

Oral and sublingual immunotherapy in paediatric patients

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Purpose of review

Sublingual immunotherapy is becoming a routine treatment for respiratory allergy in several countries and it has been validated in international documents. This article will review the available literature on oral and sublingual immunotherapy, discussing the possible use of sublingual immunotherapy in paediatric patients.

Recent findings

As oral immunotherapy was found to be poorly effective in clinical trials, its use has been discontinued. In contrast, several controlled studies have shown the efficacy of sublingual immunotherapy in children with allergic asthma and rhinitis, and a postmarketing survey has confirmed its safety. Moreover, new data on the long-lasting efficacy of this treatment and on the absence of local immunological effects have recently been published.

Summary

The clinical efficacy and the optimal safety profile of sublingual immunotherapy make it a good candidate for treating respiratory allergy in children. Some aspects, such as the dose–response relationship and preventive effect, will be a research challenge for future developments and better definition of indications in children.

Keywords

respiratory allergy, children, sublingual immunotherapy, safety, clinical efficacy

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Abbreviations

OIT oral immunotherapy
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. At variance with drugs, immunotherapy affects the immunological response towards allergens at its earliest stages [1], and therefore it can be regarded as a biological response modifier. This means that immunotherapy can reduce symptoms and the need for rescue medications, but it can also alter to some extent the natural history of allergic disease. This fact has been well demonstrated during the last decade in several experimental studies. In particular, it has been shown that immunotherapy can prevent the inception of new sensitizations [2,3] and the onset of asthma in children with allergic rhinitis [4•]. Furthermore, it was shown that immunotherapy could maintain its clinical efficacy for several years after discontinuation [5,6•]. Based on these observations, it is reasonable to regard immunotherapy as a particularly advantageous treatment in paediatric patients. In contrast, the traditional subcutaneous immunotherapy (SCIT) is burdened with the risk for severe adverse events, ranging from asthma and urticaria to anaphylaxis [7•]. The safety aspect was the major boost for the studies with noninjection or local immunotherapy, in particular those administered orally. The rationale for giving the allergen orally is that the gastrointestinal tract has an abundant mucosal immune system (gut associated lymphoid tissue) and therefore an effective antigen presentation can be expected [8]. There are two modalities for administering the allergen orally: the oral route (oral immunotherapy, OIT) and the sublingual route (sublingual immunotherapy, SLIT). With SLIT, the extract is kept under the tongue for 1–2 min and then swallowed (sublingual swallow). whereas in OIT the allergen is immediately swallowed. The common aim of these methods is obviously to improve the safety and make the treatment more acceptable for the patients.

Starting from the mid-1980s, a conspicuous number of controlled studies with OIT and SLIT were published. In 1998, a panel of experts of the World Health Organization [9], based on an extensive review of the available literature, concluded that SLIT is a viable alternative to the injection route, at least in adults, whereas OIT proved to be poorly effective. These conclusions were confirmed in a position paper of the European Academy of Allergology and Clinical

Immunology [10]. Subsequently, clinical trials and postmarketing surveillance studies were conducted in paediatric patients, and in 2001 the review on 'Allergic rhinitis and its impact on asthma' [11••] extended the indication of SLIT to paediatric patients.

We will review herein the available experimental data concerning the efficacy and safety of OIT and SLIT, with particular attention to paediatric patients.

Oral immunotherapy

The pure oral route represents, from a historical perspective, the starting point for the diffusion of SLIT. Initially, some trials [12,13] reported negative results and brought OIT into disfavour. Nevertheless, subsequent trials performed by Scandinavian groups with very high doses of allergen renewed the interest in oral administration. Nine trials of OIT are reported here, conducted with rigorous modalities [14–22], as summarized in Table 1. All the trials evaluated the effects of OIT on rhinitis (symptoms and drug intake) and the majority of them were conducted in children. Only three out of nine studies [16,18,19] showed a statistically significant improvement in symptoms. Of particular note, in a dust-mite study [19], a clinical improvement of rhinitis was achieved after 2 years of treatment, and improvement of asthma became significant only after 3 years. In several studies many untoward effects (although not life-threatening) were reported, including gastrointestinal complaints (nausea, vomiting, abdominal pain) and these were clearly dose-related [17]. The use of gastroresistant capsules did not ameliorate the profile of therapy [16,17,21,22]. Overall, OIT showed a marginal clinical efficacy and therefore it did not seem to be cost-effective. For these reasons its clinical use was abandoned from the early 1990s.

Sublingual immunotherapy

During the last 10 years, sublingual immunotherapy (SLIT) has been the subject of an impressive number of clinical trials that investigated different aspects of the treatment. Therefore, we have now available reliable

data concerning the efficacy, the safety and the immunological aspects. It is also true that some points still need to be fully elucidated.

