

Sublingual immunotherapy: an update

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Purpose of review

Sublingual immunotherapy is now officially accepted as a viable alternative to the traditional subcutaneous route, and it is widely used especially in European countries. Despite the large amount of experimental evidence on the safety and efficacy of the method, some concerns still exist, and several aspects need to be clarified: magnitude of the efficacy, adherence, long-lasting effect and others. Recently published studies have provided answers to some of these points.

Recent findings

The most recent studies have shown that sublingual immunotherapy exerts a long-lasting effect up to 5 years after discontinuation and that it is able to prevent the onset of new sensitizations. Moreover, when systematically assessed, the adherence to treatment is quite satisfactory, despite the treatment being self-administered. In addition, evidence has been provided that sublingual immunotherapy is effective in treating allergic conjunctivitis, and a metaanalysis has confirmed its efficacy in rhinitis. Moreover, some studies have addressed the possibility of simplifying the schedule of administration by shortening the build-up phase.

Summary

More and more new data on sublingual immunotherapy are rapidly appearing in the international literature. These data confirm the clinical value of this treatment and show that it is comparable to subcutaneous immunotherapy from several points of view.

Keywords

sublingual immunotherapy, long-lasting effect, adherence, efficacy

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Abbreviations

SCIT subcutaneous immunotherapy
SLIT sublingual immunotherapy

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Introduction

Allergen-specific immunotherapy, together with drug therapy and allergen avoidance, is a cornerstone in the management of respiratory allergy in both adults and children. Immunotherapy used to be administered only via the subcutaneous route (SCIT) from the early 1900s until the mid-1980s, when serious concerns about its safety were raised [1]. Starting from that time, clinical research with noninjection routes rapidly developed and sublingual immunotherapy (SLIT) has been regarded as a preferred alternative to SCIT since its introduction in 1986, especially because of its optimal safety profile. Indeed, during the last 15 years, much evidence on the clinical efficacy of SLIT in rhinitis and asthma has been provided in the international literature [2], together with a concomitant objective assessment of its safety. Based on controlled trials and the post-marketing surveillance studies [3,4], an international panel of experts, on behalf of the World Health Organization, has recently validated SLIT for routine clinical use in adults and children [5], with the same indications that are suggested for SCIT. To date, SLIT is commercialized 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 (about 3–300 times higher), so it is defined as 'high-dose SLIT'.

Despite the official positions and the relatively wide clinical use, it is still claimed that many aspects of SLIT need to be elucidated, especially in comparison to the results previously obtained with SCIT. The main concerns about SLIT are (1) the long-lasting efficacy, (2) the capacity of exerting a preventive effect, (3) the complete lack of data on the adherence of patients, and (4) the extent or magnitude of its clinical efficacy. During the last 2 years, new studies plus a metaanalysis evaluation have been published, and therefore some answers to the aforementioned questions could be provided.

Recent experimental results

The interest in SLIT is testified by the increasing number of studies published yearly, aimed at investigating not only the clinical aspects (efficacy and safety), but also the mechanisms and mode of action.

New data on the efficacy

SLIT was firstly investigated in a double-blind, placebo-controlled trial in 1986 and, to date, 25 controlled trials

conducted with adequate methods have been published (Table 1). In addition to the articles previously reviewed [6•], three further randomized controlled trials were recently published [7•,8•,9•]. In the first trial [7•], the authors evaluated 60 patients with perennial allergic conjunctivitis for 24 months and found a clear-cut increase in the threshold dose for conjunctival provocation and a significant clinical efficacy over placebo starting from 12 months of treatment. In a double-blind versus placebo study, Andr   *et al.* [8•] examined the efficacy of SLIT with a ragweed extract given to 99 patients for 6 months. This study also confirmed the efficacy of the treatment on rhinitis symptoms and reported a lower occurrence of asthma in the active group. The magnitude of the efficacy seemed to be at least in part dose dependant. Ippoliti *et al.* [9•] evaluated the effects of SLIT in 86 children with asthma and rhinconjunctivitis due to mites and found, after 6 months of treatment, a significant improvement in asthma and rhinitis symptoms, and a significant effect on the forced expiratory volume in 1 s. A recent article [10] provided the results of an uncontrolled and nonrandomized retrospective study involving 288 children treated with SLIT. The authors reported that complete remission was obtained in about 80% of the patients, and this was accompanied by significant changes in objective parameters such as rhinomanometry.

Overall, in the available studies, the magnitude of clinical efficacy ranged between about 20 and 50% –

fairly superior to an eventual placebo effect. Despite this, some concerns were raised about the extent of efficacy [15]. Indeed, very recently, Wilson *et al.* [16•] evaluated the efficacy of SLIT in allergic rhinitis in a metaanalysis. Twenty-two randomized, placebo-controlled trials were included, four of them performed in children, and involving 979 patients. The metaanalysis concluded that SLIT significantly differs from placebo in reducing symptoms and need for medication in allergic rhinitis, and that the safety overall is satisfactory.

