

Sublingual immunotherapy: what lessons can we draw from recent studies?

Immunothérapie sublinguale: quelle leçon tirer des études récentes?

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Abstract

Allergen-specific immunotherapy, together with drugs and allergen avoidance, is a cornerstone in the management of respiratory allergy. The traditional subcutaneous route is burdened by the risk of severe adverse events; therefore, safer routes of administration (e.g. local routes) have been developed and are being investigated. Controlled clinical trials have failed to demonstrate the clinical efficacy and the safety of oral or bronchial administration, and these routes have been abandoned. Local nasal immunotherapy proved effective and safe in 17 of 18 controlled trials; thus it could be considered to be a viable route of immunotherapy. Nevertheless, nasal immunotherapy is effective in rhinitis only and requires a particular administration technique; therefore, its use is slowly declining. In contrast, the efficacy of sublingual administration in the treatment of asthma and rhinitis in adults and children is supported by numerous controlled trials. The safety profile, assessed in clinical trials and post-marketing surveillance studies, is satisfactory; the most frequent side effects are gastrointestinal complaints, which can be easily managed by proper adjustment of the dose. The World Health Organization now considers sublingual immunotherapy as a valid alternative to the subcutaneous route, including its use in children. The long-lasting efficacy of treatment via the sublingual route has been documented recently but a number of points still need to be investigated, including mechanisms of action, optimal dosage, cost-effectiveness and patient's adherence.

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Résumé

L'immunothérapie spécifique, ainsi que les drogues et l'éviction l'allergène, est très importante dans la gestion de l'allergie respiratoire. L'immunothérapie sous-cutanée traditionnelle est chargée du risque d'événements défavorables graves ; donc, les voies d'administration plus sûres (ou voies locales) ont été étudiées et développées. Les études n'ont pas démontré l'efficacité clinique et la sûreté de l'administration orale et bronchique, et ces voies d'administration ont été abandonnées. L'immunothérapie nasale locale a démontré être efficace et sûre dans 17 entre 18 études contrôlées ; ainsi on la considère comme un itinéraire viable de l'immunothérapie. Néanmoins, l'immunothérapie nasale n'est efficace que contre la rhinite, mais elle exige une technique particulière d'administration et n'est plus guère utilisée. L'immunothérapie sublinguale est soutenue par de nombreuses études montrant son efficacité contre l'asthme et la rhinite chez les adultes et les enfants. Le profil de sûreté, évalué dans des épreuves cliniques et des études postmarketing de surveillance, est satisfaisant ; les effets secondaires les plus fréquents sont des troubles gastro-intestinaux, qui peuvent être facilement contrôlés par l'ajustement approprié des doses. L'immunothérapie sublinguale est maintenant également acceptée par l'Organisation mondiale de la santé chez les enfants comme alternative valide à la voie sous-cutanée. Bien que l'efficacité durable ait été récemment documentée pour la voie sublinguale, plusieurs points doivent toujours être élucidés, y compris les mécanismes d'action, dosage, rentabilité, et adhérence optimaux.

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1. Background

Allergen-specific immunotherapy or allergen vaccination is the practice of administering subjects with allergy increasing amounts of allergen(s) (the allergenic extract or vaccine) to achieve a hyposensitization and to reduce the symptoms occurring during the natural exposure to the allergen(s) itself. Since its discovery, immunotherapy has been commonly given subcutaneously (SCIT). Nevertheless, other modalities of administration were proposed and investigated during the last century, involving the administration of vaccines via gastrointestinal, nasal, or bronchial routes. Those routes have been variously named, i.e. alternative, nonparenteral, non-injection, or local routes. Presently, it is agreed that the most proper terms are local and non-injection, which are equivalent, whereas the word *alternative* has been abandoned because it might generate confusion with other unconventional medicines.

It is important to distinguish between the “pure” oral route and the sublingual. In fact, the experimental evidence showed that only this latter one is clinically effective. In sublingual immunotherapy (SLIT), the extract is usually kept under the tongue for 1–2 min and then swallowed; thus this route is also called sublingual-swallow. Indeed, in some studies a different method was adopted; the allergen was kept under the tongue and then spat out (sublingual-spit). Presently, on the basis of clinical results and pharmacokinetic considerations, only the sublingual-swallow route is used; therefore, throughout the text SLIT will indicate the sublingual-swallow modality.

