

Sublingual immunotherapy: update 2006

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Purpose of review

Sublingual immunotherapy is currently accepted as a viable therapeutic option, and is widely used in many European countries. In the past 2 years, new data concerning clinical, immunological and practical aspects of sublingual immunotherapy have been published, and many critical points have been addressed.

Recent findings

In addition to the new data on clinical efficacy, the most recent studies have shown that, similar to the injection route, sublingual immunotherapy can also prevent the onset of new sensitizations and the onset of asthma. Moreover, several postmarketing surveys have confirmed the satisfactory safety profile, even in very young children, and compliance has been measured. The good safety profile has also suggested the possibility of using sublingual immunotherapy without the up dosing phase. Finally, the mechanisms of action have been systematically investigated and the biodistribution of sublingual allergens has been further clarified.

Summary

More new data on sublingual immunotherapy are rapidly appearing in the international literature. These data consistently confirm the value of this treatment and show that sublingual immunotherapy is a viable and useful form of immunotherapy.

Keywords

efficacy, safety, subcutaneous immunotherapy, sublingual immunotherapy

Introduction

Subcutaneous immunotherapy (SCIT) remained for several decades the only available administration route for immunotherapy. SCIT is effective and safe when properly prescribed and administered, but a remote risk of severe side-effects is present [1], and the occurrence of technical errors is still not negligible [2]. The problem of the risk/benefit ratio was a strong impulse to the search for safer administration routes (nasal, bronchial, oral) [3], including the sublingual route (sublingual immunotherapy; SLIT) that was introduced in 1986 [4]. Only 20 years have elapsed from the first clinical trial of SLIT, and 13 years from its first mention in an official document [3], but the treatment has rapidly accumulated robust experimental support [5] and, therefore, gained credibility. In official documents, SLIT is now considered as a viable alternative to the classic injection route [6,7] for both adults and children.

SLIT is now commercially available and routinely used in many European countries. The most common way to administer SLIT is to keep the extract under the tongue for a couple of minutes and then to swallow it; for this reason, this modality is also called 'sublingual swallow'. In all studies, the dose of allergen used for SLIT is greater than for SCIT (approximately 3–300 times higher), so that it is termed 'high-dose SLIT'.

Despite the official positions and relatively wide clinical use, it is still claimed that the efficacy needs confirmation and many aspects of SLIT need to be elucidated, especially in comparison with the results previously obtained with SCIT. The main concerns about SLIT are: (1) the capacity to exert a preventive effect; (2) the problem of adherence; (3) its safety in children; and (4) the optimal doses. During the past 2 years, new studies have been able to provide answers to the aforementioned questions.

Recent experimental results

In the past few years new data have become available on the efficacy and safety of SLIT. Large controlled trials have been performed and postmarketing surveillance results have been added to the existing information.

Clinical efficacy

To date 36 double-blind placebo-controlled studies have been conducted on SLIT. After the last extensive reviews [8,9], many additional studies have become available [10–15,16^{••},17,18^{••}], as summarized in Table 1. All the studies consistently confirm that SLIT is effective in

Curr Opin Allergy Clin Immunol 6:449–454. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2006, 6:449–454

Abbreviations

SCIT subcutaneous immunotherapy
SLIT sublingual immunotherapy

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1528-4050

Table 1 Randomized controlled trials of efficacy published in 2004–2006

Author (Ref.)	Age range	Act/Pla	Allergen	Duration	Dose	Disease
Tonnel <i>et al.</i> [10]	7–45	15/17	Mites	2 yrs	1.28 mg Der p1	R
Bufe <i>et al.</i> [11]	6–13	68/74	Grasses	3 yrs	Cumulative: 2,650,000 AU= 9.6 mg Phl p5	R/A
Smith <i>et al.</i> [12]	18–60	45 1 yr, 46 2 yr 46 pla	Grasses	1 yr 2 yrs	6.2 mg Lol p 1, 3.6 mg Dac g 1 /year	R
Rolinck-Werninghaus <i>et al.</i> [13]	3–14	39/38	Grasses	3 yrs	Cumulative: 188 mcg group 5 allergens	R
Bowen <i>et al.</i> [14]	6–52	36/40	Ragweed	4 mths	Cumulative: 10 to 30 mg Amb a 1	R
Dahl <i>et al.</i> [15]	18–64	61/32	Grass	6 mths	Cumulative 2.7 mg Phl p 5	RC
Niu <i>et al.</i> [16**]	6–12	49/48	Mites	6 mths	Cumulative 1.7 mg Der p and 3 mg Der f	A
Passalacqua <i>et al.</i> [17]	56	28/28	Mites	2 yrs	Cumulative: 104,000 AU (Allergoid)	R
Durham <i>et al.</i> [18**]	18–60	815	Grasses	4 mths	0.06 mg Phl p 5/4 mths; 0.6 mg Phl p 5/4 mths; 1.8 mg Phl p5/4 mths	R