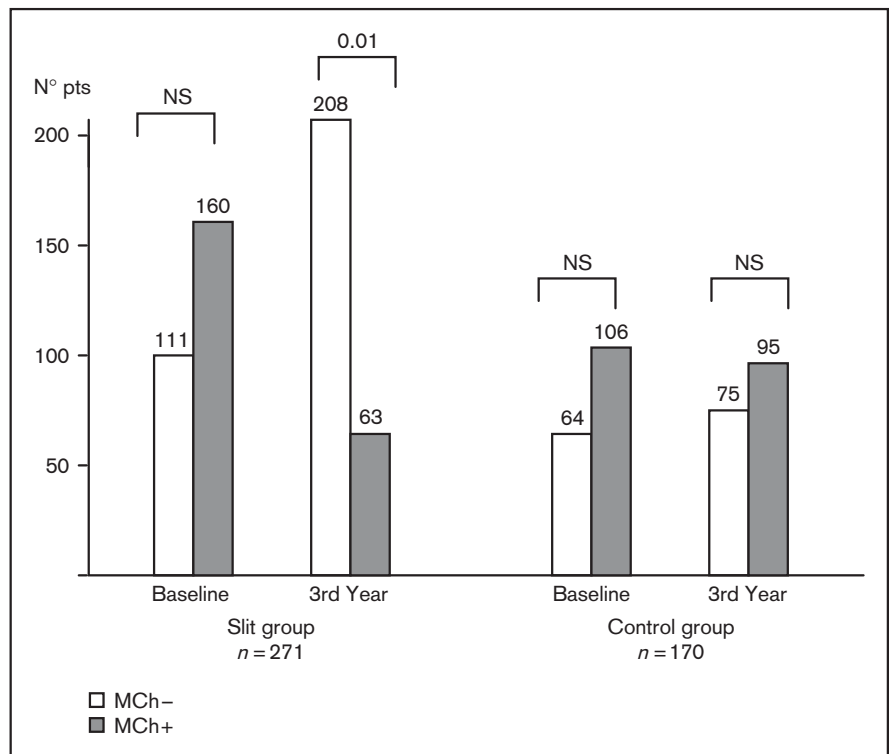
Finally, the authors can now provide the results of a study on a very large number of patients in a real life setting [17]. More than 500 patients, with rhinitis or mild intermittent asthma, were randomized to receive either SLIT ($n=319$) or pharmacotherapy ($n=192$). Clinical scores, adherence, skin sensitization and methacholine responsiveness were recorded in the subsequent 3 years. The dropout rate was 15% in the SLIT group and 12% in the control group ($P=NS$). The clinical score approximately halved in the active group versus baseline, starting from the first year of therapy, and the improvement was even greater after 3 years. Interestingly, there was a significant change in nonspecific bronchial hyper-reactivity: methacholine negative patients were 160/271 at the beginning and 63/271 at the end of the study in the active group ($P=0.01$), whereas in the control group the positivities were 106/170 at the beginning and 95/170 at the end (Fig. 1). The adherence to treatment was over 80% in 72% of patients and over 60% in 18%. The rate of occurrence of new sensitizations was 5.8% in the active

Table 1. Summary of the double-blind placebo-controlled studies of sublingual immunotherapy (for reference list see Ref. [6•])

Reference	Age range	Patients, A/P ^a	Allergen	Duration	Cumulative dose	Disease ^b
[11]	5–12	30/28	Mites	18 months	365 STU	R/A
	13–51	19/29	Grasses	17 weeks	4.500 IR	R
	14–48	18/16	Grasses	3.5 months	25 BU	R
	17–60	15/16	Parietaria	10 months	105 BU	R
	6–16	15/15	Mites	1 year	570 µg Der p 1	R/A
	15–46	10/9	Mites (monoid)	2 years	10.000 AU	R
	7–17	33/31	Olive	2 years	4 mg Ole e 1	R/A
	8–55	62/28	Grasses	6 months	28 µg Phl p 5	R/A
	16–48	18/16	Birch	4 months	250 STU	R
	18–45	30/27	Grasses	6 months	100.000 BU	R/A
	15–37	15/15	Mites	2 years	25 mg Der p 1	A
	15–42	15/15	Parietaria	8 months	16 mg Par j 1	R/A
	6–25	59/61	Grasses	4 months	5.000 STU	R/A
[12]	6–14	20/21	Parietaria	6 months	4.000 STU	R/A
	14–50	14/16	Parietaria	8 months	12 mg Par j 1	R/A
	8–15	12/12	Mites	2 years	2.4 mg Der p 1	A
	6–51	24/18	Mites	2 years	2.2 mg Der p 1	R
	4–14	24/20	Grasses	3 months	32.000 AU	R/A
[13]	19–50	10/10	Cypress	8 months	250.000 RU	R/A
	7–15	8/7	Mites	6 months	2.000 IR	R/A
	15–52	24/13	Trees	24 months	4.000 IR	R
	16–48	24/22	Grasses	18 months	16 mg Phl p 5	R
	6–60	26/19	Mites	24 months	2.2 mg Der p 1	C
	6–55	48/51	Ragweed	7 months	–	R
	5–12	47/39	Mites	6 months	12 µg Der p 1	R/A