Efficacy

SLIT was first investigated in a double-blind placebo-controlled trial in 1986 [23] and, to date, 22 trials [24–44,45•] conducted with adequate methods have been published, testifying to the rapid development of interest in this mode of administration. Nineteen out of 22 studies confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens (grass, mites, birch and parietaria), and some studies also showed a significant effect on asthma. The magnitude of clinical efficacy ranged between about 20 and 50% – quite superior to an eventual placebo effect.

SLIT was investigated in paediatric patients in seven studies (Table 2): four with mites, three with parietaria, olive and grasses. All studies, but one [28], reported a significant clinical efficacy of SLIT in reducing both symptoms and drug intake. Moreover, in some of the studies a measurable effect on skin reactivity or specific provocation tests was also reported [24,31,38]. Of particular note, in a study conducted on asthmatic children [40] treated for 2 years with mite extract, the decrease in symptoms and drug intake reached 60% on reaching the second year of treatment.

Safety

In the published trials, the most frequently reported side effect was oral/sublingual itching after taking the dose, followed by nonspecific gastrointestinal complaints (nausea, vomiting, abdominal pain). These side effects were always described as mild and self-resolving, and infrequently caused dropouts. In the recent paediatric studies, the occurrence of side effects was negligible and they were not troublesome. In a single study [38] 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, constipa-

Table 1. Oral immunotherapy double-blind placebo-controlled studies

Study	Age range (years)	Allergen	Duration	Patients, active/ placebo	Extract	Disease ^a
Cooper (1984) [14]	5–15	Grass	4 months	22/22	Aqueous drops	R
Taudorf (1985) [15]	11–44	Grass	6 months	25/27	Enteric-coated tabs	R
Moller (1986) [16]	9–17	Birch	10 months	14/16	Enteric-coated tabs	R
Mosbech (1987) [18]	15–38	Grass	12 months	24/27	Enteric-coated tabs	R
Taudorf (1987) [17]	16–47	Birch	18 months	18/21	Enteric-coated tabs	R
Oppenheimer (1994) [20]	3–13	Mite	3 years	10/8	Aqueous drops	R/A
Giovane (1994) [19]	4–14	Mites	3 years	10/8	Aqueous drops	R/A
Van Deusen (1997) [21]	19–49	Ragweed	14 weeks	12/11	Capsules	R
Litwin (1997) [22]	21–50	Ragweed	4 months	20/21	Capsules	R

^aR, rhinitis; A, asthma.

tion or urticaria have been reported only sporadically and their incidence did not differ from the placebo groups (Table 3). Noticeably, no severe systemic adverse event was reported in the literature over 15 years. André *et al.* [46] recently reviewed the safety aspects of the controlled trials performed with the vaccines of a single manufacturer. Six hundred and ninety patients were enrolled (347 active + 343 placebo), with 218 children (103 active + 115 placebo). Overall, adverse events had a

similar occurrence in active and placebo, with the exception of the oral and gastrointestinal side effects, which were more frequent in SLIT patients, although mild. In contrast, the occurrence of side effects and dropouts did not differ in adults and children. More consistent information on the safety can be obtained when SLIT is prescribed and administered in everyday clinical practice. Di Rienzo *et al.* [47] performed a post-marketing surveillance study in 268 children aged

Table 2. Sublingual immunotherapy double-blind placebo-controlled pediatric studies

Study	Age range (years)	Patients, active/ placebo	Allergen	Duration	Dose	Dose versus SCIT	Main results
Tari (1990) [24]	5–12	30/28	Mites	18 months	Cumulative: 365 STU 48 µg Der p 1/month	~ 5	↓ symptoms ($P < 0.001$) ↑ IgG ↓ skin reactivity ↑ nasal threshold
Hirsch (1997) [28]	6–16	15/15	Mites	1 year	Cumulative: 570 µg Der p 1	~ 5	↑ nasal threshold ↓ lung symptoms ($P < 0.05$) NS nasal symptoms
Vourdas (1998) [31]	7–17	33/31	Olive	2 years	Cumulative: 60 000 IR 4.05 mg Ole e 1/year	300	↓ lung symptoms ($P = 0.03$) ↓ eye symptoms ($P < 0.05$) ↓ oral steroids ($P = 0.03$)
La Rosa (1999) [38]	6–14	20/21	Parietaria	6 months	Cumulative: 150 000 IR 2.04 mg Par j 1/month	375	↓ skin reactivity = IgG, IgE, ECP ↓ nose symptoms ($P = 0.02$) ↓ skin reactivity ($P = 0.002$) ↑ conjunctivitis threshold ($P = 0.02$)
Pajno (2000) [40]	8–15	12/12	Mites	2 years	230.4 µg Der p 1 9.6 µg Der p 1/month	4	↑ IgG4; = IgE ↓ asthma episodes ($P = 0.001$) ↓ nighttime asthma ↓ medications ($P = 0.002$) = IgE, IgG1, IgG4
Caffarelli (2000) [41]	4–14	24/20	Grass	3 months	Cumulative: 37.250 AU	Not stated	↓ total symptoms ($P < 0.05$) ↓ symptom + drug ($P < 0.05$) ↓ EG2/EG1 ratio
Bahcecilier (2001) [43]	7–15	8/7	Mites	6 months	Cumulative: 7.000 IR (5.6 mg Der p 1)	~ 10	↓ asthma exacerb ($P = 0.001$) ↓ lung symptoms ($P = 0.07$) ↓ asthma medication ($P = 0.028$) ↑ PEFr; = PD20; = IgE

