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Selection of patients for sublingual versus subcutaneous immunotherapy

Allergen immunotherapy is the sole treatment for IgE-mediated allergic diseases directed at the underlying mechanism. The two widely accepted administration routes are sublingual (SLIT) and subcutaneous (SCIT). We reviewed how patients should best be selected for immunotherapy and how the optimal administration route can be defined. Before deciding SCIT or SLIT, appropriate selection of patients for allergen immunotherapy (AIT) is mandatory. To be eligible for AIT, subjects must have a clear medical history of allergic disease, with exacerbation of symptoms on exposure to one or more allergens and a corresponding positive skin or *in vitro* test. Then the route of administration should be based on: published evidence of clinical and immunologic efficacy (which varies per allergic disease and per allergen); mono- or multi-allergen immunotherapy, for SLIT multi-allergen immunotherapy was not effective; safety: adverse events with SLIT are more frequent, but less severe; and, costs and patient preferences, closely related to adherence issues. All these are discussed in the article.

Keywords: allergic rhinitis • asthma • atopic dermatitis • house dust mite • immunotherapy • patient adherence • pollen • subcutaneous • sublingual • systemic reactions

Background

Several comparisons of subcutaneous immunotherapy (SCIT) versus sublingual immunotherapy (SLIT) have been published [1–3], aiming to prove which of these methods is more efficacious. The purpose of this manuscript is to take a different approach. The authors shall not attempt to convince the reader which is better, SCIT or SLIT. Instead, this manuscript seeks to guide the clinician in the process of selecting the best treatment for each patient in each specific clinical setting. The stepwise approach of correctly selecting patients for SCIT or SLIT goes through several stages. First an IgE-mediated mechanism for the patient's symptoms has to be confirmed and the probable causative allergens have to be identified. Then the physician should consider the efficacy of an eventual treatment with immunotherapy in this particular patient which depends on several factors, such as the allergic disease to be treated, the specific allergen(s) in question, the

proposed route by which the allergens should be given (sublingual or subcutaneous) and the estimated degree of patient's adherence to the immunotherapeutic regime selected, to name some. Finally, contra-indications, costs and safety of the treatment also play a role in decision-making.

Correctly diagnosing the allergen related to the patient's symptoms

In allergic patients that fulfil the guideline indications for allergen specific immunotherapy (AIT) [4–6], the first step in correctly selecting subjects for immunotherapy is demonstrating that the patient's symptoms are really triggered by an IgE-mediated mechanism. Then the most important causal allergen or allergens should be determined, as not all sensitizations are translated into allergy.

A medical history conducted cautiously and focused on getting a detailed description given by the patient of the relation between

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an increase in his symptoms after exposure to a certain allergen is crucial [7]. Once the medical history sustains the suspicion of allergy, the presence of specific IgE directed to the allergen has to be demonstrated by skin prick or *in vitro* testing. The improved technology is making this latter method more and more attractive. Either method has its pitfalls, briefly discussed below. The diagnostic process ends with the selection of one or a few allergens for AIT. Provocation testing can help in this last step.

Skin-prick testing

The reliability of the skin-prick test (SPT) is strongly determined by which allergens are used for the testing and the quality and concentration of the test extracts. A SPT panel consisting of locally important allergens is recommended [8], as well as a timely updating of the SPT panel. Purity and concentration of the test extracts are equally important. Allergen extracts sold by the major allergen manufacturers in the US and Europe undergo stringent quality control and should generally be considered of high purity [9]; for some locally prepared extracts this is not always the case. The concentration of the SPT extracts differs between US and European extracts [10], the former being generally more potent [11–13], and even among European extracts potencies vary [14,15]. A weak positive SPT reaction to a potent extract (sensitization) is not equal to allergy to that allergen; it is the judgment of the experienced allergist that determines, which of the allergens positive in the SPT to select for the AIT.

In vitro testing

Over the last decade several techniques have passed the stage in serologic allergy testing, from RAST, ImmunoCAP and Immulite which all detect specific IgE to whole allergens, to the micro-array techniques in which specific IgE to over a hundred fifty allergen molecules can be detected [16]. For the time being, the methods based on whole allergens may give a less accurate diagnosis of the eventual presence of IgE mediated mechanisms than the skin testing.

Provocation testing

Provocation testing can be used to reduce the number of allergens for AIT from all those, positive in a SPT to only those that provoke symptoms. Moreover, it detects patients with local allergic rhinitis [17]. This method, however, is not without risks.

From sensitization to allergy

If the presence of IgE to certain allergen(s) has been demonstrated by SPT or serologic testing, the last step in the specific allergy diagnosis lies in the hands of the

experienced allergy specialist: to determine which of all positive results really seem to be the cause of the patient's symptoms. Oftentimes patients are sensitized (i.e., have a positive SPT or IgE) to several allergens, but normally not all these sensitivities are really clinically relevant. Poly-sensitized patients in reality might only have one or two real clinical allergies. This is a crucial decision, as immunotherapy should only be given with the allergen(s) eliciting symptoms. In this process the physician also uses his knowledge about cross-reactivity.

