

Sublingual immunotherapy for allergic rhinitis: an update

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Current Opinion in Otolaryngology & Head and Neck Surgery 2011, 19:43–47

Purpose of review

Sublingual immunotherapy (SLIT) has progressively gained credibility. Randomized double-blind placebo-controlled trials, meta-analyses and mechanistic studies have accumulated rapidly in the last years. We will review herein a brief history of SLIT, its indications and the safety aspects and will discuss the main unmet needs and the points to be developed in the field.

Recent findings

During the last year, new information on SLIT has become available, mainly from the so-called big trials, and some important aspects have been partially clarified. In addition, the possible indications to SLIT began to be expanded.

Summary

The dose dependency of the efficacy of SLIT and the optimal maintenance dose have been identified at least for grass allergens. The safety is well demonstrated in both adults and children.

Keywords

allergic rhinitis, efficacy, safety, sublingual immunotherapy

Curr Opin Otolaryngol Head Neck Surg 19:43–47
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1068-9508

Introduction

Subcutaneous administration [subcutaneous immunotherapy (SCIT)] was for several decades the only available route of allergen immunotherapy. SCIT is effective and well tolerated, but a certain risk of severe side-effects is still present [1]. Some risks are due to technical errors and can be avoided [2], but a fraction of side-effects are unpredictable. The problem of the risk/benefit ratio favoured the search for safer administration routes, including sublingual immunotherapy (SLIT), which was first described in 1986 [3]. In less than 20 years, due to the large amount of clinical data, SLIT achieved credibility, and was introduced in the official documents as a viable alternative to SCIT [4,5,6**] for both adults and children. Starting 10 years ago, several postmarketing surveys confirmed the favourable safety profile of SLIT, and the mechanisms of action began to be elucidated. Of note, based on the good safety profile, the possible use of SLIT in conditions other than allergic rhinitis (e.g. atopic dermatitis or food allergy) has been suggested. To date, SLIT is commercialized and routinely used in many European countries, whereas in the USA there is no product approved for this use.

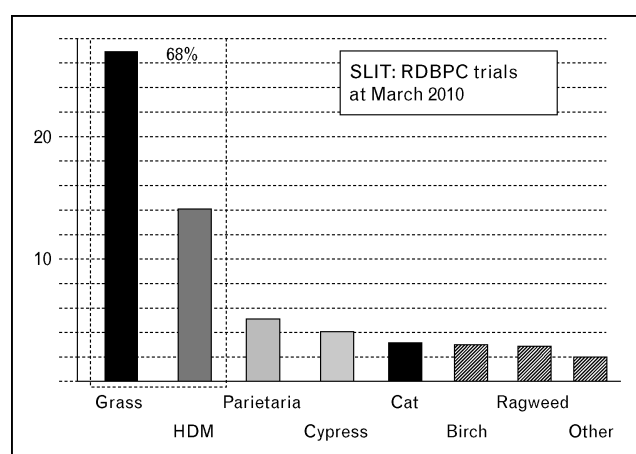
Despite this, some aspects still need to be clarified, meaning there is room for improvement. In particular, the optimal maintenance dose, the best administration regimen and the duration of the treatment are still under discussion.

Sublingual immunotherapy for allergic rhinitis

Allergic rhinitis still remains the principal indication to SLIT, and most of the data on clinical efficacy, safety and preventive effects have been studied in rhinitis patients.

Clinical efficacy

To date, more than 60 randomized double-blind placebo-controlled trials have been published (for review see [6**]). Dust mite and grass account for more than two-thirds of the clinical trials (Fig. 1). The majority of them evaluated the effects of SLIT in allergic rhinitis by means of various symptom-score systems. Some studies also evaluated the effects of SLIT in asthma, but asthma was chosen as primary outcome only in a few studies. Out of the large number of trials, only four [7–10] provided totally negative results (no difference versus placebo), and some others gave inconclusive results. The magnitude of the clinical effect is quite variable across studies and, when reported, the improvement over placebo ranges from 10 to 45%. Due to the number of trials available, some meta-analyses could be carried out. Three of the meta-analyses evaluated allergic rhinitis [11,12**,13]. The first two included all the patients, irrespective of age, whereas the second was restricted to 5–18-year-olds. Those meta-analyses concluded for a significant effect of SLIT versus placebo [14]. The reliability of the meta-analyses has recently been

Figure 1 Number of the randomized double-blind placebo-controlled trials conducted for each allergen

HDM, house dust mite; RDBPC, randomized double-blind placebo-controlled; SLIT, sublingual immunotherapy.

questioned by Nieto *et al.* [15], especially on the basis of possible publication biases, incorrect reporting and high heterogeneity. Moreover, the mentioned meta-analyses pooled together the studies with all allergenic extracts, whereas differences may exist among allergens. In this regard, a meta-analysis restricted to house dust mite SLIT was recently published, showing a significant effect on symptom and medication scores in allergic rhinitis [16[•]]. The problem of heterogeneity is inherent, as the trials had variable inclusion criteria, doses, regimens and outcome measures. It is also true that meta-analyses are the only way to summarize the results of studies when they are not directly comparable with each other.

