

EXPERT
REVIEWS

Balancing efficacy against safety in sublingual immunotherapy with inhalant allergens: what is the best approach?

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Over the last 20 years, studies and clinical trials have demonstrated efficacy, safety and cost-effectiveness of sublingual immunotherapy (SLIT) for respiratory allergic diseases. Nevertheless, it seems to be mostly used as a second-line therapeutic option, and adherence to treatment is not always optimal. Selective literature research was done in Medline and PubMed, including guidelines, position papers and Cochrane meta-analyses concerning SLIT in adult patients. The most recent reviews confirm SLIT as viable and efficacious treatment especially for allergic rhinitis, even if the optimal dosage, duration, schedule are not clearly established for most of the products. Despite an optimal safety profile, tolerability and patient-reported outcomes concerning SLIT have received poor attention until now. Recently, new tools have been specifically developed in order to investigate these aspects. Regular assessment of tolerability profile and SLIT-related patient-reported outcomes will allow balancing efficacy with tolerability and all the other patient-related variables that may affect treatment effectiveness beyond its efficacy.

KEYWORDS: adherence • effectiveness • efficacy • patient-reported outcomes • safety • sublingual immunotherapy • tolerability

Current estimates suggest that more than 150 million people suffer from respiratory allergies in Europe. With a prediction of more than 300 million in the next decade, allergies constitute a public health threat of pandemic proportion [1,2]. The importance of respiratory allergies is often underestimated [3] both by non-allergist physicians and by patients. Besides symptoms and disease progression, the impact of allergy on the quality of life and on economics should be taken into consideration. Several studies have shown that children, adolescents and adults with allergic conditions are at a disadvantage, which affects school performance, work performance and social life [4,5]. It implies consequences both on macroeconomics and health economics. Asthma and rhinitis are estimated to result in more than 100 million lost workdays and missed school days each year in Europe [6]. Moreover,

they affect the optimal productivity of people who go to work but suffer from active respiratory allergy (presenteeism). The cost of asthma is calculated at more than €25 billion yearly [7], and the current loss due to untreated allergic rhinitis-related presenteeism is estimated at approximately €100 billion annually to employers [8]. Of course, the impact of allergy on the European economy entails direct costs too. Considering asthma alone pharmaceutical costs are calculated to be €3.6 billion per year and healthcare services stand at a further €4.4 billion per year [7].

Moreover, concerning pharmacotherapy some drawbacks should be pointed out: i) lack of optimal control is reported by approximately 50% of treated patients with asthma and/or rhinitis [9]; ii) current medications do not have disease-modifying properties, so that symptoms relapse after discontinuation of daily

therapy [10]; iii) long-term use of medications is needed but it may result in adverse effects [11,12]. Allergen-specific immunotherapy (AIT) has been used for over a century and a great amount of evidences has increased the knowledge about its mechanisms, efficacy, safety, long-term effects [13]. For many years, studies and clinical trials focused on subcutaneous immunotherapy (SCIT), but more recently sublingual immunotherapy (SLIT) was demonstrated to be comparably effective and safer than the subcutaneous route and currently it is extensively performed [14,15]. Nevertheless, compared with pharmacological treatment that is currently the first-line approach, SLIT seems to be mostly used as a second-line treatment, for patients in whom the use of traditional medications is unsatisfactory [16]. AIT is able to modify the natural history of allergic disease by improving symptoms, preventing progression and reducing the risk of new sensitizations. It implies a significant reduction of direct and indirect costs of respiratory allergies [17]. Thus, when appropriate AIT should be considered as a first-line treatment strategy.

Methods

For the present review, a literature search was performed including published international guidelines, recommendations, position papers, systematic reviews and Cochrane meta-analyses concerning SLIT in adult patients. A selective search on PubMed and Medline (main keywords: sublingual allergen-specific immunotherapy, efficacy, safety, tolerability, patient-reported outcomes, effectiveness) was also carried out. Large double-blind, placebo-controlled studies during recent years have been in particular considered.

Efficacy

In the past 20 years, SLIT has emerged as a viable and efficacious alternative to SCIT and with an increased safety profile.