Selecting the patients: efficacy

After the causal allergen(s) have been detected, the physician should consider the efficacy of the possible immunotherapy regimens. Evidence for SCIT and SLIT efficacy shall be reviewed per allergic disease and per specific allergen. There exist few studies directly comparing the efficacy and safety of SCIT versus SLIT. These are reviewed in the last part of this section.

Evaluating evidence of efficacy of immunotherapy

In our search for the scientific evidence in favor of or against immunotherapy for specific allergic diseases and specific allergens, we looked for four kinds of reviews: Cochrane meta-analyses, meta-analyses (not Cochrane), systematic reviews using GRADE (see below) and dose-finding studies.

The scientific quality of publications on allergen immunotherapy varies widely [18]. The international scientific community agrees on some broadly accepted systems to appraise the methodological value of trials. The first widely accepted method of conducting evidence based medicine was proposed by Shekelle *et al.* [19] leading to the levels of recommendation: A to D. The highest level of evidence in this system comes from meta-analysis and systematic reviews. However, the recommendation of a specific clinical management action should probably not only be based on the clinical evidence. Cost, safety and culturally defined patient preferences can augment or reduce the suitability of certain clinical actions. As such, the grading of recommendations assessment, development and evaluation (GRADE) system was introduced by experts in guideline and policy making [20]. GRADE proposes a comprehensive system in which scientific quality of the clinical trials is evaluated according to multiple parameters [21] on top of the study design. Moreover, GRADE encourages taking into account the patient's preference, safety and cost to finally make a strong or weak recommendation in favor of or against certain treatment options [20].

Furthermore, demonstration of a dose-effect relationship for a certain intervention can also be considered as strong evidence in favor of the efficacy of an intervention. A Task Force of the European Academy of Allergy and Clinical Immunology searched the literature for trials in which several doses of the same extract were compared. The Task Force was able to find 15 dose-finding studies for immunotherapy; nine were on SCIT, four on SLIT and two on venom immunotherapy [22]. Data from these dose-finding trials are also considered as useful evidence in this review.

Below we discuss the evidence we found for SCIT and SLIT in papers that fulfil the above mentioned criteria to finally summarize them in **Table 1**.

Patient's selection: for which allergic diseases has allergen specific immunotherapy efficacy been shown?

Apart from the classical allergic disease, allergic rhinitis (AR), for which immunotherapy was indicated since the first guidelines [23], SCIT and SLIT efficacy

has been studied in several other IgE-mediated pathologies. The first on the list was allergic asthma, followed by allergic conjunctivitis, atopic dermatitis, allergy to latex and food allergy. Evidence for SCIT and SLIT efficacy in each of these pathologies is analyzed below.

SCIT in patients with allergic rhinitis

In a Cochrane meta-analysis Calderon *et al.* were the first to show SCIT efficacy for seasonal allergic rhinitis in 2007. These investigators showed a high standard mean difference, indicating a large effect [24] of SCIT on symptom improvement (-0.73) with a moderate-to-large effect (-0.57) on medication scores [25]. Moreover, five of the dose-finding trials [22] were of SCIT for seasonal allergic rhinitis, showing a dose-response. Thus the evidence for SCIT pollen being effective in AR is robust. For perennial allergic rhinitis, though, at this point we can only mention some DBPC-RCT, most of them conducted more than a decade ago: SCIT improved allergic rhinitis due to house dust mite (HDM) (GRADE: high quality of evidence) [26,27] and

Table 1. Immunotherapy efficacy for different allergic diseases and allergens

Efficacy		SCIT		SLIT	
		Sx [†]	Med	Sx	Med
Pathology	Allergic rhinitis	+++	+++	+++	+++
	Asthma	+++	+++	++	+++
	Allergic conjunctivitis			++	+
	Atopic dermatitis	Side effects ++		++	
	Hymenoptera allergy	+++		Only for large local reactions	++
		Efficacy SCIT		Efficacy SLIT	
Allergens	Pollen, grass	+++		+++	
	Pollen, trees	+++		+++	
	Pollen, weeds	+++		+++	
	HDM	Not for rhinitis (only scarce data) +++		++	
	Epithelia	+++		Few data	+
	Molds	++		++	
	Food	+		Experimental	++
	Latex	AEs ++		++	
	Hymenoptera	+++		Only for large local reactions.	++
Non related multi allergen IT		Old studies ++		Dual SLIT [‡] ++	

[†]A positive effect on symptoms has been shown by Cochrane meta-analysis, systemic meta-analysis or in the dose-finding studies.