Since the first empirical attempt [1], immunotherapy was administered subcutaneously and its clinical efficacy rapidly favored a widespread use. The idea of administering the allergenic extracts orally is not so recent as commonly believed; the oral route was first suggested in 1900 [2], and the first clinical attempts were made a few years later [3,4]. Subsequently, other routes of administration were proposed: the local bronchial during the 1950s [5,6], the local nasal [7,8] during the 1970s, and the oral at the beginning of the 1980s [9–11].

Except for local nasal immunotherapy, which was extensively studied starting from 1977, all the other mentioned approaches remained substantially anecdotal, because the use of the subcutaneous route was well established. In 1986 the British Committee for the Safety of Medicines [12] reported several deaths caused by SCIT and raised serious concerns about the safety and the risk/benefit ratio of immunotherapy, also because of the availability of cheap and effective drugs. Indeed, it was subsequently demonstrated that, in most cases, life-threatening events were due to avoidable human errors (wrong dose, improper prescription, incorrect administration) [13–15]. Nonetheless, the interest in non-injection routes of immunotherapy rapidly increased [16,17].

In 1998 a panel of experts of the World Health Organization, on the basis of an extensive review of the literature,

concluded that both sublingual (SLIT) and local nasal (LNIT) immunotherapy are viable alternatives to the injection route and that their use in clinical practice in adults is justified [18]. On the contrary, the pure oral and the bronchial routes were not recommended. These conclusions were soon confirmed in another position paper by the European Academy of Allergology and Clinical Immunology [19]. Finally, in 2001, the ARIA document [20] extended the indication of SLIT, also to children. Currently, SLIT is used in many European countries, whereas the use of LNIT is progressively decreasing, mainly because of technical limitations.

2. Experimental results

Currently, SLIT is the most widely used non-injection route for immunotherapy in Europe. Usually a SLIT course involves a buildup phase (extract administered at increasing doses) and a maintenance phase, in which the maximum dose is administered two or three times a week. Furthermore, SLIT can be administered preseasonally, pre-coseasonally, or continuously; pre-coseasonal schedules are the choice for pollen allergy, whereas continuous treatments are preferred for perennial allergens.

2.1. Efficacy

SLIT was first investigated in a DBPC rigorous trial in 1986 [17]; after 12 years, in 1998, the WHO position paper mentioned four studies, [18] and the EAACI/ESPACI document published in the same year considered six studies [19]. To date, 29 DBPC trials [21–49] conducted with adequate methods and analysis have been published in peer-reviewed journals (Table 1), thus testifying to the rapid development of the clinical interest in this route of administration.

All the studies but three [25,36,38] confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens such as grass, mites, birch, and *Parietaria*. There are also single positive studies with olive [28], cypress [39], ragweed [47] and mixed-trees [41] extracts. The magnitude of the clinical efficacy ranged between about 20% and 50% reduction of symptom or medication scores, thus quite superior to the placebo effect and close to the effect of SCIT.

Indeed, a very recent controlled study [42] failed to demonstrate a significant clinical effect (symptom score and medication intake) of SLIT in rhinitis due to grass, although the self-evaluation made by the patients was largely positive and a systemic immunologic effect was also apparent. Also in two other studies conducted with mite extracts [25,36] SLIT performed poorly; a trend toward clinical improvement was seen in the active groups, but it did not reach statistical significance. This fact is well known also for SCIT, which is usually less effective in patients with mite allergy than in patients with pollen sensitivity. In patients with mite allergy, the duration of the treatment seems to be crucial; in fact, those treatments lasting at least 2 years gave positive results [30,32,37].