A, asthma; RC, rhinoconjunctivitis; R, rhinitis.

reducing symptoms of rhinoconjunctivitis, and, when present, also concomitant asthma. It was recently shown that SLIT is also significantly effective in mild persistent rhinitis [16**], and therefore an extension of the indications for SLIT also to this situation is possible. A recent multi-centre study in more than 800 grass-allergic subjects clearly displayed the dose-dependence of the clinical effect of SLIT [18**]. A study by Niu *et al.* [16**] showed that 6 months of SLIT was able to reduce asthma symptoms and the need for medication significantly. In addition, Marogna *et al.* [19], in a randomized controlled open study in birch pollinosis, clearly showed evidence of the beneficial effect of SLIT on both subjective and objective parameters (e.g. pulmonary function test and methacholine reactivity). Similarly, Pajno *et al.* [20], in a randomized double-blind study in children with parietaria allergy, showed that SLIT abrogates in-season non-specific bronchial hyperresponsiveness. A previous meta-analysis on 22 subjects and 979 patients up to and including September 2002 in allergic rhinitis concluded that there was a significant efficacy of SLIT over placebo [21**], but there were too few studies on the use of SLIT to treat allergic asthma to form a meta-analysis. Another meta-analysis on the treatment of allergic rhinitis with SLIT in paediatric patients [22], involving 10 trials, showed that it is effective as assessed by symptom scores and rescue medications.

Safety

The good safety profile is one of the major advantages of SLIT. Looking at the literature, no severe or life-threatening event has ever been described or reported in approximately 20 years of trials and clinical use. Moreover, several postmarketing surveys conducted on large populations and in real life have consistently reported an overall occurrence of adverse events (including mild local reactions) of less than 10% of the patients and less than one per 1000 doses [23–28,29**]. In recent years, much attention has been paid to safety in children. As immunotherapy acts as a biological response modifier, its early use is expected to produce great clinical benefits. It is well known that the age of 5 years is considered to be a

relative contraindication for SCIT, mainly because in young children any reaction may be more severe and more difficult to treat than in adults. In the past year, several postmarketing surveys have been conducted in the paediatric population, some of them also involving children aged between 3 and 5 years [27,29**]. The safety profile has also been confirmed to be optimal in the case of young children. The rate of all adverse events has never been reported as greater than 10% (Table 2), but it is important to notice that at least 80% of the adverse events were local, mild and self resolving. The most troublesome side-effects, reported only in a minority of patients were gastrointestinal complaints such as stomach ache or nausea. A controlled dose finding study of safety [30**] 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 approximately 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.

Looking at the published controlled trials, the relationship between dosage and side-effects is not completely defined, although local effects (oral itching) seem to be dose dependent [30**], whereas systemic effects are too few to provide clear information. On the other hand, a recent review of the published studies [31] demonstrated that local side-effects are even more frequent with low doses of allergen, whereas gastrointestinal complaints are clearly dose related. In that review it was clearly shown that the overall occurrence of all adverse events is not related to the dose administered.

