

Review article

Sublingual immunotherapy in the treatment of children

Children with controlled intermittent mild-to-moderate asthma, controlled rhinitis and a single sensitivity may be appropriate candidates for sublingual immunotherapy (SLIT). Positive effects of SLIT may depend on initiation in early childhood and a long duration of treatment. To ensure optimum compliance, sociological, economic and familial factors should also be taken in to consideration when prescribing SLIT. Evidence from recent long-term trials indicates that SLIT interfered with the atopic march and the allergic progression from rhinitis to asthma without any severe adverse side effects. Local immune response has been seen to be blunted with SLIT, which suggests that treatment has an immunomodulatory effect. In addition, it may also decrease the risk of new sensitizations. Ongoing developments in SLIT, particularly advances in dosing and new indications, such as food allergies, will increase the use of this treatment modality in children.

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Sublingual immunotherapy (SLIT) is a desensitization method approved for clinical use in respiratory allergies (1, 2). The WHO ARIA statement acknowledges that the use of SLIT in children with respiratory allergies is evidence based (1). Its excellent safety profile makes SLIT a good candidate for the management of IgE-mediated allergy in children and, particularly, in very young children (3, 4). In addition to preventing or delaying the onset of asthma in atopic children (5), SLIT may also decrease the risk of developing new sensitizations. Despite these findings, investigators acknowledge that some issues with SLIT still need to be addressed, such as the magnitude of clinical efficacy, the effect on bronchial hyper-reactivity and adherence to treatment (6). This paper reviews the evidence supporting the use of SLIT in children.

Efficacy of SLIT in children

Specific immunotherapy (SIT) is a recognized method of treating IgE-mediated allergies, particularly allergic rhinitis in paediatric patients (7–15). Although data may be insufficient to draw firm conclusions (16) in some studies the clinical outcome of SIT for the treatment of allergic rhinitis appears to be greater in children than in adults (17). However, only limited data are available regarding the capacity of SIT with a single allergen to prevent the onset of allergic sensitivities. One study of both children and adults found that the improvement in symptom/medication scores was significantly better for the paediatric group (6). Other studies showed that SLIT significantly diminished symptoms of rhinoconjunctivitis and asthma and decreased reactivity to allergen, as assessed

by the conjunctival or skin allergen provocation test (18, 19). Nonetheless, one meta-analysis of SLIT studies involving children showed no significant improvement in either symptom or medication score. The authors acknowledged that this meta-analysis was hampered by the small numbers of children included, and suggested this accounted for the lack of significance (20). In addition, meta-analysis results should be viewed with caution because paediatric trials are necessarily open-label trials due to the difficulty and questionable ethics of studying children in a double-blind setting in which asthma is a possible outcome, if untreated (21).

More recent studies have demonstrated the efficacy of SLIT in children with allergies to grass pollen (21, 22), house dust mites (5, 23), and both pollen and perennial allergens (6). These more recent studies were not included in the meta-analysis of Wilson *et al.* (Table 1).

Allergic rhinoconjunctivitis and asthma are different manifestations of atopy. The treatment of the rhinitis may prevent development of the asthma. Indeed, subcutaneous immunotherapy (SCIT) studies as early as 1967 showed that SIT prevented the progression of rhinitis to asthma and reduced the severity of asthma in a paediatric cohort, and over the years the weight of evidence to support this finding has increased (21).

A short-term, co-seasonal protocol of grass pollen allergen administered by SLIT to a group of children with rhinoconjunctivitis suggested that the risk of developing asthma was reduced (21). However, as with SCIT, there is a need for longer duration of treatment to determine the effect with perennial allergens, such as house dust mites (23).

Encouragingly, despite the difficulties associated with long-term studies in children, SLIT is proving acceptable

Table 1. Studies of sublingual immunotherapy in children: effects on asthma and rhinitis

Study reference	Age (years)	Allergen	Duration of treatment (months)	Effect on rhinitis	Effect on asthma
Tari et al. 1990 (8)	5–12	Mites	18	Symptom score	Bronchial reactivity
Vourdas et al. 1998 (9)	7–17	Olive pollen tree	24	Symptoms	Symptoms
La Rosa et al. 1999 (18)	6–14	<i>Parietaria judaica</i>	6	Symptom score, conjunctival reactivity	Medication score
Pajno et al. 2000 (10)	8–15	Mites	24		Symptom score
Caffarelli et al. 2000 (11)	4–14	Grass pollen	3	Symptom score	Symptom score
Bahceciler et al. 2001 (12)	7–15	Mites	6	No improvement	Symptom score and medication
Ippoliti et al. 2003 (13)	5–12	Mites	6	Symptom score	Symptom score
Wuthrich et al. 2003 (14)	6–13	Grass pollen	24	Medication score	Medication score
Bufe et al. 2004 (22)	6–13	Grass pollen	36	Symptom score in the group with severe symptoms	
Rolinck-Werninghaus et al. 2004 (15)	3–14	Grass pollen	36	Symptom score and medication	
Novembre et al. 2004 (21)	5–14	Grass pollen	36	Symptom score and medication	Symptom score and medication

to parents over long-term studies because it is less invasive than SCIT. Nevertheless, at present only one study has assessed the long-term efficacy of SLIT. In this study, the incidence of asthma was greatly reduced 4–5 years after discontinuation of treatment (5). This long-term effect is potentially of interest for the future of SLIT in paediatric patients if it can be confirmed that they will not develop asthma (5, 6, 21, 23). The beneficial long-term (3 years) effects of SLIT may be particularly important in children with severe symptoms (22).