SLIT has been extensively studied in Europe and in the USA, where it appears to carry a minor risk of severe systemic reactions. Actually, it is also widely used in clinical practice in many European countries [18] and its practice is also increasing in the USA [19]. It should be noticed that in the absence of the US FDA-approved extracts, the increase in SLIT use in the USA is off-label, unregulated and often performed by non-allergists [20]. Moreover, in Europe too, the optimal dosage (differently from SCIT) [21], duration and treatment schedule are not clearly established making a consensus on treatment difficult at present [20]. However, the clinical efficacy has been evaluated in many trials performed with different SLIT extracts that can be administered in the form of drops or dissolving tablets and that can be standardized using both biologic or immunologic methods. Today, the most widely used system to classify and grade the strength of experimental evidence is that proposed by Shekelle *et al.* [22]. According to this system, the results of meta-analyses of randomized controlled trials (RCTs) offer robust evidence of the efficacy (or non-efficacy) of a treatment/intervention. Additional data can be obtained from meta-analyses, such as quality of the trials and heterogeneity of variables considered. Therefore in our review, we refer to the results of these studies concerning SLIT efficacy.

Several meta-analyses have been performed on SLIT, four in allergic rhinitis and three in allergic asthma (TABLE 1). The first meta-analysis included 484 SLIT patients and 475 controls (adults and children) from 22 studies published up to September 2002. A significant reduction of symptom and medication score was only demonstrated in adults [23]; in addition, the authors did not identify a greater improvement according to the treatment duration. The same group published recently an updated systematic review [24]. The studies suitable for the inclusion were 49. A significant reduction of symptom and medication score compared with placebo was confirmed but in

Table 1. Last published meta-analyses on sublingual immunotherapy.

Study (year)	Allergic disease	Patients (n)	Symptom score SMD (95% CI)	Medication score SMD (95% CI)	Ref.
Wilson <i>et al.</i> (2005)	Rhinitis	959 (A, C)	0.42 (-0.69, -0.15) $I^2 = p < 0.001$	0.43 (-0.63, -0.23) $I^2 = p < 0.001$	[25]
Calamita <i>et al.</i> (2006)	Asthma	1706 (A, C)	-0.38 (-0.79, -0.03) $I^2 = 64\%$	-0.91 (-1.94, -0.12) $I^2 = 92\%$	[30]
Compalati <i>et al.</i> (2009)	Asthma	452 (A, C)	-0.95 (-1.74, -0.15) $I^2 = 93\%$	-1.48 (-2.70, -0.26) $I^2 = 96\%$	[31]
Di Bona <i>et al.</i> (2010)	Rhinitis	2971 (A, C)	-0.32 (-0.44, -0.21) $I^2 = 56\%$	-0.33 (-0.50, -0.16) $I^2 = 78\%$	[28]
Calderon <i>et al.</i> (2011)	Conjunctivitis	3458 (A, C)	-0.41 (-0.53, -0.20) $I^2 = 59\%$	-0.10 (-0.22, -0.03) $I^2 = 34\%$	[27]
Radulovic <i>et al.</i> (2011)	Rhinitis	5684 (A, C)	-0.49 (-0.64, -0.34) $I^2 = 81\%$	-0.32 (-0.43, -0.21) $I^2 = 50\%$	[26]
Lin <i>et al.</i> (2013)	Rhinitis/asthma	5131 (A, C)	n.d.	n.d.	[29]

A: Adults; C: Children; n.d.: Not declared; SMD: Standardized mean difference.

this paper a trend of greater symptom reduction in studies lasting more than 12 months was observed. Furthermore, better results were also recorded in studies treating house dust mite allergy compared with those treating grass pollen allergy. A meta-analysis only addressed the allergic conjunctivitis [25]. Forty-two trials including 3958 participants were considered as suitable. SLIT induced a significant reduction of total ocular symptom score, but did not affect eye drops use. Subjects actively treated showed an increase in specific threshold dose. Lately, an Italian meta-analysis has evaluated only the allergic rhinitis due to grass pollens. SLIT [26] significantly reduced symptom and medication score in comparison with placebo and was more effective in adults than in children. A pre-seasonal schedule lasting more than 12 weeks improved the clinical efficacy. According to these results, a recent systematic review, including adult and children, supports that SLIT improves asthma symptoms, as 8 of 13 studies reported more than 40% improvement with respect to comparator. The clinical result was less impressive in allergic rhinitis as 9 of 34 studies showed a more than 40% improvement [27].