Ig, immunoglobulin; SCIT, subcutaneous immunotherapy; ECP, eosinophil cationic protein; PEFr, peak expiratory flow rate; STU, standardized units; IR, index of reactivity; AU, allergenic units; PD20, provocation dose 20%.

Table 3. Dropouts and side effects in the controlled studies of sublingual immunotherapy in pediatric patients

Study	Patients	Dropouts		Side effects	
		Active	Placebo	Active	Placebo
Tari (1990) [24]	66	8 not related to the study		3 urticaria 4 gastrointestinal	0
Hirsch (1997) [28]	30	1 side effect	–	1 asthma	0
Vourdas (1998) [31]	66	1 worsening	1 not related	8 oral itching	2 oral itching
La Rosa (1999) [38]	41	4 side effects 1 poor compliance	1 side effects 1 worsening 1 not related	8 oral itching 19 gastrointestinal 1 conjunctivitis 1 rhinitis	4 oral itching 1 gastrointestinal 1 conjunctivitis 1 rhinitis
Pajno (2000) [40]	24	0	2 not related 1 asthma	1 generalized itching 4 tiredness 2 oral itching	1 asthma 1 tiredness
Caffarelli (2000) [41]	48	0	1 not related 1 gastrointestinal	0	0
Bahcecilier (2001) [43]	15	0	0	0	0

between 2 and 15 years and receiving SLIT for up to 3 years. These authors showed that the overall incidence of systemic side effects was 3% of the patients and 1/12 000 doses. Out of eight side effects, only one (urticaria) was moderate and required treatment with oral antihistamines. Overall, discontinuation of the treatment was never required. Finally, the possible effects of the sublingual administration of allergens in children was investigated by measuring the mucosal level of tryptase and eosinophil cationic protein (ECP): no change in the levels of these mediators could be detected at all, even in one patient reporting oral itching after SLIT intake [48••].

Mechanisms and pharmacokinetics

Much is known about the possible mechanisms of action of SCIT, whereas SLIT has so far been studied mostly from a clinical point of view. Nevertheless, some interesting data have been published. First, SLIT has been demonstrated to be capable of reducing *in vitro* the proliferative response of T lymphocytes [49]. Second, a significant modulator effect of SLIT on allergic inflammation (cell influx and intercellular adhesion molecule type 1 expression) could be observed *in vivo* both in the nose [34] and the conjunctiva [33]. Very recently, an open study in 10 children confirmed that SLIT was able to reduce intercellular adhesion molecule type 1 expression on nasal epithelial cells and to decrease methacholine responsiveness [50•]. A relevant effect of SLIT on immunoglobulins could be observed only in a few studies [38,40,45•]. Recent studies have found an association between respiratory allergy, particularly asthma, and the type of microbes and microbial products colonizing the gastrointestinal tract. Reduced colonization of the gastrointestinal tract with Gram-negative bacteria such as *Lactobacillus* strain in children and previous hepatitis A infection are associated with reduced prevalence of asthma [51,52], suggesting that the orofecal born gastrointestinal tract infections and the type of gastrointestinal microflora could play a role in the maturation of the immune system, having an influence on the regulation of the respiratory immune response [53]. It has been suggested that both OIT and SLIT may use mucosal tolerance mechanisms, and they potentially could elicit allergen-specific tolerance and immune deviation through regulatory T cells [54••].