Mechanisms

The majority of clinical trials conducted so far with SLIT have mainly focused on efficacy and safety, and only few data on the mechanism of action were provided. Nevertheless, in the past few years the immunological aspects of SLIT have begun to be investigated. In some studies SLIT was associated with modest increases in

Table 2 Adverse events reported in the postmarketing surveys

Ref.	No. patients	Age range	Average follow-up	Allergens	Cumulative dose/year	AE % of patients	AE/1000 doses
Di Rienzo <i>et al.</i> [23]	268	2–15 years	3 years	54% mites 25% grass 6% parietaria 16% mixed	200 µg Der 1 39 µg group 5 24 µg Par j 1	3%	0.083/1000
Lombardi <i>et al.</i> [24]	198	> 14 years	3 years	35% mites 38% grass 23% parietaria 4% others	104 000 AU for all allergens	7.5%	0.5/1000
Pajno <i>et al.</i> [26]	354	5–15 years	3–4 years	42% mites 20% parietaria 11% grass 7% olive 20% mixed	120 µg Der 1 30 µg Par j 1 72 µg group 5432 µg Ole e 1	6%	0.15/1000
Drachenberg <i>et al.</i> [25]	159	6–60 years	< 1 year	16% mites 37% grass 12% trees 35% other/mix	Not stated	6.3%	Not stated
Agostinis <i>et al.</i> [27]	36	3–5 years	2 years	House dust mites 19 Grasses 17	90 000 AU for both allergens	5%	0.07/1000
Di Rienzo <i>et al.</i> [29**]	128	3–5 years	2 years	62% mites 22% grass 12% parietaria, 4% others	174 µg Der 1 39 µg group 5 24 µg Par j 1	5.6%	0.2/1000
Fiocchi <i>et al.</i> [28]	64	3–7 years	8 months	68% mites 8% parietaria 18% grass 6% other	Mean cumulative 36 000 ± 2000 IR	18%	Not stated

AE, adverse event.

IgG, a transient increase in IgE, suppression of eosinophil recruitment and activation in target organs [11,32,33**,34,35]. On the contrary, other studies failed to demonstrate changes in systemic T-cell and cytokine response [36,37] or local changes in the sublingual mucosa [32]. Interestingly, two studies reported an increase in production of the regulatory cytokine IL-10 [38*,39], and another study showed a reduction of the T helper type 2 cytokine IL-13 [40]. Savolainen *et al.* [41] demonstrated *in vitro* that SLIT reduces the expression of IL-5 and enhances the expression of IL-10 in peripheral blood mononuclear cells stimulated with the allergen. Further studies are needed to determine whether the same or alternative mechanisms are important for the effects of SLIT. Overall, the clinical effects of SLIT resemble those of SCIT, and the data available suggest that the mechanisms of action of the two routes are partly similar [42**]. Nevertheless, a more detailed definition of the mechanisms of action of SLIT is mandatory, and it will probably represent a major research field.

Concerning the biodistribution of allergens in humans, the only studies available up to now had been conducted with the Par j 1 allergen and allergoid [43]. The studies clearly showed that the direct passage of the allergen through the mucosa of the mouth is absent or negligible, thus disproving the claimed risk of a too rapid absorption. Very recently, similar results were obtained in allergic volunteers with the purified Der p 2 allergen and its allergoid [44*]. This finding confirms that the biodistribution (no oral absorption, long persistence in the mouth, absorption of the intact allergoid) of allergens does not depend on the type of molecule.

Prevention

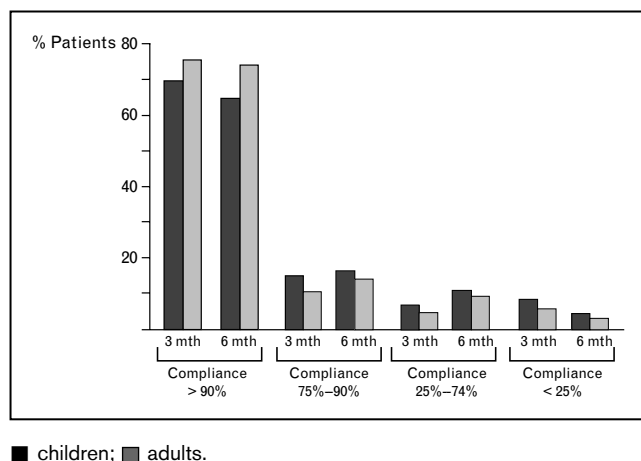
As a result of the fact that SLIT has only been available for the last 15 years, some aspects are obviously still unresolved. For example, it was claimed that SCIT is