The efficacy of SLIT in asthma has been evaluated by three meta-analyses. The first included 25 studies on 1706 adults and children [28]. Eight studies were for mites, 14 studies for pollens, 1 study for latex and 2 for mixed allergens. A significant improvement in symptoms was reported in eight studies as well as an increase of FEV1 in four trials. A more focused meta-analysis of nine studies in 452 adults and children treated with house dust mite SLIT for their allergic asthma proved a significant improvement in symptom and medication scores [29]. However, some drawbacks of meta-analyses and systematic review have to be considered. In fact, they are statistical procedures that incorporate the results of different independent studies pooled together in order to provide a quantitative estimate of treatment effects. Included studies have different indications, age groups and allergen preparations. Furthermore, schedule and duration of treatment are diverse and a high heterogeneity can weaken the final data [30,31]. Therefore, the results of meta-analyses can give a general indication about a treatment but cannot give any indication about

the single treatment. Very recently, Bachert *et al.* addressed this problem suggesting to specify the SIT product in any study including it in the title and to avoid unjustified general statements on application routes or patients group [32]. More practically, the clinical benefit of immunotherapy has to be referred to a single brand and not generically to SLIT as a high number of different extracts are now available on the market with different clinical effect and safety profile. An overcoming of the heterogeneity of the meta-analyses and more practical indications come from the so-called big trials of immunotherapy (comprising more than 100 individuals per treatment arm) (TABLE 2). In the first trial after a preliminary dose finding study, which identified as the best option the treatment with rapidly dissolving tablet (Grazax® ALK Abello, Denmark) containing 15 µg of Phl P5 (75.000 SQ-T) [33], a second randomized study was performed using the optimized daily dose according to a pre-coseasonal schedule (4 months prior and during the grass pollen season) [34]. A significant reduction of symptom and medication scores was proved, observed for any individual nasal symptom, including nasal obstruction and eye symptoms, compared with placebo. A second study, using sublingual tablets (Oralair Grasses® Stallergenes, France) with five grass mix (orchard, meadow, ryegrass, seet vernal and timothy species) identified the 300-IR (25 µg of group five major grass allergens) as the optimal dosage for treatment [35]. After a 4-month schedule, an efficacy comparable with the previous study was observed. A more prolonged trial (18 months) with sublingual drops at high dose (40 µg) of six grasses (Allergovit®, Allergopharma, Germany) confirmed the results of the previous studies [36]. It should be noticed that the different timing of the assessment of clinical results makes the studies discussed above not fully comparable. Grazax was also evaluated in the USA with clinical efficacy comparable with the European study [37]. However, all these studies were performed on allergic rhinitis due only to grass pollen. More recently, a multicenter study performed in the USA and in Europe including 784 adults evaluated the clinical efficacy of ragweed immunotherapy, using fast dissolving tablets (12 units of *Ambrosia artemisiifolia*). After 52 weeks with the active treatment, a 27%

Table 2. Big trials of sublingual immunotherapy.

Study (year)	Patients (A/P)	Allergen	Formulation	Mean study duration (weeks)	Reduction symptom Score (%)	Reduction medication Score (%)	Ref.
Durham <i>et al.</i> (2006)	153/150	<i>Phleum P5</i>	Tablet (15 µg PP)	18	-16	-28	[35]
Dahl <i>et al.</i> (2006)	316/318	<i>Phleum P5</i>	Tablet (15 µg PP)	20	-30	-38	[36]
Didier <i>et al.</i> (2007)	155/156	5 grass mix	Tablet (25 µg g5)	20	-27	-46	[37]
Worm <i>et al.</i> (2006)	94/96	6 grass mix	Drops (40 µg g6)	72	-46	NR	[38]
Nelson <i>et al.</i> (2011)	231/225	<i>Phleum P5</i>	Tablet (25 µg PP)	20	-20	-18	[39]
Creticos <i>et al.</i> (2013)	316/318	<i>Ragweed</i>	Tablet (12 U Ambrosia)	52	-27	-36	[40]

A: Active; g5: Five grasses mix; g6: Six grasses mix; NR: Not reported; P: Placebo; PP: *Phleum pratense*; U: Unit.

reduction of symptom score and 36% of medications score was detected [38]. A marked placebo response was observed in these studies, shared with most of immunotherapy trials. The 'clinical trial effect' secondary to more intensive medical care in a therapeutic environment may account, at least in part, for this phenomenon. Nevertheless, there is a remarkable consistency in results among these trials. It is to note that effect sizes reported for SLIT compare favorably with those reported in a recent Cochrane review and meta-analysis of anti-allergic drugs that includes anti-leukotrienes, antihistamines and intranasal steroids [39].

