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Unmet Needs in Understanding Sublingual Immunotherapy to Grass Pollen

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Additional information is available at the end of the chapter

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Abstract

The lack of medication for allergy symptoms at the end of the last millennium has been the promoter of the idea of treating allergies as if you were treating an infectious disease, by vaccination prophylaxis. Two forms of AIT 1) subcutaneous immunotherapy (SCIT) and 2) sublingual immunotherapy (SLIT) are used in the world. Considerable interest has emerged in SLIT both scientifically and especially financially. SLIT is not a new treatment modality. First description dates back to 1900 when H. Curtis. It was relatively widely used until the late 1970's mainly in US by homeopathic therapists.

A number of case series describing experience with the oral route were published during the 1920s and 1930s, but it seems to have been perceived not as efficacious nor as well tolerated as subcutaneous immunotherapy. The companies producing allergen immunotherapy have an alliance with important opinion leaders on both shores of the Atlantic.

If SLIT did not work for 40 years, why should it work for respiratory allergic diseases today? This question is the mother of all questions in the field of respiratory allergic diseases. The purpose of this chapter is to provide past and current information about immunotherapy, and discuss controversies over efficacy and safety, and dosing considerations for SLIT to grass.

Keywords: subcutaneous immunotherapy (SCIT), Sublingual immunotherapy (SLIT), Allergic rhinitis, Grass pollen, Evidence-Based Medicine

1. Background

For everything there is a season. This sentence from the Bible indicates and explains the history of sublingual immunotherapy (SLIT) in a nutshell. We must remember that allergy

treatment is a hybrid specialty. Respiratory diseases that come to the allergist are not uniquely his, but are shared with other specialties. Of the two major manifestations of respiratory allergic diseases, asthma and hay fever, the internist and pneumologist have plenty of opportunities to observe asthma and nose-and-throat specialists have great familiarity with hay fever.

The drugs given for relief of allergic symptoms are familiar to physicians in general. After the characterization of immunoglobulin E (IgE) in 1967, a variety of *in vitro* tests to detect it and quantitative serum specific IgE have been developed. *In vitro* testing has since become more common [1].

Consequently, of two areas belong exclusively to the allergist, *in vivo* testing and allergen immunotherapy, only the latter has remained, used exclusively by allergists. Although AIT has been used to treat allergic rhinitis for over 100 years, its role remains controversial. AIT is accepted in full by most allergists, but only with many reservations by other medical specialists of diseases of the respiratory tract. Currently, two forms of AIT (1) subcutaneous immunotherapy (SCIT) and (2) sublingual immunotherapy (SLIT) are used in the world. Considerable interest has emerged in SLIT both scientifically and especially financially.

Compared with SCIT, SLIT is easy to administer, does not involve administration of injections and may be administered at home, avoiding the inconvenience of office visits and finally it can be prescribed by general practitioners, otolaryngologists and dermatologists as well as allergists [2].

In the mid-1950s, antedating by several years the more recent publications dealing with SLIT by Europeans, [3] a group of Midwestern physicians, headed by Dr. Herbert J. Rinkel, practiced a form of unconventional allergy that included a technique of administering preparations of allergenic extract beneath the tongue [4]. Rinkel changed the oral route suggested by Curtis 11 years before Noon's publication on subcutaneous immunotherapy [5].

A number of case series describing experience with the oral route were published during the 1920s and 1930s, but it seems to have been perceived not as efficacious nor as well tolerated as subcutaneous immunotherapy. Subsequently, the method fell out of favor [6, 7].

The genesis of this procedure, like all homeopathic therapies, was engendered by a strong belief, considerable imagination and although successful according to anecdotal reports from its practitioners, the technique lacked the rigor of scientific proof [8, 9].

The value of SCIT to the allergist was unquestioned until 1998. The allergist often asks skeptics of SCIT: how could SCIT have survived to this day, unless it was of genuine value? Unfortunately, the value of AIT is not to be determined by the fact that this procedure has survived a century. Bloodletting in medicine lasted for a much longer time as a therapy for pneumonia [10], but today it is not considered a rational therapy.

However, evidence-based medicine must be taken into account in the field of medicine, which is based on rigorous research and the scientific method. The companies producing allergen immunotherapy have an alliance with important opinion leaders on both shores of the Atlantic [11].

A search of published literature under the topic “sublingual immunotherapy and RCT” revealed 24 citations in English before 2000 and 102 citations after 2000 (inception to July 30, 2016), demonstrating the growing interest of companies and opinion leaders in SLIT for allergic rhinitis.