[‡]With dual SLIT we refer to SLIT given with two different un-related allergens simultaneously, be it from the same vial or from different vials.

AE: Adverse events; AR: Allergic rhinitis; HDM: House dust mite; Med: Medication; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy; Sx: Symptoms; Syst.rev.: Systemic reviews.

Quality of evidence: +++ High; ++ Moderate; + Low quality/ negative data (Data from: [Cochrane] meta- analysis, syst.rev. and dose-finding studies).

Box 1. Factors that influence reported efficacy of sublingual immunotherapy in trials.	
	Higher efficacy is found when:
Dosing	Higher doses (for effective grass SLIT the daily SLIT dose was the monthly SCIT dose)
Frequency of administration	Daily dosing
Administration schedule	Starting 12 weeks [40] - 4 months [41] before season [†]
Mono-polysensitized	Mono-SLIT in patients sensitized to allergens with overlapping season might not be as effective [42]
Asthma maintenance inhaled corticosteroid dose	Efficacy can better be shown when inhaled corticosteroid doses are gradually tapered
[†] Although improvement has also been documented when starting co-seasonally, the best improvement seemed to be obtained when starting well before the allergen season.	

to cat (GRADE: moderate quality of evidence) [28–31] with even some effects five years after discontinuation (GRADE: low quality of evidence) [32], but the results with dog extracts were contradictory (GRADE: low to very low quality of evidence) [32,33].

The exact allergens used in the trials mentioned above, including those from the Cochrane meta-analysis were mostly pollens: mixed grass (16 trials), ragweed [12], tree (9: birch, cedar, *Juniperus ashei*, cocos), parietaria [6] and the pollens of timothy grass [5], orchard grass [2] and one bermuda grass. Allergens used in the dose-finding studies were animal dander [3], ragweed [2] and timothy grass pollen [1]. See **Table 1** in which all these findings are resumed

SLIT in patients with allergic rhinitis

In a Cochrane meta-analysis Wilson *et al.* were the first to show SLIT efficacy for allergic rhinitis in 2005 [34]. Adding the latest trials, these data were confirmed more recently with a higher standard mean difference in a Cochrane meta-analysis by Radulovic *et al.* [35]. As opposed to the SCIT meta-analysis mentioned above, here trials on both seasonal and perennial AR were included. Investigators found a moderate effect of SLIT on AR symptoms and medication scores (-0.49 and -0.32, respectively). In systematic reviews carried out by our group on SLIT, in children in which the quality of the evidence was evaluated with Delphi [36] and later with GRADE [37,38], we concluded that the efficacy of SLIT depends on several factors (see **Box 1**). Moreover the quality of the evidence also depends on the allergen. High quality evidence exists for high-dose grass SLIT and the evidence on HDM SLIT in AR was very recently up-graded to high-moderate quality [39]; before publication of this last trial it was of moderate-low quality because almost all HDM trials had been done in asthmatics. The evidence for mold efficacy is of low-quality. Most lately conducted high-quality trials were with tablet formulations of grass, ragweed and

HDM. As such, total quality of evidence for the tablet formulation outweighs that for liquid SLIT.

A similar analysis by Lin *et al.* that included all age-groups concluded that there was moderate evidence for a decrease in rhinitis symptoms [43].

The exact allergens used in the SLIT trials on AR included in the meta-analysis (Radulovic) were grass pollen [23], tree pollen [9], house dust mite [8], parietaria [5], ragweed [2] and cat [1]. The allergens used in dosing studies were grass [2], tree and ragweed pollen (each 1). From the SLIT trials some basic rules that might improve SLIT efficacy have been learned, see **Box 1**.

SCIT in patients with allergic asthma

5 years after a negative paper in the late 1990s set back the use of SCIT in allergic asthma [44] Abramson *et al.* were able to reverse the public opinion with a positive Cochrane meta-analysis [45]. 7 years later an updated Cochrane meta-analysis by the same group was able to show with even more conviction the positive effects of SCIT on asthma in the sense of a reduction in symptoms and a reduction in medication scores [46].

An even more recent systematic review on SCIT in children [47] concluded that there exists high quality evidence for HDM SCIT efficacy in pediatric asthma symptom and medication reduction, but the evidence for mold (low quality) and grass pollen (very low quality) SCIT in seasonal asthma is very scarce. Another systematic review of SCIT in pediatric patients concluded that the evidence for asthma symptom reduction was of moderate strength and low for the reduction in medication scores, without a detailed analysis per allergen [48].

Allergens used in studies included in the Cochrane meta-analysis were HDM [45], pollen (27, several grasses, ragweed, olive, birch), animal dander [10], *Cladosporium* [2], latex [2] and 2 studies used multi allergens. Allergens used in the three dose-effect studies were HDM [2] and allergen mix. Again, see **Table 1** in which all these findings are summarized.