This putative long-lasting effect of SLIT could be similar to that seen with SCIT previously, such as the study in asthmatic children treated with house dust mite extract by SCIT, which resulted in a decrease of symptoms and drugs scores that reached 60% at the second year of treatment (17). However, with SLIT Pajno *et al.* (24) found that there was no additional benefit on seasonal asthma when SLIT (pollen) was used in combination with fluticasone propionate, apart from improvement in nonbronchial symptoms. Further prospective paediatric studies should confirm that SLIT is as efficient as SCIT, and that SLIT combined with anti-asthmatic treatments has additive or synergistic effects on bronchial hyper-reactivity (25).

Immunomodulation by SLIT

Immunological evidence indicates that SLIT causes changes in both the local and systemic immune response (26). SCIT may participate in immune modulation, which reduces the development of other sensitisations and allergen reactivity (cutaneous, conjunctival and bronchial reactivities) but without complete protection (27). This was demonstrated in a 6-year follow-up study of children with house dust mite allergy in which 24.6% of treated children developed further sensitizations compared with 67% of untreated controls (17). Of the further sensitizations, most were due to pollen, the onset of which is known to be later than house dust mite, and those due to animal dander only occurred if the patient had an animal at home. This effect was less clear in another study in

which three (8.5%) of 35 patients developed further allergic responses with SLIT; the rate was similar in the placebo group (5).

Local immune response has been seen to change with SLIT; reduction in nasal eosinophil cationic protein and nasal IgE were recorded with active treatment and also with an induction of T regulator lymphocytes (28). These changes became significant, compared with baseline values, for the active treatment group by the end of the third year (23). Several parameters of the local allergic reaction were downregulated by 1 year's treatment with SLIT and these improvements were consolidated over the second year. Clinical improvement reflected the local immunological changes, notably inflammation markers changed more quickly than clinical markers (23). The immunological effects observed in the paediatric studies may be related to the doses used in the protocols. Further studies should consider higher doses of allergens, which may have more positive clinical effect (29).

Recent studies suggest that SLIT may also have a role in treating food allergy, in reducing the allergic reaction by increasing the IgG4 and IL-10 levels (30).

Safety and compliance with SLIT

The excellent safety profile of SLIT, which has been demonstrated over the past few years, makes it an appropriate candidate for allergen-SIT in young patients.

It is known that SCIT can induce systemic and anaphylactic reactions and that these adverse effects are more frequent in asthmatic than rhinitis patients (31). By contrast, SLIT has been used in both rhinitis and asthmatic patients without occurrence of anaphylactic reactions (32, 33). Its safety profile has also been confirmed in clinical trials with children under 5 years old in which the most frequently reported side effects were related to local itching and oral discomfort (4, 34). Gastro-intestinal discomfort and diarrhoea occurred in some cases, which could be ameliorated by spitting-out the allergen rather than swallowing. Dose reduction was similarly effective (4). These trials found no difference in

safety profiles between different allergens (mites, grass pollen) and no one allergen was more likely to cause side-effects than another (4).

Compliance with specific-allergen immunotherapy is key to its efficacy, and lack of compliance may be associated with the occurrence of side effects (3). In a review of eight European studies of SLIT, André et al. (3) found that treatment discontinuation was most often because of repeated buccal and gastro-intestinal complaints. Nevertheless, compliance with SLIT is generally good. In a clinical trial of SLIT in 354 children aged between 5 and 12 years, only five children were withdrawn because of worsening symptoms, such as rhinoconjunctivitis, wheezing and urticaria (31). Poor compliance in longer-term SLIT trials, uniquely seen in paediatric patients, is probably due to the influence of parents who see continued treatment as unnecessary intervention once symptoms improve. This effect was notable in the study by Novembre et al. (21) in which no children were withdrawn because of safety concerns (see Table 2).

Sublingual immunotherapy represents an advance in immunotherapy because it relies completely on patient self-administration, whereas, by contrast, SCIT is administered by a health-care professional. Therefore, sociological factors, such as the educational and economic status of the family, should be taken in consideration when prescribing SLIT because successful adherence is dependent on the parents' understanding and motivation (35).

Another factor impacting on adherence is the formulation of the vaccine. Tablets, which are more convenient than drops in adult patients (36), can be adapted for use in children. However, more studies of compliance among paediatric populations are needed and, in particular, the quality of life should be assessed in long-term cohort studies.

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Table 2. The number of adverse reactions and treatment discontinuations from adverse events reported in a series of studies of sublingual immunotherapy (SLIT) in children

Study [number of children]	Rate of side effects		Treatment stopped because of side effects	
	SLIT	Control	SLIT	Control
Novembre et al. [47] (21)	5	1	0	0
Andre et al. [103] (3)	50	35	6	1
Pajno et al. [354] (31)	34	ND	5	ND
Di Rienzo et al. [126] (4)	7	ND	0	ND

Further studies are needed to evaluate the use of anti-histamine during the beginning of the treatment with the aim of reducing the side effects without diminishing efficacy.

Conclusion

The use of SLIT is recommended in paediatric patients because of its good efficacy, safety profile and long-term improvements. This is coupled with good adherence to treatment. The appropriate candidates for SLIT may be children with controlled intermittent mild-to-moderate asthma, controlled rhinitis and a single sensitivity. Developments in SLIT raise the possibility of improving efficacy, with the use of high doses of allergen. In addition, SLIT may also have a role in treating food allergy (30). The more widespread use of tablets may help increase the use and compliance of SLIT among atopic children. Further studies should perhaps consider the use of higher doses, and adherence in the long-term treatment of paediatric populations.

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