the requirement of a particular administration technique, the use of this technique has declined. Meanwhile, the efficacy and safety of the sublingual route was documented by numerous controlled trials in children and adults with asthma and rhinitis sensitized to house dust mite (HDM) or pollen [12,13]. Furthermore, long-lasting and steroid-sparing [14] effects have been documented with a preventive effect on the progression of the allergic disease and the development of asthma [15,16]. Moreover, our understanding of the underlying immunological mechanism is substantially increasing.

Subcutaneous immunotherapy has the capacity of skewing T-cell immune response from Th2- to Th1-type related to an increased IFN- γ and IL-12 production, with a reduction in Th2 activity through a mechanism of anergy or tolerance, the latter being related to the generation of allergen-specific Tregs, which are

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capable of producing cytokines such as IL-10 and TGF- β [17]. The sublingual route of administration was suggested to have similar mechanisms as SCIT [18], with a particular involvement of mucosal dendritic cells (DCs) [19].

In this article, clinical efficacy, safety and immunological mechanisms based on currently available data will be presented and those two modes of specific immunotherapy will be compared in these aspects.

Clinical efficacy

■ Subcutaneous immunotherapy

Allergic rhinitis is certainly the disease in which SCIT efficacy is the most documented and proved. A meta-analysis was published in 2007 in the frame of the Cochrane collaboration [20]. A total of 51 trials including a total of 2871 participants were considered. None of them was conducted exclusively in children, but participants younger than 18 years of age were included in nine studies. Allergens tested were ragweed ($n = 12$), mixed grass ($n = 16$), Timothy ($n = 5$), *Parietaria* ($n = 6$), birch ($n = 4$), orchard ($n = 2$), cedar ($n = 3$), Bermuda ($n = 1$), *Juniperus ashei* ($n = 1$) and cocos ($n = 1$). A total of 15 studies suitable for symptom score analysis demonstrated a significant reduction. The medication score analysis (13 studies) showed a significant reduction in the specific immunotherapy group. It is worth noting that there was a significant heterogeneity among these studies. Passalacqua and colleagues updated this work in the frame of the GALEN network by collecting 15 recent studies published between 2000 and 2006 [21]. Reduction of symptoms and/or the need for medications were confirmed with grass, birch, *Parietaria* and ragweed pollens, and HDMs. In addition, SCIT-treated patients' quality of life significantly improved [22–24].

The proof of SIT efficiency in asthma has long been served by a meta-analysis by Abramson and colleagues, first published in 1995 [25], and then kept regularly up to date in the frame of the Cochrane Institute [26–28]. The allergens used in the trials were dust mite, pollen, animal dander, *Cladosporium*, latex and multiple allergens.

The latest Cochrane meta-analysis including 88 trials demonstrated a significant improvement in asthma symptom scores (standardized mean difference: -0.59; 95% CI: -0.83 to -0.35) and it would have been necessary to treat three patients (95% CI: 3–5) with immunotherapy to avoid one deterioration in asthma symptoms. Overall, it would have been necessary to treat four patients (95% CI: 3–6) with immunotherapy to

avoid one requiring increased medication. This meta-analysis also showed significant reduction in specific bronchial hyper-reactivity [29].

■ Sublingual immunotherapy

To date, sublingual immunotherapy (SLIT) has been tested in rhinitis and asthma in approximately 40 double-blind, placebo-controlled (DBPC) studies. Indeed, four meta-analyses were published in the frame of the Cochrane collaboration [12] or with the Cochrane collaboration method [30–32].