^aA/P, active/placebo; ^bR, rhinitis; A, asthma; C, conjunctivitis.

Figure 1. Absolute number of patients with positive (MCh+) and negative (MCh-) methacholine challenge in the two groups, before and after 3 years of sublingual immunotherapy



group and 38% in the control group ($P < 0.001$). This study showed for the first time that SLIT exerts a preventive effect on new sensitizations. This is in agreement with the observation previously reported for subcutaneous immunotherapy [18,19].

Long-lasting efficacy

SCIT has been shown capable of modifying the natural history of the disease (i.e. the onset of asthma in rhinitis patients) [20**] and of preventing the onset of new sensitizations. Moreover, a long-lasting effect of SCIT after discontinuation has been repeatedly shown in several clinical trials [21]. Very recently, a controlled trial also confirmed the long-lasting efficacy for SLIT. Di Rienzo *et al.* [22**] performed a prospective parallel groups controlled study in 60 children (mean age 8.5 years) suffering from allergic asthma/rhinitis due to mite. Thirty-five underwent a course of SLIT with standardized extract and 25 received only drug therapy. The patients were evaluated at baseline, at the end of SLIT and 4–5 years later. A significant difference was found in the SLIT group compared with baseline concerning the presence of asthma ($P < 0.001$) and the Peak Expiratory Flow Rate (PEFR) even 5 years after discontinuation, whereas no difference was observed in the control group. Madonini *et al.* [23] carried out a retrospective open study with a mean follow-up time of 11.6 months after

discontinuation of SLIT. They found that 80.8% of patients maintained the previously achieved benefits. Moreover, during the follow-up, only 1% of patients without asthma reported the onset of lower respiratory symptoms, and only 9.6% of patients showed new skin sensitizations. The clinical benefits seemed linked to the duration of the treatment.

Reduction of priming

Recently, Cirila *et al.* [24] demonstrated a reduction in priming due to tree allergy in patients sensitized to both birch/hazel and grass pollen. The patients received an associated preseasonal SLIT/SCIT. Thirty-six out of 49 patients with double sensitization were matched in 18 case-referent couples. During 2 years all patients were administered pre-seasonal grass SCIT and one patient in each couple also received birch/hazel SLIT. The follow-up documented a significant increase in grass and birch-specific IgG and a decrease in grass-specific IgE. The Grass-Specific Nasal Provocation Test threshold was clearly higher in the SLIT–SCIT group and only in this group did PD20-methacholine improve significantly.

New administration schedules

The optimal safety profile of SLIT, including the absence of severe side effects even when high doses are given, suggested the possibility of simplifying the

administration schedule. This previously included local nasal immunotherapy; however, it was shown that a build-up phase with gradually increasing doses was not needed [25,26]. Indeed, accelerated build-up phases have been proposed in the past, with favorable results [12]. This would obviously result in a more easy management of the treatment by patients. Nevertheless, the best simplification would be the complete abolition of the build-up phase itself. This means starting with the maximum (maintenance) dosage and continuing the course with the same steady dose. One recent four parallel group study [27•], with different build-up regimens, showed that starting with higher doses (100-fold with respect to traditional schedule) does not modify the safety profile of the treatment.

Adherence

Adherence in medicine may be defined as 'the degree to which a patient's behavior coincides with the physician's recommendations for treatment'. For drug therapy, as with immunotherapy, adherence to the scheduled regimen is critical for the successful outcome of the treatment. In the case of SLIT, the adherence has always been considered a major concern, since the treatment is self-administered. Conversely, the adherence to SCIT is commonly believed to be optimal because it is administered by the physician. Indeed, looking at the few studies available for SCIT, the rate of spontaneous discontinuation ranges between 10 and 34% [28–30]. The problem of the adherence to SLIT was systematically addressed in a real-life setting [31]. Consecutive patients receiving SLIT in tablets for mites or pollens underwent random telephone interviews and were asked to count the remaining tablets at that moment. By means of a computerized program, it was possible to establish exactly the number of tablets taken versus the number expected at a given time. After 1 year of observation, the data from 35 patients (mean age 26.5) were available. The adherence was 95% for pollen immunotherapy and 97% for mite immunotherapy. There were four dropouts in the pollen groups, due to early beginning of the pollen season and subsequent discontinuation of SLIT.