SLIT in patients with allergic asthma

There is no Cochrane meta-analysis on SLIT in asthmatic patients; although the latest complete Cochrane meta-analysis on SLIT included trials in patients with allergic rhinitis with or without asthma, no separate analysis on asthma outcomes was presented [35].

The joint conclusion of the meta-analysis [49] and the systematic reviews [38,43,48] is that there exists strong evidence exists for a reduction in symptoms and asthma medication. However, the evidence mostly comes from HDM-SLIT trials. Evidence for grass pollen SLIT in seasonal asthma, in both adult and pediatric patients, is scarce.

Allergens used in studies included in the meta-analysis and systematic reviews were HDM [10], grass pollen mix [2] and pollen mix, olea pollen and alternaria (each one). The tree-SLIT drops dosing study [50] recruited children with AR, but 40% had also seasonal asthma.

SCIT for allergic conjunctivitis

No meta-analysis or systematic reviews have been done specifically on SCIT in patients with allergic conjunctivitis (AC). In one systematic review on immunotherapy in pediatric patients, the authors concluded in a sub-analysis of SCIT for AC that the strength of the evidence was low for SCIT improving conjunctivitis symptoms [48]. Another systematic review found high quality evidence for a reduction in conjunctival provocation testing [47]. Most randomized trials report on the total nasal symptom score, which ocular symptoms are part of. Ocular symptoms are rarely reported separately. Charpin *et al.* conducted a double blind placebo control (DBPC) trial in ARC patients and reported a 41% reduction in AC symptoms ($p = 0.02$) [51]. One of the very few randomized trials of SCIT in AC concluded with statistical significance that SCIT (62% pollen, 19% HDM) was more effective than local pharmacotherapy in reducing the AC symptoms [52].

SLIT for allergic conjunctivitis

A Cochrane meta-analysis showed a moderate reduction in symptoms scores (SMD -0.41), without finding any effect of SLIT on AC medication scores. The conclusions of systematic reviews were in the same line: there is moderate evidence that SLIT reduces AC symptoms, but no effect on medication scores was found [43,48].

The allergens included in the reviews were grass pollen [19], tree pollen [10], HDM [6], weeds [6] and cat [1].

SCIT & SLIT for atopic dermatitis

Immunotherapy for atopic dermatitis has only recently been studied. One of the problems seen in this context is the initial flare in dermatitis (AD) symptoms that prevent a considerable number of patients from

continuing the hyposensitization treatment. Even so, there exists now one meta-analysis of randomized controlled trials of SCIT in patients with atopic dermatitis concluded that SCIT has a significant positive effect on atopic dermatitis (numbers needed to treat: three); consequently the authors remark that there is moderate-level evidence for the efficacy of SCIT against atopic dermatitis [53].

For SLIT in AD patients a DBPC trial with HDM SLIT in children showed statistically significant improvement in the mild-moderate AD group from nine months of treatment onward [54].

Evidence of efficacy for dual and poly-allergen immunotherapy: SCIT & SLIT

In the general population poly-sensitization is more prevalent than mono-sensitization [55,56]. The same holds true for patients with allergic rhinitis and mild-moderate asthma [57-59], and for the majority of the subjects recruited recently in most clinical trials on immunotherapy [60]. Thus the question about the efficacy of multi-allergen immunotherapy is highly meaningful, as many patients are poly-sensitized and probably many of them poly-allergic, but almost all trials have been conducted with mono-allergen products. Multi-allergen SCIT was effective in several of the first DBPC trials on SCIT conducted decades ago. Johnstone convincingly demonstrated the efficacy and dose-responsiveness of SCIT in asthmatic patients in a 14-year DBPC study [61]. Some years later Lowell and Franklin did their elegant experiments displaying the effectiveness, specificity and dose-response effect of ragweed immunotherapy, given in a mix with other allergens [62,63]. Contrarily, the only multi-allergen trial included in the Abramson Cochrane meta-analysis [44] was negative. However, no randomized, multi-allergen SCIT trials have been carried out with today's standardized extracts.