However, the medication for allergic rhinitis currently in use is highly effective and nasal steroids are of particular value [12].

In some ways it would be the same as supporting the use of cromolyn for the therapy of allergic rhinitis rather than nasal steroids. A significant obstacle in evaluating the clinical value of SLIT is choosing the best criteria to prove clinical efficacy. Our position is that the best indication of efficacy is improvement in symptoms and decrease in medication that contributes significantly to the patient’s quality of life. The optimal study design for investigating clinical efficacy to evaluate SLIT includes pretreatment monitoring of symptom score for a season. This gives the advantage of elucidating the clinical relevance of allergen exposure in eliciting symptoms, representing the only possible way of ensuring an equal balance of disease severity in active and control groups. The magnitude of the clinical improvement is also important. It is of course critical to document a statistically significant difference between the active group and the control group, but *p-values* do not *per se* guarantee the effectiveness of a specific treatment. In 1991, Varney documented that immunotherapy has a clinical capacity to reduce, in actively treated patients, symptoms and drug intake by about 20% compared to the placebo-treated group [13].

If sublingual immunotherapy (SLIT) did not work for 40 years, why should it work for respiratory allergic diseases today? This question is the mother of all questions in the field of respiratory allergic diseases. The purpose of this chapter is to provide past and current information about immunotherapy and discuss controversies over efficacy and safety and dosing considerations for SLIT to grass. Allergy to grass is the most important form of seasonal pollinosis.

Several persistent misconceptions or “false beliefs” have been built up around AIT and its use in allergic rhinitis (AR), in particular regarding sublingual immunotherapy (SLIT). These misconceptions largely arose because of improper use of evidence-based medicine that was widespread in this field until the 1990s.

2. Evidence-based medicine (EBM)

Initially EBM was identified with the frequency with which you reach health interventions proven effective (more helpful than harmful) and which prevents interventions more harmful than useful. Three Doctors, an Englishman, Archie Cochrane, an American, Alan Feinstein and a Canadian David Sackett, can be considered the founders of this movement [14].

They identified the combination of carrier EBM in the interaction between research evidence with patient preferences. This paradigm was, however, revised by Sackett in 1996 in an article published in the BMJ that clarified that EBM cannot be considered without also

considering that clinical expertise. Only research or expertise alone could not be considered EBM [15].

In 2002, Haynes et al. quoted a famous phrase from Osler, “The value of experience is not much to see but see wisely” and then EBM defers to center the patient that must be studied with the findings that emerge from research and patient preferences that all should be handled with the clinical expertise of the physician [16, 17].

A few years later Shekelle et al. classified the literature data on primary sources that include expert opinion, observational studies, case studies-final control, cohort studies, clinical trials (RCT) and on secondary sources that include systematic reviews with or without meta-analysis of RCT [18].

The importance of the evidence is maximum for systematic reviews with meta-analysis and the risk is minimal for bias in systematic reviews with meta-analyses. Secondary sources are always the representation of primary studies but should be guaranteed from the critical analysis of who writes them. They use an explicit method and systematic examination of primary studies. Finally, the tertiary sources are represented by evidence-based clinical guidelines [19].

The limits of primary studies are often related to sponsorships and thus influenced by the results, as reported by Ioannidis in this article a few years ago published in PLoS Medicine [20]. EBM is in crisis for the misuse and overproduction of primary studies, often useless because they duplicate other studies and in publication of therapeutic advantages with marginal shift of attention from individual research to therapy [21].

For these reasons, the EBM approach must be reevaluated critically, trying to customize the decisions not only by referring to the available evidence or patient preferences or adherence to therapy but also considering the cultural and financial aspects of the patient who must decide, investment in training doctors both in pre and postgraduate education and indicating the use of secondary studies rather than primary ones [22–25].

3. From subcutaneous immunotherapy to sublingual immunotherapy: the return to the past

In a document published in 1993 in allergy about immunotherapy, the authors wrote in the preface: why does a diagnostic etiology in a patient with allergic respiratory disease indicate the specific therapy as the only logical solution of this specific diagnosis [26].

Immunotherapy is the scientific path that Leonard Noon published in the Lancet in 1911 [27]. The route was started by Bostock who described hay fever, i.e., allergic rhinitis and that proved to be the one that Backley demonstrated to be caused by grass season [28]. The studies of immunotherapy by Noon (who died prematurely from a form of tuberculosis), were continued by the pioneer John Freeman [29, 30]. It is necessary to remind readers that the use of antihistamines was reported in 1952 [31].