In addition to a significant early clinical effect, a sustained effect of SLIT after its discontinuation was demonstrated for all these grass studies, lasting currently up to 2 years [40–42]. Besides the double-blind placebo-controlled trials mentioned above, some open studies have been performed. A long-lasting effect after SLIT discontinuation is confirmed, even if the different methodology doesn't allow a direct comparison. A prospective open controlled study including patients with different sensitizations with a 15 years follow-up period found that the effects of a 4-year course of immunotherapy persisted more than 5 years [43]. Another 6-year randomized open trial by Tahamiler *et al.* showed that the improvements in allergy symptoms achieved with SLIT were maintained for 3 years after treatment discontinuation [44].

As SCIT, some open studies document that SLIT can modify the natural history of allergic diseases and limit the progression from allergic rhinitis to asthma, when used in pediatric age. A study used grass pollen SLIT according to a coseasonal schedule for 3 years and observed that the risk of asthma development was 3.8 times greater in control than in treated group [45]. Another study performed on 216 children with allergic rhinitis with or without intermittent asthma were randomized to pharmaceutical treatment only or plus SLIT for 3 years. At the end of the study, the incidence of mild asthma was significantly lower in the SLIT-treated arm (odds ratio [OR]: 0.04; 95% CI: 0.01–0.17) along with a decrease of methacholine reactivity [46]. Concerning the possibility that SLIT can prevent the onset of further sensitizations, controversial data are reported in literature [20,45,46].

Despite the favorable results, some unmet needs have to be addressed. The meta-analyses showing clinical efficacy of SLIT are mainly based on the results of RCT performed on grass and mite-allergic patients (68%), whereas only few controlled studies evaluated other relevant sensitizations, such as birch, ragweed, cat and *Alternaria*. Other two problems come currently out in the daily routine such as the patient with multiple sensitizations as well as the elderly allergic patient. Two recent *post hoc* analysis performed in two large studies conducted with grass allergen tablets showed that the clinical improvement is not different between mono- and polysensitized patients in large studies [47,48]. The potential role of SLIT in elderly population has also been recently assessed. A similar trend of efficacy and safety between young (18–28 years) and older (55–65 years) patients was proved by an open Italian study [49] as well as a

significant improvement has been observed in a double-blind controlled trial performed in elderly patients with mite-allergic rhinitis [50]. Additionally, the clinical improvement of SLIT seems to be less impressive in asthma. In fact, many studies were not formally sized and adequately powered for asthma. Several studies of SLIT for grass and mites have failed to show functional improvement or exacerbations reduction. However, it has to be considered that in some of these studies most of patients had minimal symptoms at baseline and throughout the study, likely precluding a detection of a beneficial effect of immunotherapy.

At last, it is worth pointing out that currently clinical efficacy of immunotherapy in patients with allergic asthma and/or rhinitis is mostly evaluated by means of symptoms and medication scores. These tools are not always validated and they are highly affected by variability. Moreover, clinical manifestations represent one of the faces of allergic respiratory diseases. Reliable predictive surrogate markers or biomarkers that may correlate with real clinical end points are necessary both for choosing a tailored immunotherapy treatment and for follow-up. At present, *in vivo* (early and late skin reaction) and *in vitro* (IgE levels, IgG subclasses, mucosal IgA, lymphocyte subsets, cytokines and systemic inflammatory markers) have been proposed as potential surrogate markers. However, an ideal surrogate marker is still not available, given the poor reproducibility, the high costs and the lack of extensive availability of most of these parameters in daily clinical practice [51].

Safety, tolerability & effectiveness

International guidelines for appropriate SLIT clinical trials recommend evaluation of adverse events (AEs) to SLIT as a secondary outcome [52,53]. Nevertheless, data concerning safety are not uniformly and consistently reported in published studies. The lack of a standard grading system for local reactions until now may account for it. In order to achieve the missing goal, a World Allergy Organization (WAO) Task Force has very recently proposed a clinically based grading of the severity of local AEs caused by SLIT after examining the available literature and the post-marketing surveillance data [54]. In general, SLIT has a very good safety profile that is better than SCIT [20]. This advantage allows for home administration [14].