As for sublingual immunotherapy, dual SLIT with two non-related allergens is effective given separately and not mixed together. After some preliminary encouraging trials [64], recently generated high quality evidence supports the clinical and immunological effectiveness of a dual SLIT with HDM-grass pollen drops, with beneficial effects even persisting one year after a 12-month treatment in allergic children [65]. Multi-allergen SLIT with ten allergens, however, does not seem to work [66]. For the mono-allergen grass tablets two post-hoc analysis showed SLIT efficacy was at least as strong in multi-sensitized rhinitis patients, compared with mono-sensitized patients [60,67]. In drawing conclusions out of these last observations it must be taken into account, however, that the polysensitized patients were sensitized to allergens not present

Table 2. Subcutaneous immunotherapy and sublingual immunotherapy safety under certain conditions [†]			
		SCIT	SLIT
Age	3+ years	Doubtful/minor	Doubtful/minor
	4+ years	Doubtful/minor	No
	5+ years	No	No
Medical conditions	Pregnancy, continue if already on IT	No	Doubtful/minor [‡]
	History of organ transplant	No	?
	Cancer in remission	No	?
	Cerebro-vascular disease	No	?
	HIV sero[+]	No	?
	Hypertension	Doutful/minor	?
	AIDS	Doubtful/minor	?
	Cancer still under treatment	Doubtful/minor	?
	Pregnancy: start immunotherapy	Doubtful/minor	?
	Coronary artery disease, arrhythmias	Doubtful/minor	?
	Autoimmune disease	Doubtful/minor	?
	Severe asthma	Major	?

HIV sero[+]: patients with seropositivity to human immunodeficiency virus, but not yet AIDS; SCIT: Subcutaneous immunotherapy; SLIT: sublingual immunotherapy.
[†]Data in this table on medical conditions are based on the results from an AAAAI membership survey 2012. (References: 84 and 85)
[‡]Reference 100.
Coding safety issues: major; doubtful/minor; no= no apparent safety issues; ?= do not know.

during the grass-pollen season and outcome measures were related solely to the grass-season.

Direct comparisons of SCIT & SLIT in the same trial

Very few trials have directly compared SCIT to SLIT. The only reliable design of such comparison is a randomized, placebo controlled, double-blind double dummy setup. Three such studies have been published till today and one more is being carried out at this moment. Danish investigators reported the first results of 71 birch allergic adults with hay fever, treated for three years [68]. The other two studies were with HDM [69,70]. In all three trials the conclusions were in the same line: both SLIT and SCIT were superior to the placebo or control groups and there was a tendency for SCIT being superior to SLIT; the latter without reaching clear statistical significance in most parameters. Details of these trials have nicely been reviewed in recent publications [71,72]. Dretzke *et al.* conducted an indirect meta-analysis of the comparison of SCIT and SLIT for the treatment of seasonal allergic rhinitis. The investigators concluded that although there is clear evidence of effectiveness of both SCIT and SLIT, superiority of one mode of administration over the other could not be consistently demonstrated through indirect comparison [1].

Long-term efficacy

There are no meta-analysis nor systematic reviews on the long-term efficacy of SCIT or SLIT, but there do exist some individual trials that have shown the long-term efficacy of SCIT and SLIT. Twelve years after a three year’s treatment of grass pollen SCIT, nasal symptoms and seasonal asthma were still reduced in the active group, although skin test reactivity was slowly returning. The well-known PAT study showed reduced development of asthma in children with allergic rhinitis seven years after a three year course of SCIT [73]. With SLIT, efficacy has been seen many years after termination of treatment [74]. In a SLIT study by Margogna *et al.* a reduction in the development of asthma in AR children was shown [75]. Disease modification was demonstrated by AR symptom reduction seen two years after discontinuation of a 3 year’s course of timothy grass sublingual tablets [76,77].

Safety: adverse events & contra-indications

It is common knowledge that SLIT is safer than SCIT, with no fatal events reported for SLIT at this time and severe systemic adverse events are extremely rare [78]. As SLIT has been administered to young children, more safety data exist on SLIT in the under-five age group [79–81]. However, local adverse events, e.g. itchy mouth, are quite common for the first weeks of sublingual

allergy tablets, as with the tablet as there is no up-dosing or up-dosing is done with only three steps. The dose-response effect for SLIT safety had already been shown in early studies [82]. With drop SLIT up-dosing is generally accomplished within a month; with this dosing schedule the author's experience is in line with data from trials, observing a low frequency of local side-effects and very rare gastro-intestinal symptoms.

As SLIT is considered safer than SCIT, it is tempting to switch patients with systemic adverse reactions from SCIT to SLIT. Two reports in literature of anaphylaxis after the first dose of the SLIT grass tablet in patients with systemic adverse reactions to SCIT previously might encourage this practice [83]. The authors agree that patients with systemic reactions due to SCIT should not receive the direct full maintenance dose of SLIT as is the case with the grass tablet SLIT. However, careful up-dosing of SLIT drops in the physician's office might be a viable option for these patients, practiced with success (personal communication).

Historically, age and some medical conditions have been considered (relative) contraindications for allergen immunotherapy [4]. A survey among members of the American Academy of Allergy, Asthma and Immunology showed, however, that there is experience among membership in treating patients with certain chronic medical conditions with SCIT [84,85]. Based on this experience it seems that SCIT in patients with a past history of cancer or a solid organ transplant or HIV seropositivity but not yet AIDS does not pose any additional risk of importance (see Table 2). Also the age-limit for SCIT is no longer set at five years [4]. This is a field that still needs further exploration. For SLIT there are some data on children from three years up, and the continuation of SLIT during pregnancy, but no data is available for SLIT in patients with other chronic medical conditions.