However, the lack of medication for allergy symptoms has been the promoter of the idea of treating allergies as if you were treating an infectious disease, by vaccination prophylaxis [32].

In other words, the comparison between immunotherapy and placebo was based for many years on two symptomatic criteria: the number of days during the season in which eye symptoms were noted; the number of days in which nasal symptoms were noted [27, 29, 30].

Immunotherapy has spread rapidly around the world and the first study compared to placebo was done by Frankland and published in *Lancet* in 1954 [33]. Another study was performed on ragweed in the United States and published in the *New England J Medicine* [34].

From a purely subjective assessment of both the patient and the allergist, the outcome of the studies is beginning to consider the evaluation criteria more objectively. At the end of the 1960s, the number of antihistamine pills taken for the relief of symptoms was evaluated [35].

However, a sort of skepticism around this therapy remained until Ishizaka and Johansson discovered IgE and showed that they were the cause of allergic reactions [36, 37].

The fact that the antibodies played a role in patients treated with immunotherapy had already been suggested by Sherman et al. [38].

Finally, we must remember that chemical pharmacology was born in the nineteenth century. The first antihistamine was synthesized by Bovet and Staub in 1937, the molecule was the 2-isopropyl 5 methyl phenoxyethyl diethylamine, demonstrating mild antihistamine action and considerable toxicity. In 1949, Bovet synthesized pyrilamine maleate, a diethylamine essentially free of toxic effects. But only in 1972, did Black et al. succeed in synthesizing antihistamines selective for the different receptors [39, 40]. Later, in 1974, beclomethasone dipropionate, became, the most important goal for the treatment of allergic rhinitis after that of antihistamines [41].

Allergy has been involved in a process of globalization. Before the 1980s there was no allergen standardization; this resulted in marked variations in allergenic strength among allergen vaccine batches produced in different phases. Immunotherapy was considered "Galenic" drugs, because they were prepared upon request of the allergist for a specific patient. The article of the Committee on Safety of Medicine challenges the use of ITS in the UK antihistamines and nasal steroids are marketed because they have been validated through controlled clinical trials as effective and safe [42].

However, in a study published by Reid et al. the problem of fatal reactions as a result of ITS is now widely known [43]. Alarm about the safety of ITS, the use in clinical practice of antihistamines and nasal corticosteroids with fewer side effects, the lack of full understanding of the mechanisms of action of ITS bring specific immunotherapy into a crisis. International scientific allergy companies, such as EAACI, produce important opinion-based scientific articles that, however, enhance the use of immunotherapy [44].

European allergists request single specific allergens for immunotherapy, rather than the allergen mixtures that had previously been requested and the companies, operating in the manufacturing sector of the allergen, participate more actively in the scientific debate. The companies begin to understand that the field of respiratory allergy, particularly that of

allergic rhinitis, is very rewarding financially. They also understand, however, that it is a field of medicine that is very closed and allergists are very jealous of AIT. They do not believe that it can be shared with other doctors [45–48].

In 1998, Malling published: immunotherapy as an effective tool in allergy treatment [49] in the allergy: a symposium review. The authors of this review stated on the bases of a number of DBPC studies, they could affirm that the clinical efficacy of immunotherapy in rhinitis and asthma, when potent and standardized extracts were applied in carefully selected patients, was well documented. Immunotherapy has the potential to reduce symptoms and the need for drugs significantly and furthermore possibly prevent progression into more severe disease.

SCIT has been evaluated on an arbitrary grading of the magnitude of clinical efficacy (**Table 1**).

1	No efficacy (symptom/medication scores improved by <30%)
2	Low efficacy (improvement 30–44%)
3	Moderate efficacy (improvement 45–59%)
4	High efficacy (improvement of >60%)

Table 1. Arbitrary grading of the magnitude of clinical efficacy by Malling [49].

Malling et al. wrote that: “this grading is arbitrary and controversial, but in daily clinical practice it is more operational than statistical *P* values. Compared with the efficacy of drug treatment of allergic diseases, the grading seems sensible. A symptom/medication score amelioration of <30% does not seem to justify the immunotherapy involving a potential risk of side-effects and will probably not be considered worthwhile by patients” [49]. Fifteen RCTs investigated the efficacy of SCIT in grass-pollen allergy [13, 50–63], of which 14 proved clinical efficacy. Only the RCT of Doltz et al. demonstrated a clinical effect of 10% improvement [62].