Anaphylactic reactions

Life-threatening reactions after SLIT administration are extremely rare [14,55]. The last published systematic reviews [27], including English language RCTs of SLIT through December 2012, confirm the same observation, since there were no reported episodes of anaphylaxis, life-threatening reactions or death in any treated patient across studies. Apart from clinical trials, to our knowledge 12 cases of anaphylaxis following SLIT administration have been published so far [56–62]. It should be noticed that analysis of those cases points out suboptimal administration conditions, deviating from international guidelines: use of non-standardized extracts, administration of products containing a mixture of many allergens, use of rush

schedule for up-dosing phase, omission of up-dosing phase, over-dosing, administration of SLIT despite previous repeated severe AEs occurred with SCIT. Moreover, one of the reported cases refers to SLIT with latex, a particular allergen that may cause anaphylaxis besides immunotherapy.

Systemic reactions

Non-life-threatening systemic AEs account for a minority of SLIT-related side effects [14,55]. However, the rate of systemic reactions is quite variable in the reported studies. In literature, a matter of concern seems to be the definition of systemic side effects itself. The term 'systemic' indicates a reaction that occurs far from the site of administration. Rhinitis, ocular symptoms, asthma, urticaria, angioedema and hypotension are univocally considered systemic reactions [63]. Since the administration of any allergen, regardless of the administration route, can lead to systemic adverse effects, the WAO grading system for SCIT-related systemic reactions [63] can be properly used for SLIT too. The lack of a uniform classification emerges in regard of side effects involving upper (nausea, stomach ache, vomiting) and lower (abdominal pain, diarrhea) gastrointestinal tract. They are classified as 'local' according to the Medical Dictionary for Regulatory Activities (MedRA) [101] and in general published studies base safety information on that definition [64–66]. Nevertheless some works, including post-marketing surveys [67–71] and a recent systematic review [27], report gastrointestinal manifestations as systemic reactions. The aforementioned WAO document about the grading system for local side effects of SLIT [54] suggests that the gastrointestinal tract reactions should be considered as local, unless they occur in the context of other systemic manifestations. According to that classification, the incidence of systemic AEs can be estimated between 1 and 34% and may occur both during dose escalation (when the up-dosing phase is performed) and maintenance phases [72,73]. A treatment schedule without up-dosing phase has proven to be well tolerated and does not increase the incidence of side effects [35,74,75]. Considering the studies reported in the 2009 WAO position paper [14] and in other reviews [20,64], the overall occurrence of systemic reactions is similar between

placebo and active group. Recent large trials (>200 patients) performed with grass extracts [35,74,75,76–79] confirm the same data. The potential relationship between type of allergen, dose and systemic AEs is not clear because of the small sample size in many of the controlled studies and because of the wide heterogeneity of allergen extracts and treatment schedules. A dose–response relationship is reported in two RCT dose–effect safety studies with grass tablets [76,77] with systemic AEs occurred only in the higher-dose groups. Moreover, severe rhinitis and severe asthma were reported in two different patients who had exceeded their maximum dose of immunotherapy. The manifestations resolved when the patients returned to a lower dose [78].

Excluding suboptimal administration conditions (use of non-standardized extracts, administration of products containing a mixture of many allergens, overdosing), no patient-related risk factors for systemic reactions have been clearly defined [55,80]. Cardiovascular diseases and long-term therapy with non-cardioselective beta-blockers are usually considered non-specific risk factors for systemic AEs [55]. Uncontrolled asthma, oral lesions or infections and previous repeated severe AEs occurred with SCIT may represent specific risk factors [55,79] (TABLE 3).