The first meta-analysis of SLIT for allergic rhinitis included 22 trials up to September 2002 and 979 patients. It concluded that SLIT was significantly more effective than placebo [33], but the studies in allergic asthma were too few to perform a meta-analysis. A meta-analysis in asthma was recently repeated, including 25 trials (either open or blinded) and involving more than 1000 adults and children [34]. This meta-analysis demonstrated a significant effect of SLIT for most of the considered outcomes (symptoms plus medications, pulmonary function and overall improvement), with the exception of asthma symptoms alone. Another meta-analysis [30] of SLIT for allergic rhinitis in pediatric patients (aged 4–18 years) involved ten trials and 484 subjects demonstrating that SLIT was significantly more effective than placebo, as assessed by the reduction in both symptom scores and rescue medication usage. Although all the studies were of high methodological quality, there was a relevant heterogeneity ($I^2 > 80\%$) owing to the large variability in study design, duration, outcome measures and inclusion criteria. Finally, a meta-analysis was also performed for asthma in pediatric patients [31]. This article included nine DBPC trials and 441 patients, and found a significant effect of SLIT on both asthma symptoms and rescue medication usage. Also in this case, the heterogeneity of the trials was very large ($I^2 > 90\%$). The meta-analyses mentioned pooled together all the allergens, whereas a systematic evaluation of the efficacy of one specific allergen is available only for HDM [35] with positive results. In addition, it is noteworthy that in some pollen studies, positive results were delayed to the second year of treatment [36,37] and studies using a mix of various pollen extracts are negative [38] or marginally positive [39].

The studies previously reported were mainly conducted with sublingual drops of extracts. Recently, sublingual orodispersible allergen tablets were developed in grass pollen immunotherapy, and are expected to rapidly replace the

liquid formulation. During the last 3 years, adequately powered, well-designed, DBPC randomized controlled trials involving several hundreds of patients with allergic rhinitis and/or asthma using standardized grass pollen tablets were published [40–46]. In those studies, the magnitude of the effect, defined as the reduction in diary symptom and rescue medication scores compared with placebo was reported as 16 and 28% [40], 30 and 38% [46], 35 and 46% [41], 28 and 24% [43], 24 and 34% [45], respectively.

Only few studies were specifically designed to assess the effect of SLIT tablets in asthma [42,47–52], and most of them confirmed a significant effect on symptoms and/or medication intake. In the three asthma studies that reported negative results [42,50,51], the patients were almost completely free of asthma symptoms at enrollment and remained so during the trial, so that the absence of efficacy is not substantiated. Only two DBPC randomized controlled trials assessed the efficacy of multiple **noncross-reacting allergens** [53,54]. The first one used grass and olive extracts, and confirmed the efficacy of SLIT in rhinitis. The second one compared the efficacy of SLIT with grass alone or with grass plus nine other pollens and found that the treatment with a single allergen had more effect on immunological parameters than that with multiple allergens. Owing to the low pollen count, no clinical difference between the two groups and placebo was observed in this study.

Safety

■ Subcutaneous immunotherapy

The adverse reactions during SCIT depends on numerous factors, including the presence and severity of asthma, dosing, specially accelerated schedules (rush immunotherapy) and high-dose allergen, new vials, treatment during peak pollen season, extensive sensitivity to the offending allergen and concomitant β -blocker use [55].

In a review evaluating 38 SCIT studies using inhalant allergens, the rate of systemic reactions during conventional SCIT per injection ranged from 0.05 to 3.2% mostly associated during the build-up period [56].

In a study of conventional immunotherapy with grass pollen or HDM allergens, 4.8% of patients experienced systemic reactions, of whom 84% had asthma. Reactions mostly occurred during the build-up phase with none being life threatening [57]. In addition, there were 141 non-fatal reported systemic reactions between 1981 and 2000 in a report from Europe evaluating 4600 SCIT patients [58].

Fatal reactions ($n = 46$) to SCIT had been reported by the American Academy of Allergy Asthma and Immunology (AAAAI) committee on allergen standardization with an estimation of one in 2–2.5 million doses administered [59]. Two additional surveys found similar results with 17 fatalities in each. These surveys had different time spans: one was 10 years and the other was 12 years. Asthmatic patients accounted for more than 75% of deaths, 50% being on build-up therapy with an onset of symptoms within 30 min of injection [60].

■ Sublingual immunotherapy

Frequently reported side effects from SLIT include oral itching and irritation [41,61,62]. Those side effects mostly remitted with ongoing treatment. Meanwhile, patients rarely experience abdominal pain, nausea or diarrhea [63].

In a review of 66 SLIT studies involving 4378 patients, no serious life-threatening reactions were reported. The rate of adverse events was 2.7 per 1000 doses affecting 12% of patients [64].