However, we must make two important observations: (1) SCIT is clinically effective, i.e., symptom/medication scores diminished by >30% in the actively treated in 72.3% of the studies and precisely in 93.3% of RCTs that investigated the efficacy of SCIT in grass-pollen allergy, in 69.2% of SCIT in ragweed, in 66.6% of SCIT in various allergens (Mountain cedar, Parietaria, Cupressus and Cocos) and in 60% of SCIT in DHM; (2) to satisfy an accurate indication for immunotherapy, this should be done by an allergist [49].

In other words, Malling et al. reiterate that only an allergist can decide if, when and how to do AIT. Certainly, this statement has not induced large investments from companies. However, the risk that AIT would remain a niche therapy managed only by allergists, is realistic.

In the same year, Malling et al. published a position paper of the European Academy of Allergy and Clinical Immunology entitled *Local immunotherapy* in allergy [3].

In this position paper, the authors examined the noninjective administration of specific immunotherapy in allergic disorders such as rhinitis and asthma, recommending to replace the

term “alternative immunotherapy” with “local immunotherapy” since the former may generate misleading associations and confusion with other, scientifically undocumented therapies used in allergic diseases, e.g., acupuncture, hypnosis, homeopathy and other methods [64]. Local immunotherapy included local nasal (LNIT), local bronchial (LBIT), oral (OIT) and sublingual (SLIT) administration of allergen extracts.

Of these routes, both OIT and SLIT, like all homeopathic therapies, were engendered by a strong belief, considerable imagination and although successful, according to anecdotal reports from its practitioners, the technique lacked the rigor of scientific proof [8, 9].

The companies understand that SCIT would hardly be accepted by patients because the loss of time it takes is very significant—the time to go to the Allergist’s office, plus the time of the turn to take the shot, then wait at least 30 minutes after the shot. Overall, the time required for a shot was about 2 hours. However, it was necessary to give credibility to alternative routes of administration of specific therapy, using the methodology of evidence-based medicine. For this reason, Malling et al. presented the inclusion criteria of the studies in the chapter, reported in **Table 2**. We will report, as for SCIT (see above), only the studies for allergy to grass pollen, performed with four choices of local immunotherapy.

1	Placebo-controlled, double-blind (PCDB) studies
2	Allergen extracts and doses defined
3	Treatment protocol and statistical analysis appropriate including an adequate sample size (over seven patients per group)
4	Studies published in peer-reviewed journals in English
5	Symptom/medication scores provided.

Table 2. Criteria used in position paper published in *Allergy* in 1998 [3].

3.1. Nasal immunotherapy

The authors included only five RCTs with grass allergens and all studies showing clinical efficacy [65–69]. However, Malling et al. concluded that LNIT demonstrate “The side-effects do not appear to present a significant problem” [3].

3.2. Bronchial immunotherapy

RCTs for allergy to grass pollen with local bronchial immunotherapy (LBIT) have not been published. However, the comments about LBIT were the following words: “LBIT is not sufficiently documented and there is concern about potentially serious immediate and delayed side-effects” [3].

While Crimi’s RCT about LBIT concluded that: “We conclude that LIT may be an effective and safe alternative to traditional immunotherapy” [70].

3.3. Oral immunotherapy

The authors examined three RCTs with grass [71–73]. None of these RCTs demonstrates clinical efficacy. The authors concluded that: “Only two studies indicate clinically relevant efficacy with either birch pollen administered in enteric-coated capsules or after treatment with aqueous mite extract for at least 1 year” [3].

3.4. Sublingual immunotherapy

The author considered only two RCTs with grass [74, 75]. Considering these two studies, the major innovation in the field of allergy is the presence of employees of the company that manufactures and sells the SLIT in the authors of the publication. Another important consideration is that Bjorksten, coauthor of this chapter, wrote an Editorial about the RCT of Sabbah entitled: “Local immunotherapy is not documented for clinical use” [76].

The comment of the authors about sublingual immunotherapy was: “Sublingual immunotherapy has been shown to reduce rhinitis symptoms and/or medication needs in six RCTs. The documentation of efficacy is based on a limited number of studies including around 120 patients” [3].

However, Malling et al. had excluded two RCTs with grass from their review, because one did not supply data on allergen doses [77] and the other did not include a placebo group [78].

After Malling’s position paper, the largest systematic reviews of sublingual immunotherapy, which reported on two primary outcomes, i.e., symptom score (SS) and medication score (MS), were performed in 2003 [79] and updated in 2010 [80] and published in the Cochrane collaboration database.