Local reactions

SLIT AEs mostly consist of local reactions (oropharyngeal or gastrointestinal). TABLE 4 reports the most frequently described symptoms. The incidence of local AEs can be estimated between 50 and 85% [72,81], the rate reported in post-marketing studies is less than 10 per 1000 doses [68,71]. They generally occur with a rapid onset within the first days of treatment, they are self-limiting and subsequently resolve without medical intervention as treatment is continued [14,41,42]. A dose–response relationship is not clearly demonstrated [56,72,73]. According to the review by Gidaro *et al.*, upper and lower gastrointestinal symptoms were more frequent with higher doses, while oral manifestations occurred mostly with low doses of allergen [64]. It should be noticed that at present the distinction between 'low' and 'high' dose sounds totally arbitrary because of different reference materials and methodologies for the determination of

Table 3. Potential factors associated with sublingual immunotherapy related reactions.

Factors	Systemic reactions	Local reactions
Administration-related factors	Non-standardized extracts Allergen mixtures Overdose	Non-standardized extracts Allergen mixtures Overdose
Aspecific patient-related factors	Cardiovascular diseases Long-term therapy with non-cardioselective beta-blockers	
Specific patient-related factors	Uncontrolled asthma Oral lesions or infections Previous repeated severe AEs occurred with SCIT or SLIT	Oral lesions or infections Previous AEs occurred with SCIT or SLIT

AE: Adverse event; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

allergen contents used by different manufacturers [56]. The treatment schedule does not seem to clearly correlate with the incidence of local AEs [55,73], even if local reactions are more frequently reported after the first administration and during the up dosing phase [14,81]. However in many studies, the treatment begins with maintenance dose and no evidence of increased risk of local AEs has been shown to be related to a treatment schedule without up dosing phase [35,74,75]. The potential relationship between the type of allergen and the onset of local AEs is not clearly defined. Potential factors associated with increased incidence of local AEs are: previous severe local reactions to SLIT or SCIT, oral infections or lesions (e.g., ulcer, gingivitis, periodontitis, and so on) [55,80]. Administration procedures that deviate from international guidelines as specified above also represent a risk factor [55] (TABLE 3).

Tolerability & effectiveness

Local AEs threaten neither patient safety nor his/her health. Nevertheless, they are quite frequent in daily clinical practice and may result in poor treatment tolerability, which correlates with the rate of 'dropouts'. In fact, severity, persistence or simply poor awareness of local reactions increase the risk of treatment discontinuation, despite its efficacy [14]. In other words, local AEs may affect the final effectiveness of SLIT. Our group has recently conducted a systematic review of dropout levels in double-blind, placebo-controlled randomized clinical trials (DB PC

RCTs) of SLIT for allergic respiratory disease published up to June 2011 [SENNA G, MAKATSORI M, SCADDING G *ET AL*. DROPOUTS IN SUBLINGUAL ALLERGEN IMMUNOTHERAPY TRIALS – A SYSTEMATIC REVIEW (2013), SUBMITTED]. The overall dropout rate is below 20% in the included studies without significant differences related to study population size, schedule, age and formulation. The dropout rate is actually quite low, but first of all it should be noticed that most of the included trials are not specifically designed to evaluate treatment tolerability and dropout rate. Moreover in many studies, dropout reasons are not extensively reported and described, and not uniformly graded. Second, the RCT setting is quite far from daily clinical practice. In RCT, patients are widely investigated, regularly followed-up and deeply evaluated at each timepoint, and much time is spent for their education. In addition, no cost concerns are present. On the contrary, in daily clinical practice time for deep evaluation of the patient at each visit, and for his/her education is often few and a regular follow-up may be difficult for many reasons [82,83]. Moreover, cost concerns play a crucial role. The different setting in RCT and in real life may account for a different 'dropout' rate that seems to be higher in daily clinical practice [82,83]. Poor attention to treatment tolerability is one possible explanation. In fact, the potential underestimation of local AEs and of their role in treatment discontinuation certainly affect patient adherence [82]. On the other hand, assessment of local AEs is not so easy, since no objective parameters, such as changes in FEV1 or in blood pressure, are available in order to clearly identify them and quantify their severity. The aforementioned document recently stated by a WAO panel of experts [54] will certainly help to improve the approach to local reactions to SLIT. It provides a clear definition of local AEs, according to the MedRA [101]. Moreover, it proposes a grading system based on the previous WAO grading of the systemic side effects [63]. From a scientific point of view, a universally accepted classification and grading of SLIT-related AEs will allow more extensive information about tolerability, more effective comparison between studies and identification of potential risk factors both in clinical trials and in post-marketing surveys. In daily clinical practice, it is expected to enhance doctors' and patients' awareness of local AEs of SLIT. In order to finally improve treatment adherence, it is crucial that the doctor is able to recognize and grade local adverse effects and that the patient knows that they may happen without any risk for his/her safety and health. An unmet need concerns treatment and management of local reactions. No international guidelines focus on the role of premedication, dose adjustment, discontinuation and re-administration, nor operative protocols are available according to the severity of local AEs [63,64]. The proposed grading system for SLIT-induced local reactions may represent the background for the development of shared strategies.