A severe systemic reaction associated with SLIT was reported in a 31-year-old woman with allergic rhinitis and mild intermittent asthma treated with a mixture of allergens including alternaria, cat, dog and pollens. The patient experienced generalized pruritus, angioedema of hands and feet, dyspnea, wheezing and dizziness on the third day within minutes after administration of SLIT [65]. Another severe systemic reaction was experienced in an 11-year-old girl with asthma/allergic rhinitis receiving a mixture of HDMs in the morning and a seasonal pollen mixture in the night during the peak pollen season. Within 3 min of administering pollen drops, she developed lip swelling accompanied by chest and abdominal pain, high fever and nausea [66]. Both of these patients were treated successfully with reliever medication not requiring epinephrine. In another report, a 16-year-old girl who took six-times the normal dose of HDM SLIT developed generalized pruritus, flushing, urticaria, wheezing and hypotension within 5 min. She was treated in the intensive care unit and recovered over a 24-h period [67]. Two patients on sublingual pollen tablet experienced systemic reactions within minutes after administration and were treated with reliever medications [55].

Mechanisms of specific immunotherapy

Subcutaneous allergen SIT has been used most successfully in allergy to insect venoms, and in allergic rhinitis [68–70]. This mode of therapy

has been shown to ameliorate allergen-induced symptoms including antibody responses (upregulation of blocking antibody responses and downregulation of allergen-specific IgE responses) [71,72], T-cell responses (reorientation of allergen-specific T-cell responses from Th2 to Th1 and/or regulatory T profile) [73–75] and inflammatory cells (reduction in the numbers and activation of proinflammatory cells such as mast cells and eosinophils) [76,77].

The oral mucosa belongs to the sophisticated network of the mucosal immune system, where tolerance induction towards a variety of antigens from commensal bacterial and nutritional products predominates to maintain local immunostasis [19]. Oral mucosal tissue demonstrates excellent wound healing without severe scar development and without acute inflammation in spite of high bacterial colonization [78]. With regards to SLIT, the tolerogenic potential of oral mucosal tissue is reflected by the lack of inflammatory cells within oral mucosal tissue after allergen administration in sensitized individuals [79]. Furthermore, oral mucosal tissue displays high permeability for allergens as it has been shown that orally applied allergen as well as monomeric allergoid retains within oral tissue for up to 20 h [11,80,81]. What then makes the oral mucosa efficient in immunological processes leading to a reduction of allergic symptoms during SLIT? It is postulated that, most likely, Langerhans-like local DCs are critically involved in this process [68]. During SLIT, the allergen is captured within the oral mucosa by Langerhans-like DCs and, subsequently, DCs mature and migrate to proximal draining lymph nodes. The significance of the role of these local lymph nodes in successful allergen SIT lies in the preferential production of blocking IgG antibodies and the induction of T lymphocytes with suppressive function [69].

Antibody responses

Successful SCIT may involve blunting of the seasonal increase in serum pollen allergen-specific IgE concentrations [82] in addition to substantial increases in allergen-specific IgG₄ [73,82,83]. The increase in the ratio of specific IgG₄:specific IgE may be crucial. Recent studies have confirmed elevations in allergen-specific IgA after SCIT [73,84]. It is possible to measure the functional activity of these antibodies. IgG₄ is noninflammatory since it is unable to fix complement and does not form immune complexes. B cells are able to take up allergen bound to IgE via the surface receptor

CD23. They subsequently process this allergen and present epitopes to T cells. This results in effective T-cell activation at low concentrations of allergen. Complexes bound to CD23 on the surface of B cells can be quantified by flow cytometry. Serum obtained from subjects with hayfever after successful immunotherapy has been shown to inhibit allergen–IgE binding to B cells [82], with the effect mediated by IgG₄. This system has provided an *in vitro* assay of the efficacy of ‘blocking’ antibodies induced by immunotherapy.

