

EXPERT
REVIEWS

Sublingual immunotherapy in preschool children: an update

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Allergen immunotherapy is a subject widely debated by allergists. Currently, 'pro' and 'con' sessions are focused on the sublingual route. Sublingual immunotherapy (SLIT) has so far been used in Europe, Asia and Australia for the treatment of allergic respiratory diseases. The minimum age to start specific immunotherapy with inhalant allergens in children has not been clearly established, and position papers discourage its use in children younger than 5 years. Nevertheless, it is known that SLIT efficacy is higher when SLIT is started at an earlier age. The aim of this review is to focus on studies on preschool children evaluating SLIT safety and efficacy, in order to improve this practice at an earlier age in childhood.

KEYWORDS: efficacy • literature revision • preschool children • safety • sublingual immunotherapy

During the last few years, allergen immunotherapy has been a topic widely debated by allergists. For many years, the discussion on allergen immunotherapy has focused on its subcutaneous route (subcutaneous immunotherapy [SCIT]), but currently the debate is focused on the sublingual route (sublingual immunotherapy [SLIT]). SLIT has been used worldwide [1] for the treatment of allergic respiratory diseases and is now considered an efficacious and safe alternative to SCIT [2,3]. Apart from respiratory diseases, recent literature data have also shown the efficacy of SLIT in patients with food allergy [4] and in children with mild atopic dermatitis [5].

Several historical studies with the traditional form of SCIT have been performed in 3- to 14-year-old children [6,7], and no serious and/or life-threatening side effects were ever reported. Nevertheless, in 1998, Bousquet *et al.* conducted a trial reporting the following events in children less than 5 years of age: severe asthma, generalized urticaria, angioedema and anaphylaxis [8]. Since then, according to these results, the preschool age has been considered as a 'wise' limit for immunotherapy in order to avoid a possible risk of severe side effects [9], which are more difficult to treat in very young children, above all when SCIT is performed in such very young children [10]. Recent data, however, have demonstrated that SLIT is safe in preschool age children and offers new possibilities for the treatment of patients of this age group [11,12].

As modern medicine is focusing on the prevention of chronic diseases, the aim of our

review is to state the safety and efficacy of SLIT in preschool children, evaluating the possibility of an earlier introduction of this kind of therapy, from the preschool age.

Oral tolerance & mucosal immunity induced by SLIT

In recent years, SLIT has attracted greater interest than SCIT, as demonstrated by the large number of double-blind, placebo-controlled trials carried out in Europe [13]; however, some issues with SLIT still need to be addressed, such as the standardization of the optimal dose of vaccine, the standardization of the induction and maintenance doses and the pivotal challenge of early intervention in young allergic children. Moreover, there is a need for clinical trials to propose a better standardization of vaccine quality and relationship of the vaccine's allergen composition to the patient's allergen molecular composition. Such trials could avail of the recent widespread molecular diagnosis (such as ImmunoCAP ISAC® [Thermo Fisher Scientific, MA, USA] for better standardization [14,15].

During the last few years, a mechanism of induction of 'immune tolerance' has been proposed for SLIT, even if its mechanism still remains unclear. It seems that one explanation for the specific mechanisms of action of SLIT may be linked to the existing difference between both oral APCs and oral Langerhans cells and their skin counterparts [16–18].

As far as the mode of action of SLIT is concerned, it is believed that IgE receptor-bearing

dendritic cells in the oral mucosa take up allergens from allergen solutions and tablets and induce a specific T-cell response. In SLIT, this immune response is mainly observable locally at mucosal sites, in contrast to what happens with SCIT where the local reaction is limited to the skin counterpart. In this regard, it has been demonstrated that the amount of allergen-specific IgE in the nasal mucosa decreases during SLIT [19–22]. Moreover, it has been demonstrated that SLIT induces a decrease in the number of inflammatory cells infiltrating target organs, an increase of circulating IgG4 and IgA, a decrease of eosinophilic cationic protein and a heterogeneous influence on T-cells in the peripheral blood, expressed as T-cell suppression [19,23–25].