Another crucial component of treatment effectiveness, together with tolerability, are patient-reported outcomes (PRO) [84]. The term refers to any health-related report coming from the patient, without involvement or interpretation by physician or others, including symptoms, health-related quality

Table 4. Described sublingual immunotherapy-related local side effects.

District		Symptoms
Oropharyngeal		Altered taste perception Itching of lips Swelling of lips Itching of oral mucosa Swelling of oral mucosa Swelling of tongue Glossodynia Mouth ulcer Tongue ulcer Throat irritation Uvular edema
Ear		Itching of ears
Gastrointestinal	Upper	Nausea
		Stomach ache
		Vomiting
	Lower	Abdominal pain
		Diarrhea

of life (HRQoL), illness perception, satisfaction or adherence to treatment [85]. Patient's perspectives, along with traditional parameters of safety and efficacy, play a pivotal role in the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) system [86] that is considered the best criterion for grading evidence and developing guidelines. WHO has recently adopted the GRADE system as a cornerstone in the formulation of recommendations toward diagnostic and therapeutic interventions.

It goes to show the increasing value of PROs and their importance in drawing together research trials and real-life setting. Some position papers have been stated in the last years specifically concerning PROs in allergy, asthma and rhinitis and many validated tools have been developed for their assessment [84,87].

Until now the impact of SLIT on PROs has been investigated in few studies, most of them referring to HRQoL only and conducted on a small population sample [88–92]. Baiardini *et al.* has recently published a cross-sectional study aimed at exploring patients' personal point of view on several aspects of SLIT and SCIT [93]. A 28-item questionnaire covering knowledge, perception, expectations and satisfaction was administered to a large cohort of patients treated with SLIT or SCIT. Concordance between patients' and physicians' answers has also been assessed. The questionnaire is not a validated tool but authors have developed it based on their experience and literature review. One of the most intriguing findings is that about 40% of patients did not show adequate knowledge about SIT, concerning in particular treatment duration, timing of effects and the role of regular pharmacotherapy. It can lead to misconceptions and inadequate expectations that are risk factors for poor adherence and low treatment effectiveness [82]. On the other hand, both patients and physicians reported a high grade of treatment satisfaction with the effects of SLIT, as far as symptoms, need for medications and HRQoL are concerned, and they are all confident about a positive outcome of the treatment on several aspects of allergic disease.

Treatment satisfaction is one of the most crucial aspects of PROs, since it affects patient's treatment-related behaviors and, finally, the effectiveness of therapeutic interventions [94,95]. A strong correlation between treatment satisfaction and adherence has been shown [82,96]. Justicia *et al.* have recently validated the first treatment-specific questionnaire for the assessment of patient satisfaction with AIT in allergic patients (ESPIA – Escala de Satisfacciòn de Pacientes que reciben Inmunoterapia con Alérgenos) [97]. The 16-item questionnaire, until now validated in Spanish language only, explores many pivotal aspects of patient's subjective experience: perceived efficacy, daily life activities, cost–benefit balance and general satisfaction. It is noteworthy that the cost–benefit balance section aims at investigating if the daily 'inconveniences' derived from the logistics of administering the treatment are compatible with patient's lifestyle and if they are compensated by SIT efficacy. Despite this aspect seems to be a crucial determinant of adherence, it is not

specifically focused by the commonly used tools for PROs assessment. Along with efficacy evaluation by means of traditional measures (symptom scores, medication usage), the ESPIA questionnaire or similar tools should become part of daily clinical practice in order to join patients' needs and preferences, reduce dropouts and finally improve treatment effectiveness beyond clinical trials.