These two systematic reviews of sublingual immunotherapy suggested that the SLIT benefit in symptom improvement and drug use reduction is higher than placebo. But, the conclusions of the above mentioned meta-analyses were based on studies conducted in patients with allergies to both perennial and seasonal allergens, while the efficacy of SLIT for grass allergens was assessed by a subgroup analysis [79, 80]. However, other RCTs have been published on SLIT with grass allergens for AR [81–86]. Two RCTs presented results that remain inconsistent and the overall assessment of the treatment efficacy is still difficult to evaluate [85, 86]. Fourteen other RCTs on grass were published between 2004 and 2009 [87–100].

Our in-depth meta-analysis found that in seasonal allergic rhinoconjunctivitis, SLIT with grass allergens provided a statistically significant improvement of symptoms and a significant reduction of anti-allergic medication compared with placebo. The data from 19 RCTs representing a pooled total of 1518 patients receiving SLIT and 1453 receiving placebo, indicate the available evidence is sufficient to conclude: (1) SLIT with grass allergens improves rhinosinusitis symptoms and reduces the use of anti-allergic medications compared with placebo but the overall effect is clinically modest, (2) prolonged pre-season treatment significantly increases the response rate, and (3) a course of treatment no longer than 12 months with a monthly allergen dose of 450mg seems to be the best treatment choice. However, further studies are needed to clearly determine the role of SLIT with grass allergens in children [101].

Several reviews have reported an equivalent clinical efficacy between SCIT and SLIT for seasonal allergic rhinitis to grass pollens [102, 103]. SLIT has also been shown to be relatively safe and fairly well tolerated. These features account for the increasing use of SLIT in Europe. Improved safety and easy administration compared with SCIT are important advantages [104]. However, the relative efficacy of SCIT and SLIT has not yet been clearly shown. The only published study comparing the two treatments has been performed without placebo [85].

Therefore, to clarify this issue, we performed and published a meta-analysis to compare SCIT and SLIT with a fairly large number of double-blind, placebo-controlled trials on SCIT and SLIT (updating the previous published meta-analysis) [101] in patients with seasonal allergic rhinitis to grass pollens [105]. This meta-analysis of data from 36 RCTs, 10 with SLIT drops [75, 81, 83, 87, 88, 92, 94–96, 98], 12 with SLIT tablets [82, 84, 89, 90, 91, 93, 97, 99, 100, 106–108] and 14 with SCIT [13, 52, 54, 55, 61–63, 109–115].

These studies included a total of 3014 patients treated with immunotherapy and 2768 controls who received placebo. They provide indirect evidence that in patients with seasonal allergic rhinoconjunctivitis to grass SCIT is more effective than SLIT in the control of symptoms and in the reduction of anti-allergic medication use. There is significant heterogeneity in the results of individual RCTs, in particular for SCIT studies, which raises some concern. However, any degree of heterogeneity is acceptable if both the predefined eligibility criteria for the meta-analysis are sound and the data are correct [116].

Some of the SCIT trials included in our analysis were performed more than two decades ago on small sample sizes, but the quality of the studies has been considered sufficient to justify their inclusion not only in our meta-analysis but also in some Cochrane meta-analyses [79, 80, 117]. Our study suggests that the choice of SLIT is mainly based on safety reasons. In fact, the number of reactions requiring epinephrine was higher in SCIT RCTs (12 in 960 patients), than in SLIT RCTs (1 episode in 4046 patients). However, the number of mild to severe adverse events was higher in SLIT than in SCIT (**Table 3**).

	SCIT		SLIT	
	Treated	Placebo	Treated	Placebo
Total EAs, no.	960	456	4046	1856
Total AEs/patients	0.86	0.50	2.13	0.99
Withdrawals for AE, no.	18	5	78	25
Withdrawals for AEs/patients %	0.0019	0.005	0.04	0.0013
Anaphylactic reactions, no.	12	2	1	0

Table 3. Total adverse events (AE) related to SCIT and SLIT [105].

Moreover, our data provide indirect evidence that SCIT with grass allergens is more effective than SLIT to improve symptoms and reduce antiallergic medication for seasonal allergic rhinoconjunctivitis. However, trials directly comparing the two different routes of immunotherapy are needed to confirm these data [105]. An ideal comparative study would be a

randomized, placebo-controlled, double-blind, double-dummy study that enrolls a large number of patients from a single center or a single country or a few countries with similar pollen exposure and patients of similar ethnicity. The treatment should be started at least 16 weeks before the expected beginning of the pollen season and last 1 or 2 years. A vaccine with a dose of the main extract ≥ 275 mg for SLIT should be used. The ideal dose for SCIT vaccines has yet to be determined. Nonetheless, no one should be surprised by the criticism of our meta-analyses because the critics are authors who supported the use of SLIT [118, 119].