Concerning allergic rhinitis due to grass pollen, the recent so called 'big trials' [17–22] have provided relevant

information. Those trials were all conducted with extracts in tablets and enrolled more than 200 patients each, in some cases reaching up to 600 patients. The big trials invariably showed an effect of SLIT versus placebo ranging from 25 to more than 50% (Table 1). The cut-off of 20% is unanimously considered the threshold for a clinically relevant effect [23]. In addition, some of those big trials had a dose-ranging design, and clearly showed that the clinical effect is dose-dependent. Finally, at least for grass, the optimal dose has been identified as 15–25 µg major allergen per day, which is roughly 50 times the monthly dose of SCIT.

From a clinical point of view, the comparison of the efficacy of SLIT versus drugs is still a matter of debate. The main practical problem is that the effects of immunotherapy can be appreciated only in the long term (months). Recently, two head-to-head open randomized trials were published. One of them compared SLIT as an add-on therapy versus inhaled budesonide [24], and the other one compared SLIT and montelukast [25]. Both trials involved patients with asthma and rhinitis and both showed, in the long term (3 years), an overall superiority of immunotherapy. In particular, SLIT exerted a systemic effect which produced a contemporary improvement of nasal and bronchial symptoms. Finally, there is one single randomized double-blind and double-dummy trial directly comparing SLIT and SCIT [26], and this trial showed no clinical difference between the two treatments. The same results (similar efficacy of SLIT and SCIT) were recently reported in an open randomized trial involving children with rhinitis and asthma [27[•]].

Safety

The safety of SLIT is unanimously recognized to be superior to that of SCIT [6^{••},28], and no fatality has ever

Table 1 The 'big trials' with grass extracts

Author	Age range (years)	Patients A/P	Allergen	Duration	Main positive results over placebo
Durham <i>et al.</i> [17]	18–66	569/286	Grass Three doses	6 months	Drug score: 28% (0.012) Symptoms: 21% (0.002); only with the highest dose and no clinical change with the lowest doses
Dahl <i>et al.</i> [18]	23–35	316/318	Grass	6 months	Symptoms: 30% (0.001) Drugs: 38% (0.001) Well days: 52% (0.004)
Didier <i>et al.</i> [19]	25–47	472/156	Grass Three doses	6 months	Total and individual symptom and drug scores (<0.001)
Wahn <i>et al.</i> [20]	4–17	139/139	Grass	8 months	Symptom score: 28% (0.01) Drug score: 24% (0.006)
Ott <i>et al.</i> [21]	20–50	142/67	Grass	5 years	Combined score and symptom score significantly reduced since first season. Symptoms decrease from 33 to 47% (third season)
Bufe <i>et al.</i> [22]	5–16	126/127	Grass	Four seasons 6 months	No change medication scores Symptom score: 24% Asthma score: 64% Drug score: 34% Well days: 28%

A, active; P, placebo.

been reported in more than 20 years of clinical use. In addition, the reports of anaphylaxis with SLIT so far available in the literature are only six [29–33] over millions of doses. On the contrary, the report of an anaphylactic reaction on taking the first grass tablet SLIT [33] suggested the opportunity to give the first dose under medical supervision [6^{••}]. Safety in children deserves great attention [34]. In fact, the age of 5 years is considered as a relative contraindication for SCIT, mainly because in young children any reaction may be more severe and difficult to treat than in adults. Some of the postmarketing surveys also involved children aged between 3 and 5 years [35–37] and confirmed that the safety is not impaired at younger ages. A controlled dose-finding study of safety [38] involved 48 grass-allergic patients outside the pollen season. They received SLIT for 28-day periods at progressively increasing doses, up to 200 µg Phl p 5 allergen, which is about 40 times the amount given with one injection. The overall incidence of side-effects was 74%, all of mild or moderate intensity. The most frequently reported events were irritation of the throat and oral itching. Another safety aspect is related to the administration of multiple allergens. In this regard, two postmarketing surveys, one performed in 120 adults and the other in 250 children, showed that the use of more than one allergen does not increase the rate of side-effects [39,40].