Adherence & cost Issues: SCIT versus SLIT

According to the World Health Organization, adherence is *"The degree to which the person's behavior corresponds with the agreed recommendations from a health care provider"* [86]. As with any medical treatment, good adherence is needed to obtain the best clinical outcome. This definitely applies to allergen immunotherapy. There are different factors that affect adherence between SCIT and SLIT (Table 3). For SCIT, the inconvenience of administration in a health care facility and the risk of anaphylaxis are main issues, while for SLIT the difficulty is daily dosing. For both treatments, costs to the patient can be a major impediment to continued adherence.

Studies have shown that adherence to both SCIT and SLIT is suboptimal with minimal differences in the degree of adherence between the two types of immunotherapy treatments. In The Allergies, Immunotherapy, and Rhinoconjunctivitis Survey (AIRS) performed in the US questioning health care providers who prescribe primarily SCIT, found that only about a third completed three years of immunotherapy [87]. A retrospective review evaluated US veterans' adherence to SCIT over a 10-year period [88]. Adherence was defined as individuals who had received their first injection of AIT and who had received more than 50% of the recommended number of injections at five set intervals after initiation of SCIT: 0–3 months, 3–6 months, 6–12 months, 12–24 months, and 24–36 months. Adherence rate was 46.7% in patients 18–35 years, 58.3% in patients 36–65, and 78.7% in 66 years and older. Panjo *et al.* showed the adherence with SLIT by both tablet and drops varied with age, with only 30% of the 3–4 year olds completing 2 years of therapy with higher rates in older children [89]. A retrospective analysis of a community pharmacy database from The Netherlands evaluated immunotherapy

Table 3. Immunotherapy adherence issues.

Impediments with adherence: Subcutaneous immunotherapy	Impediments with adherence: Sublingual immunotherapy	Ways to Improve Adherence
Inconvenience having to go to a health care provider's office for administration	Inconvenience of daily treatment	Education and Dialogue with patient, parent, and/or caregiver prior to start of immunotherapy
Risk of anaphylaxis	Local side effects, especially mouth and GI	<i>What is allergen immunotherapy?</i>
Requires needle injection	Time required to see clinical improvement	<i>How does allergen immunotherapy work?</i>
Time required to see clinical improvement	Cost issues	<i>Benefits and risks of allergen immunotherapy</i>
Time loss from work or school to receive SCIT		<i>Time commitment to treatment</i>
Cost issues		<i>Which is best for the patient, SCIT vs SLIT</i>
		Cost issues
		Government and Insurance coverage
		Out of pocket costs for the patient
		Follow-up after initiation of immunotherapy
		Frequent office visits
		Follow-up phone calls by a nurse

Table 4. Some practical advice for subcutaneous immunotherapy – sublingual immunotherapy selection.

Issues to be dealt with	Pitfalls	Solution
Correctly diagnosing the causal allergens for the patient's disease	- Existence of locally important allergens. - Differences in extract potency: very potent extracts give many [+] results	Select only those very few allergen(s) of importance considering: - Detailed clinical history - Evt. + serologic testing - Evt. + provocation testing
Selecting patients: efficacy I: the disease	SCIT: for some allergic diseases efficacy has not been proven SLIT: for some allergic diseases efficacy has not been proven	For differences between SCIT and SLIT, see Table 1
Selecting patients: efficacy II: the allergens	SCIT: for some allergens efficacy has not or only poorly been proven SLIT: for some allergens efficacy has not been proven	Depending on the allergen(s) selected for immunotherapy, see which allergen has better quality of evidence of efficacy, see Table 1
Adherence	Most important: what does the patient prefer!	
	It might seem patients adhere better to: - SCIT, as there is more control on the administration: however some prefer to avoid injections/waiting time. - SLIT, as administration route is more patient-friendly: however daily administration is easily forgotten	Optimize office settings to keep waiting time pre-injection low. Administration in other doctor's office. Assistant contacting patients at regular intervals to remind them (SCIT and SLIT) Reminder with electronic devices. For more see Table 3
Costs	Multiple allergen SLIT might be too expensive	- Discuss costs with the patient: - from 6mo on IT lowers total costs - long-term benefits of immunotherapy 1st be sure to cautiously select only those (very) few allergens of clinical importance to the patient, then: - only a few allergens: SLIT could be as good an option as SCIT. - multiple allergens: SCIT
Safety	SLIT seems more safe than SCIT, but might present systemic reactions at the 1 st dose	- first dose should be taken in doctor's office. - do not switch patients with systemic adverse reactions to SCIT, directly to maintenance dose SLIT

SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

adherence from 1994 and 2009 [3]. Two thousand seven hundred ninety-six patients received SCIT, and 3690 received SLIT. Overall, only 18% of users reached the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively ($P < .001$). Other independent predictors of premature discontinuation were prescriber, with patients of general practitioners demonstrating longer persistence than those of allergists and other medical specialists;

single- allergen immunotherapy: lower socioeconomic status; and younger age.