The convenience and safety of sublingual immunotherapy (SLIT) are likely factors for its widespread use in Europe, where it is now the preferred route of administration of ASI and were licensed as drugs in September 2009 (Grazax[®], Alk-Abellò; Oralair[®], Stallergenes) [120].

The US Food and Drug Administration (FDA) announced approval of the five-grass pollen sublingual tablet (Oralair[®]) in April 2014, followed by the Timothy grass pollen sublingual tablet (Grazax[®]/ALK-Abellò, marketed by Merck in the US under the name of Grastek[®]) [121–123]. SLIT with liquid allergen extracts had been used off-label in the US before FDA approval [2].

Our previous meta-analysis showed that SLIT was effective for seasonal allergic rhinoconjunctivitis to grass, but its clinical benefit compared to placebo was modest [101, 105]. That data also showed that SLIT tablets are more effective than drops, probably because of a higher allergen content. All of the RCTs of SLIT published at that time had been performed in Europe [82, 84, 89–92, 97, 99, 100, 106, 124]. But since then five additional RCTs have been published, all conducted in North America. [107, 108, 125–127].

In our meta-analysis on SLIT tablets [128], data on symptom score were available in 13 RCTs [82, 84, 89, 90, 91, 92, 97, 99, 107, 108, 125–127], and data on medication score in twelve studies [82, 89, 90, 91, 92, 97, 99, 107, 108, 125–127]. We excluded the Caffarelli study, because he used an allergoid, Lais [106] and Horak study because it was performed in an allergen challenge chamber [100] and the Halken study [124], which is a secondary analysis on a previously published dataset [102]. The 13 RCTs included a total of 4659 patients. Seven studies were conducted in Europe [82, 84, 89, 90, 92, 97, 99] and five in North America [107, 108, 125–127] and one in both Europe and Canada [91].

The SS and MS were assessed as outcome measures of the treatment effect. Outcome data were continuous, but different scoring systems and scales for symptoms and medication were used by the authors. To compare the results, analyses were performed by the method of standardized mean difference (SMD), expressing the differences in means between SLIT and placebo in terms of units of the pooled SD. The overall SMD among patients treated with SLIT and placebo was estimated using models based on both fixed effects and random effects assumptions [129]. The magnitude of the overall effect was classified according to Cohen's guidelines: effect size of 0.2, 0.5, and 0.8 correspond to small, medium and large effects [130]. Since 11 out of 13 RCTs used the same SS ranging from 0 to 18 points (the higher the score the worse the disease severity) as outcome measure, we compared the results of these studies using the original SS, reporting the results as mean difference (MD) of SS-points. Excluding the studies by Pradalier [82] and Smith [84], we could compare the studies using the original SS, which is easier to interpret. Using this method the mean difference between SLIT and placebo was -0.83 SS points (95%CI $-1.03, -0.63$, $p = 0.0001$) without significant heterogeneity ($I^2 = 16\%$). The SMD excluding these two studies did not change compared to the main

analysis performed with 13 studies (SMD -0.28, 95%CI, -0.39, -0.18; $p < 0.0001$), indicating that SMD of -0.28 corresponds to a MD of -0.83 SS points.

Data on medication score were obtained for 12 RCTs (4558 patients) [82, 89, 90, 91, 92, 97, 99, 107, 108, 125–127]. A statistically significant difference between SLIT and placebo was observed only in seven RCTs [89–92, 97, 125, 127]. The pooled estimate of treatment on medication score was statistically significant (SMD -0.24; 95%CI, -0.31, -0.17; $p < 0.0001$). An analysis using the original medication score was not performed due to the highly different scoring systems used. A total of 1817/2597 (70.0%) of patients receiving SLIT vs. 1137/2555 (44.5%) of subjects receiving placebo complained of adverse events. Probable treatment-related adverse events were reported in 9 out of 13 studies and there were three times as many adverse events in patients receiving SLIT (1384/2259, 61.2%) than in those receiving placebo (477/2279, 20.9%). Most AEs were moderately severe for both groups. The withdrawal rate for an AE was higher in the SLIT group (159 patients, 6.0%) than in the placebo group (56 patients, 2.2%). No episode of anaphylaxis was reported in the RCTs; but nine adverse events requiring epinephrine were reported in the SLIT group, of which seven were treatment related. Three serious adverse events requiring epinephrine were also reported in the placebo group, but none of them were treatment related (**Table 4**). The forest plot and the funnel plot of the data reported above can only be seen in the original publication due to copyright [128].

