Sublingual Immunotherapy in Pediatric Patients: Beyond Clinical Efficacy

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Abstract and Introduction

Abstract

Purpose of Review: Sublingual immunotherapy (SLIT) is widely used in several European countries. Many clinical trials and a meta-analysis presently support its efficacy, but limits and indications in pediatric age still need to be clarified. We review here the most recent literature on SLIT, with particular attention paid to the safety of children and to the additional clinical effects.
Recent Findings: In addition to clinical trials, post-marketing surveillance studies have confirmed the optimal safety profile of SLIT in adults and children, including those below the age of 5 years. The most recent studies have shown that SLIT, identically to the subcutaneous route, has the potential to affect the immunological response to allergens. This is testified to by the facts that SLIT can prevent the onset of new sensitizations and maintain its beneficial effect for years after discontinuation. Moreover, it has been shown that SLIT can prevent the onset of asthma in children with rhinitis.
Summary: Due to its excellent safety, SLIT would be an optimal candidate for use in pediatric age groups, where the natural history of allergy can be to some extent modified. Nonetheless, formal and rigorous studies are needed to define its exact indication and dosage.

Introduction

Allergen-specific immunotherapy is a cornerstone in the management of respiratory allergy in both adults and children,[1] since it affects the immunologic response towards allergens at its earliest stages.[2**] This means that immunotherapy reduces symptom load in the immediate term, but also it modifies the natural history of the allergic disease from several other viewpoints. This has been repeatedly shown with subcutaneous immunotherapy (SCIT), which prevents the appearance of new sensitizations and the onset of asthma in allergic rhinitis subjects.

Based on these observations, it is reasonable to regard immunotherapy as a particularly advantageous treatment in pediatric patients, where the natural history of allergy is expected to be in part modifiable. In fact, the allergic response, characterized by the overproduction of specific IgE (atopy), is of course under genetic control, but the genetic background interacts with numerous factors: maternal feeding, maternal smoking, early exposure to allergens, infections, environment and lifestyle. Many of these factors act in early infancy[3] although the exact interaction and the relative weight of each of them still remain unclear. In particular, in recent years it has become clear that environment and exposure to allergens are important determinants in the development of the allergic march: this is defined as the progression from food allergy and atopic dermatitis, to rhinitis, and then asthma.[4]

The main problem with the traditional SCIT is the risk of severe adverse events, which limits its indications, expecially in very small children. In this sense, sublingual administration (known as sublingual immunotherapy, or SLIT) would represent an advance, since it also has a very favorable safety profile in the pediatric age group. Moreover, with SLIT, the extract is kept under the tongue for 1-2 min and then swallowed (sublingual-swallow), and therefore can be easily managed at home by the children's parents.

The first randomized, controlled study of SLIT was published in 1986,[5] and in the subsequent years the literature on the treatment has grown rapidly. Presently we have available 31 randomized, controlled studies, some of them conducted with children. Moreover, many important aspects of SLIT (e.g. the preventive effect and the long-lasting action) have been documented. Based on the clinical data on efficacy and safety, in 2001 the ARIA (Allergic Rhinitis and its Impact on Asthma) document[6] confirmed the clinical use of SLIT in children.

We will review here the most important and recent clinical studies on children dealing with clinical efficacy. Particular attention will be paid to post-marketing surveys of safety and to prevention studies.

Clinical Effects

To date, 31 trials conducted with adequate methods have been published (for review see)[7**], this testifying to the rapid development interest in this mode of administration. Almost all studies clearly showed the clinical efficacy of SLIT in respiratory allergy induced by common allergens (house dust mites, and grass, birch and *Parietaria* pollen). Of note, there was also a meta-analysis performed by the Cochrane Collaboration[8] that has confirmed the beneficial effects of SLIT in allergic rhinitis.

SLIT was investigated in pediatric patients in 12 studies:[9-15,16**,17**,18-20] five with mites, four with grasses, two with *Parietaria* and one with olive (Table 1). Only one study reported almost completely negative results,[10] and one reported only partial effects,[18] whereas the remaining concluded a significant clinical efficacy of SLIT in reducing symptoms and/or drug intake. Noteworthy, in a study conducted on asthmatic children[13] treated for 2 years with mite extract, the decrease of symptoms and drug intake reached 60% at the second year of treatment. In another study conducted in asthmatic children, Pajno *et al* .[17**] compared the effects of SLIT and fluticasone propionate, and found no difference between the two treatments concerning asthma. Nevertheless, in the SLIT group there was a significant greater improvement in extrapulmonary symptoms. Bufe *et al* .[19] demonstrated that SLIT exerted a measurable clinical effect that became highly significant in those children with the more severe symptoms during allergen exposure. Another important finding in pediatric patients was that reported by Ippoliti *et al* .,[16**] showing that SLIT was able to induce a significant reduction of interleukin-13. This is of particular relevance, since interleukin-13 is a typical Th2 cytokine, and its reduction suggests a skew from the Th2 to the Th1 phenotype, as happens with SCIT. This is in agreement with the reduction in intracellular cell-adhesion molecule 1 (ICAM-1) expression that paralleled a decrease in bronchial reactivity, observed in a recent open study.[21] Finally, Pajno *et al* .[22**] showed that SLIT is able to abrogate the seasonal nonspecific hyper-responsiveness in children suffering from asthma due to *Parietaria* .