In private allergy clinics in the USA, a retrospective review of adherence of patients on SCIT and SLIT drops from 2005–2011 showed that only 32.5% of patients completed treatment; 35% of SCIT and 23.7% of SLIT patients [90]. Median time on therapy was longer for SCIT patients (3.6 years) versus SLIT patients (2.6 years). Similar patterns were seen among children, with 35.4% completing treatment and lon-

ger median time on treatment for SCIT patients (4.7 years) versus SLIT patients (3.5 years). Since SLIT was not approved by the FDA in the USA at this time, patients had to pay the entire cost of SLIT while health insurance may cover a certain percentage of the costs of SCIT. Hankin *et al.* evaluated Florida Medicaid claims data [1997–2004] of children (<18 years of age) given new diagnoses of AR and looked at factors in adherence in those children who received SCIT [91]. Approximately 53% completed less than a year and 84% completed less than three years of SCIT.

Patient costs play a major issue in adherence to allergen immunotherapy. SCIT has both direct costs related to the vaccine expense and cost for each injection. There are also indirect costs associated with missing work or school to have SCIT administered by a health care provider. With SLIT, there is only the direct cost related to vaccine expense. A study from Spain looked at adherence to both SCIT and SLIT during an economic recession in Europe [92]. They showed that patients who initiated immunotherapy before the development of the global economic crisis had better adherence compared with those treated during the recession period. The authors noted that Spanish wages have not increased at the same rate as the cost of vaccines between 2006 and 2010.

Studies show the economic benefit in the use of AIT [93–95]. Hankin *et al.* did a retrospective [1997–2009] Florida Medicaid claims analysis comparing mean 18-month health care costs of adult and pediatric patients with newly diagnosed AR who received *de novo* SCIT and were continuously enrolled for 18 months or more versus matched control subjects not receiving SCIT [96]. They found significant cost saving in both the adults and children receiving SCIT beginning at 3 months after initiation of SCIT and continuing for the 18-month follow-up. In a German study of children and adolescents with allergic asthma to dust mites, it was shown that the children that received SCIT had a reduced need for allergy medication intake and demonstrated a cost-saving effect [97]. In comparing costs of SLIT to SCIT, Pokladnikova *et al.* showed that SLIT represents a less expensive alternative relative to SCIT from both direct and indirect costs. However, from a patient's perspective, SCIT offered a less expensive alternative for patients who do not experience loss of income and travel costs associated with treatment [98].

Another aspect to consider in the cost/adherence issue with SLIT is treatment schedule. Studies with preseasonal/coseasonal and year-round therapy with SLIT timothy grass tablets have both shown efficacy in clinical symptoms and decreased need for medication. There is a suggestion that a disease modifying effect for at least 2 years may be achieved after 3 years

of year-round therapy, but costs are obviously increased if treatment is year round compared with just about 6 months out of the year [77].

What can be done to improve adherence in the patient population that would benefit from allergen immunotherapy (Table 3)? First, patients need to be clearly educated on the long-term benefits of allergen immunotherapy whether SCIT or SLIT is used. They need to understand that this is a vaccine and unlike medications, they will not see immediate improvement in their allergy symptoms. Also they must understand the need for at least a 3-year commitment to get maximum benefit from receiving allergen immunotherapy. Health care providers must engage the patient in dialogue about the pros and cons for each type of allergen immunotherapy to determine whether SLIT or SCIT is a better choice for their allergies. A partnership between the health care provider and the patient or caregiver must develop so that a truly informed decision can be made. Without patient buy-in, adherence to a long-term treatment like allergen immunotherapy is highly unlikely. As already mentioned, costs are an issue to adherence. Payers of health care such as government and insurance companies need to be informed of the cost effectiveness of the treatment so that coverage for allergen immunotherapy can be made easily available to more allergy sufferers. Patients need to know the out of pocket costs prior to initiation of treatment so that they can budget for the expense. Fundamental to good adherence is frequent follow-ups visits of the patient to the prescribing clinician. Seeing the patient back on a regular basis can reinforce adherence and thus improve outcomes [99]. In the author's experience, follow-up calls on a regular basis from the clinician's nurse can also help improve adherence.