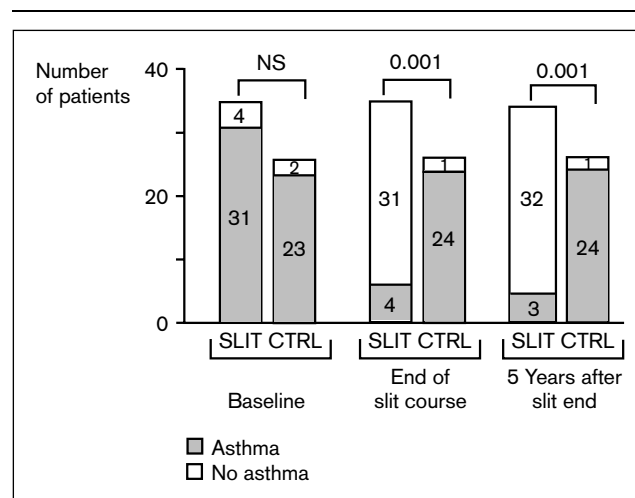
Very recently, the pharmacokinetics of local routes were studied in humans using a radiolabelled purified allergen (Par j 1) and a special procedure [55]. After the administration (oral, sublingual or intranasal) of the ¹²³I-radiolabeled allergen, sequential scintiscans, plasma radioactivity and plasma chromatographies were evaluated at different times. It was observed that no direct absorption of the allergen through the mucosae occurs: plasma radioactivity increased only after the allergen was

swallowed. Moreover, the allergen was retained for long periods of time (up to 40 h) at mucosal level, both in the nose and the mouth. Finally, the gastrointestinal absorption was relevant, but no trace of the native allergen could be detected in the bloodstream, whereas if a modified allergen was administered, traces of it could be detected in the plasma. Similar results were subsequently obtained in allergic volunteers using a commercial preparation [56•]. These data suggest that the contact of the allergen with the oral mucosa is critical and that the allergen is not absorbed in the mouth.

Long-lasting efficacy

SCIT has been shown to be capable of modifying the natural history of the disease (i.e. the onset of asthma in rhinitis patients) and of preventing the onset of new sensitizations. Moreover, a long-lasting effect of SCIT after discontinuation has been repeatedly seen in several clinical trials (for review, see [57•]). At present, such demonstrations are still lacking for local routes, since SLIT has been used routinely only in the last 10 years. We performed a prospective parallel group controlled study in 60 children (mean age 8.5 years) suffering from allergic asthma/rhinitis due to mites [58]. Thirty-five underwent a 4–5 year 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. In the SLIT group, we found a significant difference versus baseline regarding the presence of asthma ($P < 0.001$) and the use of asthma medications ($P < 0.01$) even 5 years after discontinuation, whereas no difference was observed in the control group (Figure 1).

Figure 1. Distribution of patients with and without asthma in the sublingual immunotherapy (SLIT) and control (CTRL) groups of children at three timepoints



The three timepoints are at enrolment, after 5 years of SLIT and 4–5 years after SLIT discontinuation. The inter-group differences are shown on the bars.

Open questions on sublingual immunotherapy

Although the clinical efficacy and safety of SLIT have been convincingly demonstrated, some aspects still need to be fully developed. Probably the most important point is the definition of the optimal dose to be administered. On examining the literature, we can only define a wide range of dosages within which SLIT is effective. This range extends from threefold to 375-fold the corresponding dosage of SCIT. We certainly know that gastrointestinal side effects increase in frequency when doses increase, but formal dose–response studies are still lacking. Recently, the possibility of administering SLIT without a build-up phase, starting with the maximum dosage, has been proposed [59].

Another aspect is the cost of SLIT: usually, oral vaccines are more expensive than injection vaccines (also because of the higher dose of allergen). Nevertheless, in this regard, the higher cost is effectively balanced by the reduced need for medical and nursing time, so that the global cost of SLIT is less than that of the injection route [60]. Finally, the possibility of administering SLIT to very young children (less than 5 years old) is attractive and realistic due to the safety of the treatment, but formal studies have not been performed yet.

Conclusion

The treatment of respiratory allergy is based on allergen avoidance, pharmacological treatment and immunotherapy [20]. Immunotherapy is an allergen-oriented immunomodulator which affects the immune response to allergens, developing over a long period of time (months). The local routes, SLIT in particular, represent a significant advance because of the safety and good acceptance; it appears particularly suitable in paediatric patients, in which 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 process needs careful instruction and a detailed follow-up of patients is required. Furthermore, prescription of SLIT 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 numerous controlled trials [61•]. For this reason, the initial scepticism [62] is progressively declining and SLIT is becoming, at least in principle, an ‘official’ treatment [63•,64,65]. Of course, the clinical efficacy and safety of SLIT have been confirmed in paediatric patients, although the demonstration of a preventive effect similar to that of SCIT [4•] is still lacking. In contrast, the long-lasting effect in children

has been well ascertained; therefore, the use of this modality of immunotherapy can be considered, overall, to be advantageous, especially when the optimal safety profile is taken into account.

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