Safety

In all the published trials, the most frequently reported side effect is oral/sublingual itching after taking the dose, followed by nonspecific gastrointestinal complaints (nausea, vomiting, abdominal pain). In the pediatric studies, the side effects were always mild and rarely caused discontinuation of the treatment. Only in an early study were a few cases of urticaria reported,[9] and in another study[12] the rate of gastrointestinal complaints was particularly high, but in this latter study the amount of allergen was 375 times greater than the amount administered in a standard SCIT course. Noticeably, no severe systemic adverse event has ever been reported in the literature over 15 years. Andre' *et al* .,[23] pooling the results of eight controlled trials performed with the vaccines of a single manufacturer involving 218 children (103 active+115 placebo), found that the occurrence of side effects and dropouts was similar in adults and children.

More consistent information on safety issues is obtained from everyday clinical practice, so-called post-marketing surveys (see Table 2). Di Rienzo *et al* .[24] performed a post-marketing study in 268 children aged between 2 and 15 years and found an overall incidence of systemic side effects of 3% of patients and 1/12 000 doses. Similar results were reported in another post-marketing survey[25**] involving 354 children, where the occurrence of adverse events was 6% of patients and 15/10 000 doses.

Since intervention in the progression of allergic disease should be initiated as early as possible, the safety of SLIT should also be demonstrated in very young children, i.e. below the age of 5 years. In fact, it is well known that SCIT is relatively contraindicated in small children because of the risk of severe adverse events. Very recently, the results of post-marketing surveys in children below the age of 5 have become available. In the first report,[26**] involving 35 children aged 3-5 years, the rate of side effects was 5% of patients and 0.7/10 000 doses. In another survey[27] of 128 children the side effects were 5.6% of subjects and 2/10 000 doses. In both studies the majority of side effects were gastrointestinal and of mild intensity, and no discontinuation was required.

Long-Lasting Efficacy and Prevention

It has been claimed that SCIT is superior to SLIT since it is capable of modifying the natural history of the disease (i.e. the onset of asthma in rhinitis patients),[28] of preventing the onset of new sensitizations[29,30] and of maintaining a long-lasting effect after discontinuation.[31,32] All these additional properties have been confirmed in pediatric patients.

Recently, the results of a study assessing the long-lasting effects of SLIT were reported.[33*] The study involved 60 children (mean age 8.5 years) suffering from allergic asthma/rhinitis due to mites. Thirty-five children underwent a 4-5 year course of SLIT with a standardized mite 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 a significant difference was found compared with the baseline for 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.

As far as the preventive effect on the onset of new skin sensitization is concerned, the first results with SLIT were published only very recently. In an open, controlled study[34**] involving more than 500 adult and adolescent patients, the onset of new sensitization after 3 years was 5.9% in the active group and 38% in the control group (*P* > 0.01). Thus, SLIT can also prevent new sensitization, although a demonstration of this effect specifically in children is still lacking.

Probably the most relevant effect of immunotherapy applied to children is the prevention of the progression of the disease. This effect was envisaged in 1968 when Johnstone and Dutton[35] reported that immunotherapy reduced the onset of asthma in adolescents with rhinitis. This study was criticized because it was not randomized and the selection of patients was questionable. Indeed, those results were reproduced in a randomized study, the PAT study,[28] where the preventive effect of SCIT was clearly confirmed. More recently, the preventive effect of SLIT on the onset of asthma in children with rhinitis was demonstrated. Novembre *et al* .[36**] followed 153 children with allergic rhinitis due to grass pollen for 3 years. They were randomized to receive in open fashion either coseasonal SLIT or drug therapy only. After 3 years 45 children in the active group and 44 in the control group were evaluated for the presence of asthma: eight out of 45 SLIT had developed asthma compared with 18 out of 44 controls (*P* < 0.01), as shown in Fig. 1. Thus SLIT could prevent the progression from rhinitis to asthma as previously demonstrated for SCIT.