Conclusion

In conclusion, once the decision has been made to treat the patient with immunotherapy, the selection of SCIT or SLIT should depend on the efficacy data until now available for the different allergic diseases and per allergen, as can be found in Table 1. If a patient has multiple sensitizations that are of clinical importance (multi-allergic), probably SCIT might be the better option, also taking the cost-issue into account. However, if the patient has multiple sensitizations, but only one or two allergens seem clinically important, SLIT is just as good an option. Apart from the strength of evidence for efficacy, also the patient's preference (closely linked to adherence, see Table 2), cost and safety (see Table 3) should be taken into account to make the final decision: SCIT or SLIT. In this whole process of decision-making the physician

can come across several pitfalls discussed in this paper, which are summarized in **Table 4**. For example, for a patient with HDM allergic asthma, SCIT has better clinical evidence of efficacy, but if it is moderate-severe asthma, SLIT might be a better alternative, as long as up dosing is done gradually in a careful way with the first dose taken in the physician's office. Finally, a severe asthmatic patient with multiple allergies might be better off not receiving AIT at all.

SLIT has broadened the treatment options allergists can offer to their patients. With grass and ragweed SLIT tablets near approval in the US, post-marketing experience with this modality shall accumulate over the coming years, helping us make better treatment decisions.

Future perspective

In several parts of the world (e.g., Europe and Latin America), physicians have already had both treatment options, SLIT and SCIT, for some years. In the USA, allergy specialists are about to start experiencing how to use SLIT, now that the approval of SLIT grass and ragweed tablets is imminent. In the authors' view the addition of SLIT to SCIT augments the treatment options and increases the number of allergic subjects to which immunotherapy can be offered. However, caution should be taken and the prescription of SLIT should not be allowed to non-allergy specialists, because administering SLIT in poorly selected patients might be detrimental. Some SLIT preparations have been of low quality, but with more stringent guidelines

Executive Summary

- Appropriate selection of allergen immunotherapy requires:
 - A clear medical history of allergic disease
 - The presence of indications for allergen specific immunotherapy (AIT)
 - Positive allergy testing by either a skin test or an *in vitro* method that correlates with the patient's history.
 - Eventually provocation testing can be used to confirm that the sensitization to a certain allergen is linked to the patient's symptoms.
 - Selection of only few allergens for immunotherapy: those that elicit symptoms and taking into account cross-reactivity.
- In patients with allergic rhinitis, the strength of evidence of efficacy of AIT according to allergens is:
 - pollen: subcutaneous immunotherapy (SCIT) high, sublingual immunotherapy (SLIT) high
 - HDM: SCIT high, SLIT moderate-high
 - Cat: SCIT moderate
 - Dog: SCIT low
 - Mold: SLIT low.
- In SLIT the evidence for tablets outweighs the evidence for drops. House dust mite tablets have not been licensed yet.
- In patients with allergic asthma, the strength of evidence of efficacy of AIT in general for SCIT and SLIT is moderate. According to allergens the evidence is:
 - Pollen: adult subcutaneous immunotherapy (SCIT) high, (children very low). sublingual immunotherapy (SLIT) tree pollen moderate. Grass pollen evidence is scarce.
 - House dust mite (HDM): SCIT high (both adults and children), SLIT high.
 - Mold: SCIT low, SLIT very low (scarce evidence).
- Evidence for SCIT efficacy in allergic conjunctivitis is low
- Evidence for SLIT efficacy in allergic conjunctivitis (AC) is moderate, mostly based on pollen SLIT.
- Evidence for SCIT efficacy in atopic dermatitis is moderate.
- Evidence for SLIT efficacy in atopic dermatitis is very scarce (moderate for HDM).
- Polyallergen SCIT was effective in trials published half a century ago.
- Mono-allergen SLIT in polysensitized subjects is effective.
- Duo allergen SLIT with non-cross reacting allergens is effective.
- Polyallergen (10 allergens) SLIT drops are not effective.
- For both SCIT and SLIT there are some moderate quality data on long-term effectiveness, but there are no systematic reviews on this subject.
- SLIT has a better safety record than SCIT concerning severe and anaphylactic reactions. Pollen tablet SLIT commonly has local reactions the first weeks of treatment, these generally disappear with continued administration.
- Adherence is generally the same in SCIT vs SLIT though different factors effect adherence with each type of treatment
- Cost is a major factor in adherence
- Data is accumulating on the cost effectiveness of immunotherapy in certain atopic diseases

from regulatory authorities several of these might disappear from the market in the future. Combinations of SLIT and SCIT in the same patient with the same or different allergens, simultaneously or subsequently, are treatment modalities hardly studied today that might be explored in the future. Other developments that can be expected include the development of hypoallergenic molecules, adjuvants to enhance penetration of the allergen into the body or into the target-cells, as well as adjuvants with immunologic effects and finally, a multi-allergen SLIT tablet, containing a 2–3 of the most important allergens combined with above mentioned adjuvant(s), might become available

years from now, be it for treatment or may be even for primary prevention.

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