Expert commentary & five-year view

SLIT efficacy, safety and tolerability have been widely demonstrated. Nevertheless, as popularity of SLIT increases at least in Europe, it is important that safety and efficacy continue to be investigated. Moreover, some missing goals should be achieved. In fact, many experimental data are available concerning mechanisms of action of SLIT, but both in clinical trials and in real-life efficacy is mostly evaluated by scoring symptoms and need for medication through different, not always validated, tools. Nowadays, *in vivo* (e.g., early and late skin reaction) and immunological (IgE levels, IgG subclasses, mucosal IgA, lymphocyte subsets, cytokines and systemic inflammatory markers) tests have been proposed as potential surrogate markers but most of them have poor reproducibility, high costs and lack of extensive availability in daily practice. So an ideal surrogate marker or biomarker that correlates with real clinical end points and that leads to a tailored immunotherapy treatment is still not available. The assessment of fractional exhaled nitric oxide (FeNO) represents a possible tool even if its role in the follow-up of patients treated with SLIT needs further research, especially if we consider nasal FeNO.

The favorable results about SLIT efficacy coming from meta-analyses are mainly based on the results of RCT performed on grass and mite-allergic patients; more controlled studies evaluating other relevant sensitizations, such as birch, ragweed, cat and *Alternaria* should be performed. Moreover, the clinical improvement of SLIT seems to be less impressive in asthma. It has to be noticed that asthma monitoring is a complex matter besides immunotherapy, since asthma is a multifaceted disease and a correct follow-up of asthmatic patients should include clinical aspects, functional parameters and inflammation biomarkers. However, many studies about SLIT and asthma were not formally sized and adequately powered or they did not include lung functional parameters as efficacy outcomes. Several studies on SLIT for grass and mites have failed to show functional improvement or exacerbation reduction. It has to be considered that in some of these studies most of the patients had minimal symptoms at baseline and throughout the study, likely precluding a detection of a beneficial effect of immunotherapy. Further research is needed in order to strengthen the evidence of SLIT efficacy for asthma and to identify the best biomarker to investigate it.

Many evidences confirm the optimal safety profile of SLIT, if administration conditions do not deviate from international guidelines. Nevertheless, tolerability is a crucial determinant of adherence to treatment. The recently published WAO grading system about SLIT-related AEs will increase doctors' and

patients' awareness of local reactions. It will help physicians to recognize and grade local adverse effects and patients to know that they may happen without any risk for their safety and health. Further research is needed in order to clarify the role of premedication, dose adjustment, discontinuation and re-administration, and to state operative protocols according to the severity of local AEs. The proposed grading system for SLIT-induced local reactions may represent the background for the development of shared strategies.

It is clear that further research is needed in order to achieve some missing goals concerning both efficacy and safety/tolerability, as discussed above. However, reviewing the literature so far, many data support SLIT efficacy and safety. In particular, safety seems not to arise any concern. It gives the chance to better explore dose–response relationship in SLIT in order to further improve efficacy of SLIT. Of course, it implies the development of universally accepted standards for measurement of allergen content in SIT preparations and for dosing protocols. On the other hand, it has been

demonstrated that efficacy is not the only requisite for a successful treatment. Together with tolerability, PROs and in particular patient satisfaction account for patient's behavior toward treatment. Some intriguing tools have been developed in order to assess PROs of allergic patients treated with SIT. Similar tools, along with existing efficacy assessment tools (symptom scores, medication usage), should be enhanced and regularly used in clinical practice in order to balance efficacy with tolerability and all the other patient-related variables. This is probably the best approach in order to improve treatment effectiveness beyond its efficacy.

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Key issues

- Sublingual immunotherapy (SLIT) is a viable efficacious and safe treatment for allergic rhinitis.
- Further research is needed in order to strengthen the evidence of SLIT efficacy for asthma.
- High heterogeneity in SLIT indications, age groups, allergen preparations, schedule and duration of treatment can weaken the final data about efficacy.
- An ideal surrogate marker that correlates with real clinical end points and that leads to a tailored immunotherapy treatment is still not available.
- Tolerability and patient-reported outcomes are crucial determinants of adherence and treatment effectiveness.
- Recognizing, grading and managing SLIT local adverse effects may enhance adherence to treatment.
- Operative protocols about the management of SLIT local side effects according to their severity are needed.
- Patient-reported outcomes, and in particular patient satisfaction, should be regularly assessed through appropriate tools in order to improve treatment effectiveness beyond its efficacy.

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