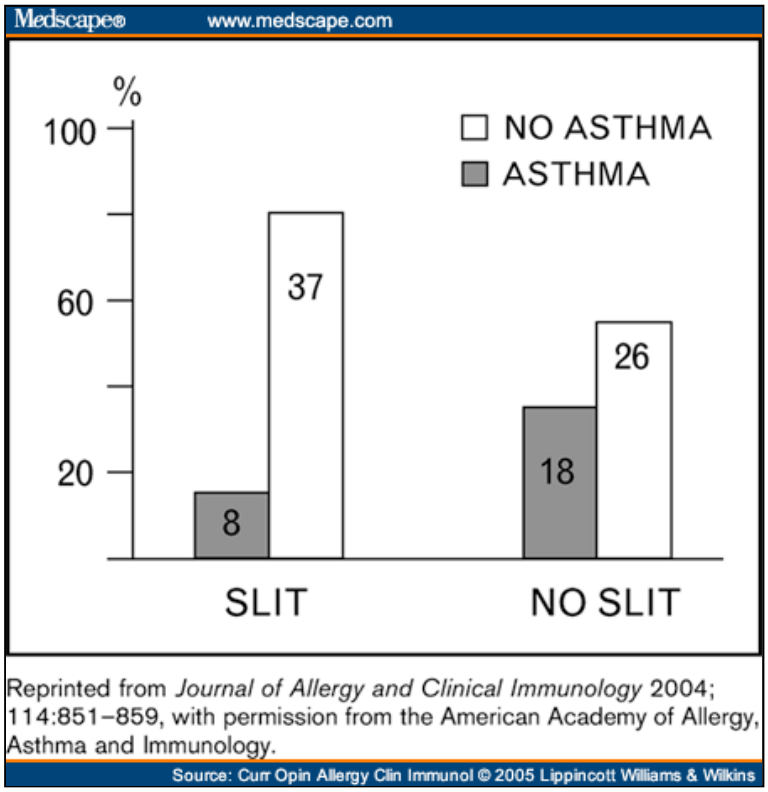

Figure 1.

Number of children with or without asthma after 3 years of SLIT or drug therapy alone

Conclusion

The treatment of respiratory allergy is based on allergen avoidance, pharmacological treatment and immunotherapy. Immunotherapy is an allergen-oriented immunomodulator which affects the immune response to allergens and the action of which develops over long periods of time (months). SLIT, introduced into clinical practice during the last decade, represents a significant advance because of its optimal safety profile.

It is recommended that immunotherapy is initiated as early as possible[1,6] in order to modify the course of allergic disease. The recent evidence would suggest that SLIT, as with SCIT, has the potential to prevent the onset of new sensitization and, more importantly, to prevent the onset of asthma in children with rhinitis. Of note, the safety of SLIT has been demonstrated recently in children below the age of 5 years. Thus SLIT would represent a suitable option in pediatric patients. Of course, several points need to be better addressed, such as the dose-response relationship, and the optimal dose needed to achieve the maximum benefit without side effects. Also, the

mechanisms of action still need to be elucidated in detail, although the more recent data are promising.

Table 1. Randomized, Double-Blind Controlled Studies of SLIT in Children.

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Reference	Age range (years)	Patients A/P*	Allergen	Duration	Disease†	Main results
[9]	5–12	30/28	Mites	18 months	R/A	↓ Nasal and pulmonary symptom score; ↓ skin reactivity; ↓ specific and aspecific bronchial reactivity
[10]	6–16	15/15	Mites	1 year	R/A/C	No difference ACT-PLA‡ in symptom scores
[11]	7–17	33/31	Olive	2 years	R/A	↓ Asthma and eye symptoms in pollen seasons
[12]	6–14	20/21	Parietaria	6 months	R/C	↓ Nasal symptom score; few changes in medication scores; ↑ threshold dose of conjunctival provocation test
[13]	8–15	12/12	Mites	2 years	A	↓ Total and nocturnal asthma score; ↓ drug intake; ↓ delayed skin reactivity
[14]	4–14	24/20	Grasses	3 months	R/A/C	↓ Nasal and lung symptom score; no change in medication score
[15]	7–15	8/7	Mites	6 months	R/A	↓ Asthma symptoms, asthma episodes and use of β2 agonists; no change nasal scores
[16••]	5–12	47/39	Mites	6 months	R/A	↓ Asthma score and nasal symptoms
[17••]	8–14	15/15	Parietaria	13 months	R/A/C	SLIT+fluticasone=fluticasone alone for asthma; ↓ Extrapulmonary symptoms in the SLIT group
[18]	6–13	11/11	Grasses	2 years	R/A/C	↓ All medication scores; no change in symptom scores and nasal challenge
[19]	6–13	68/74	Grasses	3 years	R/A/C	↓ Symptom scores only in the subgroup with more severe symptoms
[20]	3–14	39/38	Grasses	3 years	R/C	↓ Total symptom score and rescue medication intake; no immunological change

*A, active; P, placebo.
†R, rhinitis; A, asthma; C, conjunctivitis.
‡ACT-PLA, active-placebo.

Table 2. Post-Marketing Surveys of Safety in Pediatric Patients.

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Reference	No. of patients	Age range (years)	Follow-up (years)	Adverse events (% of patients)	Adverse events (per 1000 doses)
[24]	268	2–15	3	3	0.1
[25••]	354	5–15	3	6	0.15
[26••]	36	3–5	2	5	0.07
[27]	128	3–5	2	5.6	0.2

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Abbreviation Notes

SCIT: subcutaneous immunotherapy; **SLIT:** sublingual immunotherapy.

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