The immunologic response to SLIT has not been intensely studied. A previous study reported changes in specific IgG₄ levels [69], whereas others reported a lack of change in specific IgG₄ [85] and IgE levels [71]. Moreover, in some SLIT studies, investigators observed a decrease in the IgE:IgG₄ ratio [72]. A recent report of HDM-SLIT of asthmatic children demonstrated the downregulation of specific IgE in serum in combination with slight upregulation of specific IgA, but with no effect on IgG₁ and IgG₄ [72]. Two recent, large-scale, DBPC studies demonstrated dose-dependent specific antibody changes during grass pollen SLIT [40,41]. Durham *et al.* enrolled 855 individuals with seasonal allergic rhinitis from Europe and Canada [40]. Placebo or one of three different doses of grass allergen (Timothy grass) tablet; 2500, 25,000 and 75,000 SQ-T (corresponding to 0.5, 5 and 15 µg of the major allergen *Phleum* p 5) were administered daily. Administration began from approximately 8 weeks before the start of the grass pollen season and was continued for a total of 18 weeks. Specific IgG levels were raised at 8 weeks in the highest-dose group and continued to increase, along with levels in the intermediate-dose group, up to 18 weeks post-treatment. Conversely, levels of specific IgE peaked at 8 weeks and remained elevated post-treatment, but without further seasonal rise. By contrast, placebo-treated patients showed no early changes in specific IgG but significant seasonal increase in specific IgE.

Didier *et al.* performed a similar international PC trial in 628 adults with seasonal allergic rhinitis [41]. A sublingual tablet consisting of equal amounts of allergen extracts from five different grasses was used, as opposed to Timothy grass alone. Levels of grass pollen-specific IgG₄ were increased relative to placebo in a dose-dependent manner. Increases were in the region of three-times those seen at baseline – broadly similar to those demonstrated in the study by Durham *et al.* [40]. Specific IgE levels increased

only in the treatment groups. These trials show a clear relationship between dose, efficacy and specific antibody levels.

T-cell responses

Successful SCIT in patients with grass pollen [86] and with mite [73] allergy has been shown to be accompanied by increased production of IL-10 in allergen-stimulated peripheral T-cell cultures. In one study, this was accompanied by suppression of allergen-induced T-cell proliferation, possibly mediated by CD4⁺CD25⁺ T cells and inhibited by strategies that blocked IL-10 or TGF- β [73]. In addition, SCIT has been associated with alterations in peripheral T-cell responses, with immune deviation in favor of Th1 responses [87]. However, changes in T-cell responses to allergen have not been universally observed in cells derived from peripheral blood [88,89].

Studies demonstrating that SLIT is able to induce Tregs in clinical practice are emerging in recent years. Nevertheless, a preliminary study demonstrated that compared with untreated controls, SLIT increased IL-10 production in peripheral blood mononuclear cells from patients with HDM allergy following *in vitro* stimulation with *Dermatophagoides* antigens, as well as recall antigens such as *Candida albicans* or phytohemagglutinin [69]. In another study in childhood asthma with HDM allergy, 6 and 12 months of SLIT downregulated specific IgE response, while slightly increasing specific IgA [72].

A 12-month DBPC study of HDM-SLIT was performed demonstrating decreased CD4⁺ T-cell proliferation and IL-5 production along with increased IL-10 secretion and specific IgG₄ in the active group. Treg (CD4⁺CD25⁺CD127^{lo}/Foxp3⁺) function was demonstrated by suppression of allergen-specific effector T-cell proliferation and cytokine production. This was the first study demonstrating TGF- β -mediated immunological suppression of SLIT [90].

Local changes in the nasal mucosa have been measured after SCIT. These include skewing of cytokine profiles in favor of Th1 responses [91,92] and the local induction of Tregs with increases in IL-10 [82] and TGF- β [84]. Using triple immunofluorescence microscopy, increases in CD3⁺CD25⁺Foxp3⁺ phenotypic Tregs have been demonstrated in the nasal mucosa after successful grass pollen immunotherapy, with further increases after immunotherapy detected during natural allergen exposure during the pollen season [93].

Effector cells

Moreover, SCIT has been shown to decrease the numbers of effector cells at mucosal sites, both during seasonal allergen exposure and after allergen challenge [91,94], as well as reducing effector cell reactivity *in vitro* [83].