Other groups reported an enhancement of Foxp3⁺CD4⁺CD25⁺ Treg cells and IL-10 in the peripheral blood and IL-18 and the signaling lymphocytic activation molecule in peripheral blood mononuclear cells, suggesting a downregulation of tolerance induction and of Th2 immune responses [26,27]. In one study with SLIT, a decrease of T-cell proliferation was demonstrated, whereas levels of IgA in serum and bronchoalveolar and nasal lavage fluid increased [28]. Sublingual administration of a T-cell epitope peptide in sensitized mice was more effective in tolerance induction than a T-cell epitope administered to the gastrointestinal mucosa, suggesting that tolerance induction of the oral mucosa is superior to that of the gut mucosa [29]. As far as SLIT efficacy is concerned, a meta-analysis of 22 randomized clinical studies conducted on 979 adult patients [30], as well as a meta-analysis of ten studies conducted on 577 children [31], revealed that SLIT represents an effective treatment alternative to SCIT in the clinical practice. Nevertheless, the authors should consider that these meta-analyses have the limitation of a very high heterogeneity of patients, and this reduces the value of these results. Altogether, the current absence of shared standardizations of vaccines among different companies represents a drawback in the design of immunotherapy trials using similar concentration(s) of allergens.

Safety & efficacy of SLIT in preschool children

Concerns over adverse reactions and compliance have led to the development of SLIT as distinct from, and in addition to, the subcutaneous administration of allergy vaccines [32–34]. SLIT has been proposed as particularly appropriate and safe for children [35], however few studies include children younger than 5 years [36–38].

As far as safety of SLIT is concerned, in 2011, Radulovic *et al.* conducted a Cochrane systemic review on SLIT in allergic rhinitis, including Cochrane ENT Group Trials Register, Central, PubMed, EMBASE, CINAHL, Web of Science, Biosis Previews, Cambridge Scientific Abstracts, mRCT and additional sources. Authors included randomized, double-blind, placebo-controlled trials of SLIT in adults and children. Sixty studies were included with 49 suitable for meta-analysis. They found significant reductions in symptoms (standardized mean difference [SMD]: -0.49; 95% CI: -0.64 to -0.34; $p < 0.00001$) and medication requirements (SMD: -0.32; 95% CI: -0.43 to -0.21; $p < 0.00001$) compared with placebo. None of the trials reported severe systemic reactions, anaphylaxis or use of adrenaline. This updated review

reinforces the conclusion that SLIT is effective for allergic rhinitis and appears to be a safe route of administration [39].

More recently, Di Bona *et al.* published another systemic review with an indirect meta-analysis, comparing the efficacy of SCIT and SLIT with grass allergens for seasonal allergic rhinitis. Treatment efficacy was determined as the SMD in symptom and medication scores obtained with active treatment, SCIT or SLIT, compared with placebo. Studies were included if they were double-blind randomized controlled trials comparing SCIT or SLIT with placebo. A total of 36 randomized controlled trials (3014 patients; 2768 controls) were analyzed. They found indirect but solid evidence that SCIT is more effective than SLIT in controlling symptoms and in reducing the use of anti-allergic medications in seasonal allergic rhinoconjunctivitis to grass pollen [40]. Nevertheless, all these meta-analyses concern a population over 5 years of age, and at the actual state of the art, when the safety of SLIT in younger age groups should be somehow assessed, proposing SCIT as an alternative could represent a future approach, when a standardized method for SIT in preschool age will be assessed.

The 1993 European Academy of Allergy and Clinical Immunology position paper advises avoidance of immunotherapy for children younger than 5 years [41]. Thus, European healthcare professionals have been reluctant to prescribe specific immunotherapy in very young children [42]. However, the 1998 WHO position paper merely lists age for initiation of immunotherapy among ‘research needs’ and advises specialist evaluation [9]. The 2001 Allergic Rhinitis and Its Impact on Asthma Workgroup and WHO document states that immunotherapy, including SLIT, should be initiated early in the disease process, but minimum age for onset of treatment is not specified [43]. The 2003 Joint Task Force position paper of the American College of Asthma, Allergy and Immunology and the American Academy of Allergy, Asthma and Immunology mentions age at introduction of immunotherapy as a clinical problem of ‘cooperation’ [44]. Thus, the position that “there is no absolute cutoff...with respect to the youngest age at which allergen immunotherapy should be considered” remains an open-ended research question [45].