Effects on the natural history of respiratory allergy

It is well known that allergic rhinitis is an independent risk factor for the subsequent development of asthma, and a preventive effect has been demonstrated for SCIT. Concerning SLIT, an early open controlled study [41], performed in children with rhinitis, demonstrated that SLIT reduces the risk of asthma onset. More recently, a larger randomized open study, involving more than 200 children followed up for 3 years [42], reported that the occurrence of persistent asthma after 3 years was 38% in the controls and 2% in the SLIT group. In addition, this study confirmed the prevention of the onset of new sensitizations. Another important clinical aspect is the long-term effect of SLIT, in other words the persistence of the clinical benefit after discontinuation. There are two studies, one nonrandomized [43] and the other randomized and double-blind [44] demonstrating a long-lasting effect (greater than 2 years) of SLIT after discontinuation. More recently, new data from one of the 'big trials' became available. Also, in this case, the clinical benefit was maintained in the pollen season subsequent to SLIT discontinuation [45^{••}]. Of note, this trial involved more than 400 patients and was randomized and placebo-controlled. Therefore, the long-lasting effect seems to be demonstrated on an experimentally robust basis.

Unmet needs and future directions

Some aspects of SLIT need urgently to be elucidated, in order to provide clinicians with clear and evidence-based recommendations for the clinical use of this treatment.

One of the critical aspects is the need for univocal criteria or parameters to identify the best candidates for SLIT. Another relevant problem is the large variability of the doses used in clinical trials. Indeed, both positive and negative results have been obtained with both low and high doses of allergens, and the dose interval for efficacy is reported to range between 2 and 375 times the amount given with SCIT [46]. The optimal dose has been formally identified only for grass extracts, whereas the data are still lacking for the other relevant allergens. In addition, there is no consensus on the best administration regimen (e.g. preseasonal, coseasonal, precoseasonal or continuous), although for pollen allergens the precoseasonal regimen was used in most trials [47^{••}]. Also, the usefulness of a build-up phase is a matter of debate. No-updosing has been shown to be safe enough [48–50] also in children, and some of the big trials were conducted with a no-updosing regimen, but it is not clear whether this approach can be immediately transferred to all allergens and patients. Finally, there is still a great variability in the allergen and protein content of commercial extracts [51^{••}], and this makes the studies incomparable.

As happens with SCIT, there is room for improving the characteristics of SLIT and for expanding its indications. One of the most attractive proposals is the use of mucoadhesive substances that improve the contact of allergenic extracts with the oral mucosa. Mucoadhesive substances have been demonstrated to improve the immunological effects in animal models [52]. In recent years, at least two studies applied SLIT in food allergy, one with hazelnut extract [53] and the other with the Pru p 3 allergen of peach [54], and both reported positive results. The use of SLIT has also been proposed in the treatment of extrinsic atopic dermatitis. A randomized double-blind placebo-controlled trial, conducted in 30 children with mite allergy [55], reported a significant effect of mite SLIT in reducing the scoring atopic dermatitis (SCORAD) in mild-to-moderate atopic eczema. Finally, a randomized controlled trial showed that SLIT with honeybee venom (maintenance 525 µg) reduced the diameter of the large local reactions after sting challenge [56].

Conclusion

SLIT represents a significant advance in the treatment of respiratory allergy, because of its efficacy, safety and convenience. The good safety profile, in fact, seems to favour and improve the adherence to prescription [57^{••}]. The efficacy of SLIT in the treatment of allergic rhinitis

is now well established, provided that a detailed diagnosis is made and the choice of the patient is careful. In particular, patients with a few sensitizations, and when the causal role of the allergen is clearly defined, would receive the greater benefit [6^{••},23]. SLIT can also be recommended in children with allergic rhinitis. There are so far too few data for recommending SLIT as single treatment for allergic asthma, whereas in comorbid rhinitis and asthma its efficacy is well proven. Despite the general optimism, more studies are needed about the mechanisms of action [58], the pharmacoeconomic aspects and the optimal dose for each allergen. Furthermore, it is recommended that future trials are performed in a standardized way and with a uniform experimental design [59], so that the results are comparable with each other [60^{••}].

It is essential to remember that SLIT prescription must be made only by a specialist or a physician trained in allergology, after a detailed diagnosis has been established and the expected benefit/cost ratio has been carefully evaluated [61].

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- of special interest
- of outstanding interest

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