Oral mucosal immune responses

It is postulated that Langerhans-like local DCs are most likely to be critically involved in the persistence of allergen in the sublingual area [68]. One explanation for the success of SLIT is the profound difference between oral Langerhans cells (LCs) and their skin counterparts. LCs represent the predominating DC population within human oral mucosa, whereas plasmacytoid DCs (pDCs) are virtually absent [95,96]. Nevertheless, oral mucosal LCs (oLCs) differ from the classical epidermal LCs (eLCs), especially by the constitutive expression of the high-affinity receptor for IgE (Fc ϵ RI) [96,97]. Fc ϵ RI appears in early differentiation of LCs, leading to the suggestion that oLCs represent a more immature DC subpopulation, which would further underline their pro-tolerogenic character [98]. oLCs are located within the suprabasal epithelium layer, it is most likely that they bind and process allergens during SLIT. Moreover, oLCs exhibit high expression of MHC class I and II, as well as costimulatory molecules (CD40, CD80/B7.1 and CD86/B7.2), which may suggest the specific function of these cells within the regional immune system of the oral mucosa [99]. Activation of Toll-like receptor (TLR)4 on oLCs by monophosphoryl A (MPL) led to an upregulation of coinhibitory molecules B7-H1 and B7-H3 as well as to the induction of IL-10 production by oLCs [100]. Furthermore, ligation of TLR4 on human oLCs induced Foxp3⁺ Tregs to produce IL-10 and TGF- β 1 near IFN- γ -producing Th1 cells [100]. This leads to the assumption that innate immune receptors such as TLR4 on human oLCs are involved in the maintenance of natural tolerance within oral mucosal tissue.

Oral mucosal DCs as targets for adjuvants in SLIT raises the questions of whether TLR ligands could enhance the efficiency of SLIT. Recently, it has been demonstrated in a BALB/c asthma model that TLR2 activation via Pam3CSK4 together with ovalbumin (OVA) decreased airway hyper-responsiveness and Th2 responses in the cervical lymph node of mice previously sensitized to OVA along with the upregulation of IL-10 and the induction of IFN- γ - and IL-10-producing T cells in oral mucosal DCs [101]. Other adjuvants such as synthetic pseudodipeptide

molecule OM-294-BA-MP or a combination of 1,25-dihydroxyvitamin D3 and dexamethasone (VitD3/Dex) provided similar results [102,103]. Murine oral DCs could also be formed by mucosal adhesive formulations such as chitosan particles, which facilitate allergen contact to oral mucosa leading to increased induction of IFN- γ - and IL-10-producing T cells [104].

Subcutaneous immunotherapy compared with sublingual immunotherapy

There are a few number of studies including comparison of SCIT versus SLIT to date [105–108]. In a study including asthmatic adults sensitized to HDM, patients were randomized to receive either SCIT, SLIT or placebo. SCIT for 1 year significantly improved asthma and rhinitis symptom scores, whereas only rhinitis symptom scores improved in the SLIT group [107]. Meanwhile, both groups demonstrated significant decrease in medication scores in comparison with baseline values. The placebo group demonstrated no significant changes in any of the evaluated parameters. In another double-blind, controlled study in which SLIT was compared with SCIT, both symptom and medication scores improved in the treatment groups compared with placebo as well as baseline [105]. The rhinitis score decreased by 0.75 in the SCIT group and 0.36 in the SLIT group. In another study conducted in an open fashion in which patients receiving alternaria SLIT for 2 years were compared with those receiving SCIT, rhinitis scores improved more than that in the SCIT group [106]. A double-blind, double-dummy study compared SCIT with SLIT in patients sensitized to grass pollen. Significant improvements were detected in symptom and medication scores in both groups. Immunological parameters including IgG, specific IgG₄ and skin reactivity improved only in the SCIT group [108].

In a very recently published study, clinical efficacy and immunological mechanisms of SCIT and SLIT were compared in children with asthma/rhinitis sensitized to HDM. This was a prospective, open-labeled and randomized study, comparing children in this respect for the first time. A total of 48 children were randomized to receive either SCIT, SLIT or pharmacotherapy alone. SLIT and SCIT demonstrated a significant reduction of total rhinitis, asthma, medication and visual analog scale scores, skin reactivity to HDM when compared with pharmacotherapy. Moreover, titrated nasal provocative dose significantly increased in both immunotherapy groups when compared