Rienzo *et al.* [11] first evaluated the safety of SLIT in children below the age of 5 years. The authors followed up, for 2 years, 126 children aged 3–5 years with respiratory allergy receiving SLIT for allergic asthma and/or rhinitis. They prescribed immunotherapy for allergy induced by mites, grasses, *Parietaria*, *Alternaria* and olive. The authors described nine side effects in seven children (5.6% patients and 0.2/1000 doses): two episodes of oral itching, one of abdominal pain and six gastrointestinal side effects that were controlled by reducing the dose. All side effects occurred during up-dosing phase. No difference in terms of safety among the allergens used was observed. Thus, authors concluded that SLIT is also safe in children under the age of 5 years.

In a previous study of postmarketing surveillance conducted on 268 patients, 13 patients below 5 years tolerated the treatment well. In another recent report, it was shown that the occurrence of side effects in children 2- to 5-years old was low, but this preliminary survey involved only 36 patients [46].

Fiocchi *et al.* [12] have published a study on the evaluation of whether a 5-year age limitation is clinically justified on safety grounds among children receiving SLIT for asthma and allergic rhinitis. In particular, the authors did not set out to evaluate the safety of SLIT in young children, but evaluated young Italian children who received SLIT as part of the management of their asthma or rhinoconjunctivitis irrespective of the reason why SLIT had been prescribed. Thus, adverse events in response to individual allergens were not evaluated. The main result of this study was that on either side of the 5-year cutoff, there was no significant difference in occurrence of adverse reactions. This finding suggests that younger age does not rule out contemplating the prescription of SLIT when clinically indicated. The few adverse reactions that occurred were low in severity. In this series, the unweighted frequency of adverse reactions was 16.9%, which agrees with the findings from selected populations studied under placebo-controlled conditions, among whom the rate of adverse reactions to SLIT was 6.25% [47] to 49% [48].

Thus, the authors concluded that SLIT is safe in younger children, suggesting that the treatment could be started earlier, more if we consider that efficacy of specific immunotherapy is said to be higher among younger children [42].

The occurrence of the abovementioned side effects did not differ from that reported in previous surveys [36,49] with a rate per patient of about 7%, most of them involving the GI tract, as reported in clinical trials [50], that could be controlled with a reduction of the dose without discontinuing the treatment. This is in accordance to what was observed with SLIT with very high doses [51,52].

As far as efficacy of SLIT in preschool children is concerned, this topic is still a matter of debate as clinical evaluation of efficacy is difficult in preschool children when spirometry is rarely possible to perform. Moreover, the lack of data on this topic is linked to the fact that it would be desirable to obtain reliable data on the safety of SLIT before planning double-blind controlled studies to evaluate the efficacy in this age-range. Actually, this review highlights that until now, there is weak evidence for the use of SCIT and SLIT in preschool children. Nevertheless, the safe profile of SLIT should encourage research in this way, above all that Respiratory Laboratories can nowadays avail of the use of the Respiratory Interrupter Technique for the evaluation of respiratory resistances in preschool children. Thus, further research on SLIT efficacy in this age range of children should be encouraged.

Compliance to SLIT in preschool children

Specific immunotherapy is the only effective causal treatment that can modify the natural history of respiratory allergy [53]. This effect is important in children, where a secondary prevention is desirable. SLIT is accepted as a valid therapeutic option [54], and children represent an ideal population for SLIT, because of the good safety profile [54]. Nonetheless, as per all chronic treatments, adherence is essential, but no data are available in preschool children. In this regard, Pajno *et al.* [55] assessed the adherence to SLIT in children aged <6 years and analyzed the factors possibly affecting adherence itself. The authors studied children (aged

3–6 years) referred for respiratory diseases (bronchial asthma and/or rhinitis) and eligible for SLIT. No children with food allergy were enrolled. Patients receiving SLIT were stratified according to age: group A ($3 \leq \text{years} < 4.0$), group B ($4.0 \leq \text{years} < 5.0$) and group C ($5.0 \leq \text{years} < 6.0$). They found that overall, 46% of 150 children discontinued SLIT. The percentage of discontinuations during the first year was significantly higher in group A than in groups B (52 vs 18%; $\chi^2 = 12.7$; $p = 0.035$) and C (52 vs 13%; $\chi^2 = 17.33$; $p = 0.032$), whereas during the second year, there was no difference between groups ($\chi^2 > 0.5$).