	SLIT	Placebo	OR	P
Total AE, # patients (%)	1817/2597 (70)	1137/2555 (45)	2.91	<0.0001
TRAE, # patients (%) [†]	1384/2259 (61)	477/2279 (21)	5.98	<0.0001
Withdrawals for AE, # patients (%)	159/2658 (6)	58/2587 (2)	2.77	<0.0001
Anaphylactic reactions	0	0	–	n.s.
AE requiring adrenaline	9	3	–	n.s.
TRAE requiring adrenaline	7	0	–	n.s.

Note: AE, adverse events; TRAE, treatment-related adverse events.

Table 4a. Adverse events during treatment [128].

TRAD	SLIT n (%)	Placebo	p	#Studies
Oral pruritus	689/2228 (30.9)	84/2126 (3.9)	<0.00001	11/13
Throat irritation	418/2045 (20.4)	71/2006 (3.5)	<0.00001	9/13
Mouth edema	226/2105 (10.7)	17/2033 (0.8)	<0.00001	9/13
Ear pruritus	181/1524 (11.9)	32/1444 (2.2)	<0.00001	6/13
Eye pruritus	81/852 (9.5)	20/768 (2.6)	<0.00001	4/13
Oropharyngeal pain	122/1306 (9.3)	33/1309 (2.5)	<0.00001	4/13

Note: Other side effects, such as headache, cough, tongue pruritus, sneezing, rhinorrhea, nasal discomfort and nasopharyngitis, have not been reported in the table since they were reported in less than four studies.

Table 4b. Most common treatment-related adverse events (TRAE), occurring in at least 5% of patients in the treatment group.

4. The methodological problem used to evaluate the tablets grass

In the last part of this chapter, we will focus on the most critical methodological defect of the SLIT RCTs, which is the metric that has been used in RCTs to assess the clinical benefit. This metric is mathematically incorrect because, as clearly will explained in the study, it calculates the percentage difference between SLIT and placebo, not taking into account the symptom score (SS) scale range and leading to a huge magnification of the difference between groups.

By using this metric, a 1-point difference will be the same percentage difference in an 18-point scale (the te common SS scale used), a 100-point scale, or any other scale, and this is mathematically unacceptable (a detailed explanation has been reported in **Figure 1**).

Example study	SLIT	Placebo	Difference	Percentage improvement
RTSS (baseline)	15	15		
Mean SS during treatment	3	4	-1	$(3 - 4)/4=25\%$ (not including the scale)
Difference	-12	-11	-1	
Percentage improvement	80%	74%		$80\%-74\%=6\%$ (11 - 12)/15=6% (including the scale)

Figure 1. 18-point scale.

The correct metric, which takes into account the scale range, was indicated by the World Allergy Organization (WAO) [104].

Recommendations for standardization of clinical trials with allergen and is based on the comparison between the pretreatment and post treatment SSs of the active and placebo groups. Using this metric, we showed a small difference between SLIT and placebo, which is less than the US Food and Drug Administration (FDA) (15%) and WAO (20%) thresholds of efficacy. The baseline in the case of SLIT RCTs is the retrospective (prior year) total symptom score (RTSS), which is used by the investigators of the original RCTs as inclusion criteria. In other words, the RTSS is assumed by the investigators as the SS that the patients would have in the absence of any treatment (corresponding to the inclusion criteria). We acknowledge that the RTSS might be imprecise, but it should be similar to the SS of the treatment season, especially if the pollen count of the two consecutive seasons is similar, and we have shown for the Cox study, performed with 300IR 5-grass pollen sublingual tablet (Oralair®) in only US sublingual study, that this possible imprecision does not affect the results [102].

In our meta-analysis [128], we reported the difference between SLIT and placebo not only in terms of the standardized mean difference (SMD) but also in terms of the mean difference (MD), which is the difference in SS points between SLIT and placebo. We showed that this difference is -0.83 SS points (95% CI, -1.03 to -0.63). In a recent work, Devillier and the Stallergenes®, an industry that market the SLIT, estimated the minimally important difference, which is defined as the smallest improvement considered worthwhile by a patient, as 1.1 to 1.3 SS points in patients with grass pollen-related rhinoconjunctivitis [131].