with pharmacotherapy. No adverse events were reported in SLIT, while two patients in the SCIT group developed serious adverse events following injection. Der p 1-driven IL-10 significantly increased in the SCIT group at the end of 1 year. Interestingly, although Bet v 1 was used as a negative control for PBMC cultures, Bet v 1-driven TGF- β increased significantly in the SLIT group at the end of 1 year. **This result led to the speculation that increases of Bet v 1-driven TGF- β (an allergen that the patients were not sensitized to) could possibly point to the mechanism of action in the prevention of new sensitizations following SIT [109].** In a more recent open-labeled, prospective study of the same group conducted on asthmatic children sensitized to HDM, patients were randomized to receive either SCIT, SCIT plus SLIT, SLIT or pharmacotherapy. Children were followed for a duration of 12 months and were evaluated for symptom/medication scores, allergen-specific nasal reactivity and Der p 1-driven cytokine responses at baseline, 1, 4 and 12 months. An earlier improvement in symptom and medication scores was detected in the SCIT group, whereas later in the SLIT group (4 vs 12 months). Positivity of allergen-specific nasal provocation test significantly decreased at 4 and 12 months of both SCIT and SLIT groups when compared with pharmacotherapy group. **There was no significant difference in cytokine levels at baseline and 1 month. At the fourth month, the SCIT group demonstrated higher levels of Der p 1-driven IL-10 and IFN- γ while the SLIT group demonstrated higher IL-10 and TGF- β . Both immunotherapy groups demonstrated significantly higher allergen-driven IL-10 and TGF- β at 12 months when compared with pharmacotherapy group. This is the first study comparing the kinetics of allergen-driven cytokine secretion of SLIT and SCIT throughout 12 months of treatment [110].**

Conclusion & future perspective

The clinical efficacy of SCIT is well established for both rhinitis and asthma. Meta-analyses relating to its efficacy on asthma [28] and rhinitis [20] are available. SLIT has also been validated in this respect [12]. Two recent meta-analyses in children showed that sublingual delivery of allergen vaccination constitutes a safe and effective alternative to the injectable route to reduce allergic respiratory symptoms and drug intake [30,111]. Assessment of possible long-term benefits, including long-term disease remissions, suppression of new allergic sensitizations, and reduction of progression from rhinitis to asthma in children, as has been shown for the subcutaneous route, are future requirements.

The immunological effects of SLIT and how these relate to clinical efficacy are yet incompletely understood. Large-scale trials have confirmed the induction of allergen-specific IgG antibodies to be dose dependent. There is no early suppression of allergen-specific IgE antibodies and a transient early increase in specific IgE antibodies as in SCIT.

Current models of SCIT propose the induction of antigen-specific Tregs, which then orchestrate the observed antibody and mucosal changes observed during treatment. As of yet there is only scarce evidence that such mechanisms operate during SLIT. Comparative clinical studies of sublingual and subcutaneous treatment yielded heterogeneous results demonstrating efficacy of both modes, but SLIT to be a safer approach [105,107,108].

In conclusion, understanding of the interaction of allergen and antigen-presenting cells within the oral mucosa may allow improved targeting of SLIT vaccines. In the near future the combination of allergen products with adjuvants may improve efficacy of immunotherapy via the sublingual route.

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Executive summary

Allergen-specific subcutaneous immunotherapy & sublingual immunotherapy

- Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) improve symptoms in allergic rhinitis and/or asthma.
- SCIT and SLIT decrease medication use in allergic rhinitis and/or asthma.
- SCIT and SLIT improve specific bronchial hyper-reactivity in asthma.

Safety

- Fatal systemic reactions may occur on rare occasions during SCIT.
- SLIT may rarely cause oral itching, irritation, nausea, dyspnea and abdominal pain.

Immunological mechanisms of specific immunotherapy

- Upregulation of allergen-specific IgG and IgA.
- Downregulation of allergen-specific IgE.
- Redirecting allergen-specific Th2 responses to Th1/Treg profile.

SCIT versus SLIT

- Both routes of immunotherapy are clinically efficient.
- Immunological mechanisms of SCIT and SLIT are similar.

Future directions

- SLIT is a safer route of immunotherapy.
- Oral mucosal dendritic cells are targets for adjuvants in SLIT to improve immunogenicity.

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