Table 1
Summary of the DBPC studies of SLIT

Author, year	Age range	Patients A/P ^a	Allergen	Duration	Cumulative dose	Disease ^b
Tari, 1990	5–12	30/28	Mites	18 months	365 STU	R/A
Sabbah, 1994	13–51	19/29	Grasses	17 weeks	4500 IR	R
Feliziani, 1995	14–48	18/16	Grasses	3.5 months	25 BU	R
Troise, 1995	17–60	15/16	<i>Parietaria</i>	10 months	105 BU	R
Hirsch, 1997	6–16	15/15	Mites	1 year	570 mcg Der p1	R/A
Passalacqua, 1998	15–46	10/9	Mites (monoid)	2 years	10 000 AU	R
Vourdas, 1998	7–17	33/31	Olive	2 years	4 mg Ole e 1	R/A
Clavel, 1998	8–55	62/28	Grasses	6 months	28 mcg Phl p 5	R/A
Horak, 1998	16–48	18/16	Birch	4 months	250 STU	R
Hordijk, 1998	18–45	30/27	Grasses	6 months	300 000 BU	R/A
Bousquet, 1999	15–37	15/15	Mites	2 years	104 000 IR, 4.2 mg Der p 1	A
Passalacqua, 1999	15–42	15/15	<i>Parietaria</i>	8 months	265 BU, 16 mcg Par j 1	R/A
Pradalier, 1999	6–25	59/61	Grasses	4 months	11 000 IR, 0.935 mg Phl p5	R/A
La Rosa, 1999	6–14	20/21	<i>Parietaria</i>	6 months	75 000 IR, 52.5 mg Par j1	R/A
Purello, 1999	14–50	14/16	<i>Parietaria</i>	8 months	200 BU, 12 mcg Par j 1	R/A
Pajno, 2000	8–15	12/12	Mites	2 years	360 mcg Der p1	A
Guez, 2000	6–51	24/18	Mites	2 years	90 000 IR, 2.2 mg Der p 1	R
Caffarelli, 2000	4–14	24/20	Grasses (monoid)	3 months	37 000 AU	R/A
Ariano, 2001	19–50	10/10	Cypress	8 months	250 000 RU	R/A
Bahceciler, 2001	7–15	8/7	Mites	6 months	7000 IR, 0.56 mg Der p1	R/A
Voltolini, 2001	15–52	24/13	Trees	24 months	250 000 RU	R
Lima, 2002	16–48	24/22	Grasses	18 months	0.9 mg Phl p 5 per month	R
Mortemousse, 2003	6–60	26/19	Mites	24 months	90 000 IR, 2.2 mg Der p 1	C
Andre, 2003	6–55	48/51	Ragweed	7 months	Variable	R
Ippoliti, 2003	5–12	47/39	Mites	6 months	57 mcg Der p1	R/A
Pajno, 2003	8–14	15/15	<i>Parietaria</i>	13 months	23 mcg Par j1	R/A/C
Wutrich, 2003	6–13	11/11	Grasses	2 years	NA	R/A
Tonnel, 2004	7–45	15/17	Mites	2 years	1.28 mg Der p1	R
Bufe, 2004	6–13	68/74	Grasses	3 years	2650 000 AU, 9.6 mg Phl p5	R/A

^a A = Active; P = Placebo.

^b A = Asthma; R = Rhinitis; C = Conjunctivitis.

It is important to notice that SLIT exerts its effect not only on rhinitis but also on asthma symptoms. The result from some recent studies [32,35,37] showed a reduction of the days with asthma symptom [34], of the use of β_2 -agonists [32,34], of the intake of systemic steroids [26], and of clinical symptoms [32,35]. One single study also demonstrated a measurable effect of SLIT on the quality of life of patients [32], and another study showed that SLIT is effective also on mite-induced conjunctivitis [43]. Finally, in a randomized controlled study with *Parietaria* extract it was shown that SLIT significantly reduced the nonspecific bronchial hyper-responsiveness to methacholine measured during the pollen season [50].