superior to SLIT because it can exert a preventive effect on both new sensitizations [45,46] and on the onset of asthma [47]. It was also recently demonstrated that SLIT can prevent the onset of new sensitizations. In a study involving more than 500 patients, the rate of occurrence of new sensitizations was 5.8% in the active group and 38% in the control group ($P < 0.001$) [48]. More importantly, a study by Novembre *et al.* [49], performed in children, demonstrated that SLIT is capable of reducing the risk of asthma onset. In that study, 97 children with rhinitis only were subdivided into two groups receiving either drugs or drugs plus SLIT for 3 years. In the active treatment group, asthma occurred in six children in the first year, in seven in the second year, and in eight in the third year. In the control group, the corresponding numbers were six, 16 ($P = 0.06$), and 18 ($P = 0.04$). Three years of co-seasonal SLIT thus reduced the occurrence of asthma, beginning in the second year of treatment.

Adherence

Adherence or compliance may be defined as 'the degree to which a patient's behaviour coincides with the physician's recommendations for treatment'. As for drug therapy, also with immunotherapy, adherence to the scheduled regimen is critical for the successful outcome of the treatment [50*]. In the case of SLIT, adherence has always been considered a major concern, because the treatment is self-administered. On the contrary, the adherence to SCIT is commonly believed to be optimal because it is administered by the physician. The problem of compliance with SLIT was systematically addressed in two recent studies. Both studies employed the method of random telephone interviews, in which patients are asked to count the remaining tablets or monodose vials at that moment. In the first study [51] involving 126 patients, adherence was 95% for pollen immunotherapy and 97% for mite immunotherapy. In the second study [52**], conducted in more than 400 patients, the adherence rate

Figure 1 Comparison of the compliance rate by the method of random telephone interviews at 3 and 6 months, in an adult ($n = 443$) and paediatric ($n = 71$) population



at 3 and 6 months was greater than 90% in approximately 75% of the patients. A similar study was recently conducted using the same method in a population of 70 children, and the results on compliance did not differ from those in adults (Fig. 1). On the contrary, one retrospective study by Pajno *et al.* [53] showed that the adherence was slightly greater with SCIT than with SLIT, but no quantitative assessment was provided in the study.

Current and future developments

The good safety profile of SLIT is likely to allow its indications to be expanded to conditions other than respiratory allergy. A single recent study [33^{••}] demonstrated that SLIT is clinically effective in the treatment of IgE-mediated food allergy to hazelnut, and encouraging reports are available on the use of SLIT in latex allergy [54]. Another possible field of investigation is the desensitization for nickel allergy, but in this case there are only basic studies in animal models [55].

Given the safety profile of SLIT in adults and children, it has been proposed that the traditional slow up dosing phase would not be necessary; this is in order to make the treatment more patient friendly and convenient to manage. There have been some reports with ultra-rush (less than 2 h) up dosing, showing that the rapid increase in the doses does not lead to an increase in side-effects [56,57]. Subsequently, preliminary experiences with no up dosing (i.e. starting SLIT with the maintenance dosage) confirmed the feasibility of this method of administration [58]. The most recent large randomized trials [15,18^{••}] were all performed with the no-up dosing regimen, and their results in terms of safety were as favourable as those of studies using the traditional regimens. A recent randomized trial compared the safety of

the traditional up dosing regimen with no up dosing [59] in 135 patients, and found no difference in the adverse events rate between the two groups.

Conclusion

The treatment of respiratory allergy is based on allergen avoidance, pharmacological treatment and immunotherapy. Immunotherapy is an allergen-oriented immunomodulator that affects the immune response to allergens and which action develops over long times (months). SLIT represents a significant advance because of its safety and good acceptance, and it appears particularly suitable in paediatric patients, in whom an optimal safety profile is required. Although more studies are needed about the mechanisms of action, pharmacoeconomics, optimal doses and optimal patients [60^{••}], the aforementioned data further confirm the official position and justify the tangible change in the general opinion, which considers SLIT a more acceptable treatment [61]. Nonetheless, self-administration needs careful instruction and a detailed follow-up of the patients. Its prescription must be made only by a specialist, after a detailed diagnosis has been established, and the expected benefit/cost ratio has been carefully evaluated.

References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 505–506).

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