Therefore, according to the Devillier estimation, the difference that we found (-0.83 SS points) between SLIT and placebo is not perceived by the patients as clinically important, confirming the conclusions of our previous study. In **Figure 2**, we reported the 95% CI for the mean value (-1.03 to -0.63 for the random effect and even smaller for the fixed effect). This implies that we are 95% confident that this interval contains the true value of the parameter. Therefore -1.03 could be a value for the population parameter: even if it was the true value (the most favorable extreme to SLIT), the probability of observing a value of less than -1.1 is only 0.25 (25% of patients could benefit significantly from SLIT). In contrast, if the true value was that reported in our study as a point estimate, less than 0.5% of patients can show an improvement of greater than -1.1. This is in accordance with the calculation using our metric reporting an SS reduction to less than the WAO (20%) and FDA (15%) thresholds of efficacy.

Example study	SLIT	Placebo	Difference	Percentage improvement
RTSS (baseline)	95	95		
Mean SS during treatment	3	4	-1	$(3 - 4)/4 = -25\%$ (not including the scale)
Difference	-92	-91	-1	
Percentage improvement	96.85%	95.8%		$95.8\% - 96.9\% = -1.05\%$ (91 - 92)/95 = -1.05% (including the scale)

Figure 2. Hypothetical 100-point scale, with a hypothetical RTSS (baseline score) = 95, congruent with a 100-point scale.) RTSS, retrospective total symptom score (baseline). With the calculation shown in RCTs (horizontal arrow) only the mean SS during the treatment is considered, ignoring the scale range. In WAO indicated calculation, the same we propose (vertical arrow), the scale range is included. The inclusion of the scale in the calculation changes the percentage of the improvement, even if the difference between the two groups remains the same.

Regarding safety of the AIT, on the basis of what is reported in RCTs the majority of adverse events are mild to moderate and that “both SCIT and SLIT are very safe” [132] but as we showed in our previous meta-analysis [105] indirectly comparing SCIT and SLIT, the withdrawal rate for adverse events was higher in the SLIT group (78 patients; 0.04% vs 0.013% in the placebo group) than in the SCIT group (18 patients; 0.019% vs 0.005% in the placebo group). This evidence should also be considered.

5. Conclusions

Regarding the physician-patient dialog to respect patient preference according to evidence-based medicine principles [15, 16], we believe that in the case of SLIT, the patient has to be informed correctly about the small benefit of the treatment.

In the interest of patients, caution must be exercised when such a small treatment benefit is reported, especially if one considers that sponsored studies (as in the case of all SLIT RCTs) always show greater benefit compared with independent studies using the same drugs or devices [133, 134].

This chapter shows that there is an increasing interest in risk-sharing schemes by both payers and manufacturers, as they serve as mechanisms for reduce uncertainty in collecting evidence once a new drug is already being used in a health care system. In principle, they could provide additional options to payers and manufacturers, to boost overall efficiency [135]. The ambitious goal is to help reduce the likelihood of payers adopting technologies that turn out not to be cost effective, while at the same time helping manufacturers earn profitable prices to invest in future innovative technologies. Italy is one of the countries that started early with these agreements: AIFA, the Italian drug agency, agreed on its first contract in July 2006 [136].

The regulatory authorities such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Japanese Medical Device Agency are responsible for the approval of any drug. Academia (including universities, scientific institutions and societies) is another major stakeholder with an important role in influencing the behavior of prescribers. Patients and consumer associations have also an important role: patients are involved in RCTs, consumers associations are consulted in decision concerning research priorities.

Finally, pharmaceutical companies maintain a sort of monopoly in development of new drugs and promote the drug and the sales [137]. In the European Union (EU), as well as in US, medicines are authorized by the European Commission (EC) and Federal Trade Commission, respectively. After a positive evaluation by the European Medicine Agency (EMA), Food Drug Administration (FDA) uses the centralized procedure or the national agencies through decentralized procedures. According to the EU legislation and provisions of the FDA, the evaluation of medicines seeking marketing authorization is only based on their quality, safety and efficacy. No information is required on their comparative efficacy with respect to drugs already available. In our case, SLIT has been compared only with placebo in all RCTs, the indirect comparison between SCIT and SLIT has shown that the SCIT is superior to SLIT [105]. After our meta-analysis, other studies have been published that concluded that SLIT has at least non-inferior efficacy and comparable safety compared to SCIT, but a lower annual cost [138, 139].

Our review provides moderate-grade evidence to support that SCIT is superior to SLIT for reduction of allergic rhinoconjunctivitis symptoms. Finally, we do not discuss the considerations on the disease-modifying effects of AIT, because they have been evaluated in another study that is difficult to get published because of the obvious conflict of interest in peer review which is responsible for reviewing the manuscript [140].

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