2.2. Safety

The main rationale of SLIT is of minimizing the risks for adverse events; therefore, particular attention has been paid to safety in all the studies. The most frequently reported side effect was the onset of oral/sublingual itching after taking the dose. This phenomenon was always described as mild and self-resolving. In the recent pediatric studies, the occurrence of side effects was negligible and they were not troublesome [37–39]. In a single study [35] a significant rate of gastrointestinal complaints was reported, but in this study the amount of allergen was as high as 375 times the amount usually administered in a standard SCIT course. Headache,

rhinorrhea, constipation, and urticaria were reported only sporadically, and their incidence did not differ from the placebo groups. Noticeably, no severe systemic adverse event was ever reported in the literature during a period of 15 years. André et al. [51] recently reviewed the safety aspects of the controlled trials performed with the vaccines of a single manufacturer. Six hundred ninety subjects were enrolled (347 active + 343 placebo), with 218 children (103 active + 115 placebo). The large majority of events were mild. All events had a superimposable incidence in active and placebo groups, with the exception of the oral and gastrointestinal side effects, which were more frequent in SLIT patients, although mild. The occurrence of side effects and dropouts was similar in adults and in children. The information on safety provided by the controlled trials are valuable, but the populations are highly selected and the administration of SLIT is usually supervised. This situation is profoundly different from that occurring in the clinical reality. Therefore, more consistent information on safety should be obtained when SLIT is prescribed and administered in everyday clinical practice, i.e. in post-marketing surveillance studies. An early study of pharmacosurveillance [52] reported that the incidence of side effects was indeed low; oral itching represented about 50% of the untoward effects, followed by rhinorrhea and constipation. Urticaria and asthma were very rare. More than 90% of the effects were mild and did not require any kind of medical treatment. Di Rienzo et al. [53] performed a post-marketing study in 268 children aged between 2 and 15 years and receiving SLIT for up to 3 years; it showed that the overall incidence of systemic side effects was 3% of the patients and 1/12 000 doses. Of eight side effects, only one (urticaria) was moderate and required treatment with a single dose of oral antihistamine. Overall, in none of the patients the discontinuation of the treatment was required. Another pharmacosurveillance study in adult patients was recently published [54], with 198 patients observed while receiving SLIT either preseasonally or continuously during a 3-year-period. Side effects occurred in 7.5% of the patients and 0.52/1000 doses administered. Four urticaria and two gastrointestinal complaints were judged as moderate. Also in this study, side effects were controlled by a temporary dose adjustment and in no case was the treatment discontinued. It has been claimed that SLIT could be at particular risk in patients with oral allergy syndrome by possibly eliciting severe edema. Indeed, a controlled study performed in 30 patients with oral allergy syndrome did not confirm this hypothesis [55]. Finally, the possible effects of the sublingual administration of allergens were investigated by measuring the mucosal level of tryptase and eosinophil cationic protein; no change in the levels of these mediators could be detected at all, even in one patient reporting oral itching after SLIT intake [56].

2.3. Adherence

We evaluated patients receiving SLIT immunotherapy for mites and pollens in a real life setting [57], patients under-

went random telephonic interviews and were asked to count the remaining tablets at the moment. By means of a computerized program it was possible to establish exactly the number of tablets taken vs. the expected at a given time. After 1 year of observation, data from 86 patients (mean age 26.5) were available. The adherence was about 95% for pollen immunotherapy and 97% for mite immunotherapy.

Concerning the cost it is true that the dose (and the cost) of allergen given via sublingual route is high in SLIT; nevertheless it is easy to verify that the higher cost of the vaccine is balanced by reduced need for medical and nursing time and by the absence of the cost injections. Taking into account all these aspects, the global cost of SLIT is even less than the cost of SCIT [58].

3. Conclusions

Immunotherapy is an allergen-oriented immunomodulator that affects the immune response to allergens and whose action develops over a long time (months). SLIT represents a significant advance because of safety and good acceptance. Nonetheless, self-administration itself requires careful instruction and 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. The clinical efficacy of SLIT in both asthma and rhinitis is now supported by a large number of controlled trials, and a very recent double dummy study has shown that SCIT and SLIT are equivalent in terms of efficacy [59]. After a period of justified skepticism, because of the few studies available, in very recent years there has been a gradual change in the general opinion, and SLIT has become more and more accepted [60–64]. SLIT is, in general, suggested in patients showing low compliance with SCIT or with previous severe adverse reactions to SCIT, but it should not be considered as a last choice treatment. It is important to remember that SLIT must not be regarded as a substitute for SCIT, but rather as an additional choice or therapeutic tool. Similarly to SCIT, SLIT is not an alternative to drugs for controlling symptoms, but it must be used in combination with them.

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