Directions for future research

As previously mentioned, during the last years, new fields of investigation with SLIT began to be explored, mainly in order to demonstrate that SLIT is equivalent to subcutaneous SCIT. Therefore, the prevention aspects and the mechanisms of action have become crucial subjects of investigation. Despite that, some aspects of SLIT still need to be clarified.

Prevention

Obviously, due to the fact that SLIT has only been available for the last 15 years, some aspects are still

unresolved. For instance, it is not clear whether SLIT is able to exert a preventive effect on the onset of asthma in rhinitis patients. It has recently been shown that SLIT exerts a long-lasting effect and prevents new sensitizations similarly to SCIT, and for this reason, it is expected that SLIT is also capable of preventing the clinical onset of asthma in rhinitis patients. Despite this hypothesis, so far there has been no study showing an effect on the natural history of the disease, and studies in this sense are urgently needed.

Dose

Based on the literature, the effective doses of allergen range between 3–5 and 375 times the doses of SCIT, but this is the only information available. Some considerations can be made based on the literature. First, the dose interval of efficacy is quite wide, and there is no proof that one particular dosage performs better than another. Secondly, it is difficult to compare the various trials, since in most of them the amount of major allergen(s) administered is not reported. Thirdly, it is still not known whether the clinical efficacy is proportional to the dose. In fact, with both very high and very low doses, favorable and unsatisfactory results have been reported. Conversely, it has been ascertained that high amounts of allergen are associated with troublesome gastrointestinal symptoms [13].

Costs

The cumulative dose of allergen given sublingually is several times the usual dose of SCIT and therefore the cost of the vaccine is generally higher. It is expected that this cost is indeed effectively balanced by the reduced need for medical and nursing time, so that the global cost of SLIT is even lower than that of SCIT [6•]. Nevertheless, to date, a formal cost-benefit analysis is still lacking.

Mechanisms

The majority of the clinical trials conducted so far with SLIT have aimed at demonstrating its efficacy and safety and there are only few data on the mechanism of action. Nevertheless, some of the more recent studies have begun to investigate different aspects of the immunological effects of SLIT. It is well established that SLIT is capable of downregulating the expression of adhesion molecules on nasal and conjunctival epithelia and the concomitant influx of inflammatory cells [11,12]. These observations were recently confirmed in an open study on 10 children, in which SLIT was able to reduce intercellular adhesion molecule type 1 expression on nasal epithelial cells and to decrease methacholine responsiveness [32•]. Furthermore, in a double-blind controlled trial, SLIT exerted effects on systemic immunoglobulins super-imposable to those observed with SCIT [14•]. In the study by Ippoliti *et al.* [9•], no

change in CD40+ peripheral lymphocytes was detectable, but a decrease of serum eosinophil cationic protein (ECP) and IL-13 was clearly shown. This latter fact is in agreement with the hypothesis of an effect on the Th2/Th2 balance. A recent double-blind study by Marcucci *et al.* [33], conducted on 24 children with mite allergy, showed that SLIT prevents the increase of nasal tryptase after specific allergen challenge, although no change in nasal ECP could be detected. Finally, at variance with SCIT, there are consistent data on the pharmacokinetics of SLIT, showing that the contact with sublingual mucosa is critical [34].

Overall, the clinical effects of SLIT resemble those of SCIT, and the data presently available suggest that the mechanisms of action do not differ between the two routes. Nevertheless, a more detailed definition of the mechanisms of action of SLIT is mandatory and it will probably represent a major research field.

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 its action develops over a long period (months). The local routes, SLIT in particular, represent a significant advance because of their safety and good acceptance; they appear to be particularly suitable for use in pediatric patients, when an optimal safety profile is required. Even though more studies are needed to gain insight into the mechanisms of action, the potential effect of SLIT over the mucosal regulation of the immune system may confer an additional rationale for its prescription. Nonetheless, the self-administration itself 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 cost-benefit ratio has been carefully evaluated.

So far, the clinical efficacy of SLIT in both asthma and rhinitis has been supported by a large number of controlled trials. As far as rhinitis is concerned, the efficacy over placebo has also been confirmed by a metaanalysis. The more recent results have provided answers to some of the unresolved questions relating to its long-lasting effect, prevention of new sensitizations and optimal adherence. The aforementioned reasons further confirm the official position and justify the tangible change in the general opinion, which accepts SLIT as a more and more effective treatment [35,36]. Due to its optimal safety profile and the fact that it can be managed at home, SLIT seems to represent an optimal choice for pediatric patients [37], although data on its preventive effects are still lacking.

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