The most common cause for withdrawal in group A was the subjective discomfort in keeping drops/tablets under the tongue, or children's refusal, without apparent side effects. The refusal was generally attributed to unpleasant taste. For groups B and C, withdrawals were attributed to ineffectiveness, or to family problems, not better defined.

In patients who completed the 2-year course of treatment, adherence measured by returned doses remained over 80%. Adverse events occurred in 28 children (18.6%). Twenty-five had mild-moderate local reactions: tiredness and/or headache, abdominal pain, oral/lip itching. Those local reactions lead to SLIT withdrawal mainly in group A. Rhinoconjunctivitis was observed in two group C patients and wheezing in one group A patient who discontinued.

Poor adherence to therapy is a major factor contributing to poor disease control in allergic rhinitis/asthma. This holds true for SIT, which is a long-lasting disease-modifying treatment that requires optimal compliance. The available studies report high compliance rates from 60 to 90% even in the long term [5]. On the other hand, marketing data show a disappointing rate of discontinuations [6], that is, approximately 90% over 3 years. In the study of Pajno *et al.*, authors found that children below the age of 4 years had lower adherence, recorded above all early in the treatment course. Otherwise, a quite good adherence was seen from the age of 4 years onwards. Thus, authors concluded that to prevent poor adherence or immunotherapy refusal by young children, SLIT should be started preferably after the age of 4 years [55]. A strict monitoring of adherence is recommended anyway.

Conclusion

It has been demonstrated that SLIT is the only therapy that can modify the natural history of atopic diseases, causing a permanent desensitization towards the responsible allergen and modifying the immune system of the atopic patients, even if until now there is no evidence on a possible prevention role of the same therapy. Its efficacy and safety has been widely demonstrated both in adults and in children, even if the studies on preschool children are still limited. Nevertheless, the demonstration of its safety in the reported studies on preschool children is confirmatory to the already ongoing use in clinical practice, more if we think that its efficacy is higher when started at younger age. It is important to remember, however, that in very young children, a detailed diagnosis of IgE-mediated allergy made by a specialist is mandatory to justify the risk:benefit ratio. Further studies on its efficacy in preschool age children should be encouraged.

Expert commentary

We think that the present review is interesting because there is poor literature data on the use of SLIT in preschool children, even if the practice is widely used in clinical experience. Thus, in view of this wide use of SLIT in preschool children, it is useful to determine world guidelines in order to improve this clinical practice.

Five-year view

The knowledge of the safety of SLIT in preschool children allows the development of new double-blind controlled studies in this age group to determine its efficacy. Moreover, it is known that SLIT

efficacy is higher if it is started at an earlier age. Thus, this review encourages further double-blind controlled studies in preschool children, improving the use of SLIT in this age group.

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Key issues

- For many decades, the discussion on allergen immunotherapy had focused on the subcutaneous route of administration of the vaccines (subcutaneous immunotherapy); currently, 'pro' and 'con' sessions are focused on the sublingual route (sublingual immunotherapy [SLIT]).
- The historical studies with subcutaneous immunotherapy were performed in children aged 3–14 years and neither serious side effects nor life-threatening events were reported, even if the global consensus allows its use in children over 5 years of age. Nonetheless, a subsequent well-conducted trial reported severe asthma, generalized urticaria, angioedema and anaphylaxis in treated children less than 5 years of age.
- As modern medicine is focusing on the prevention of chronic diseases, the aim of our review is to state the safety and efficacy of SLIT in preschool children, evaluating the possibility of an earlier introduction of this kind of therapy, from preschool age.
- SLIT has been proposed as particularly appropriate and safe for children (33), but few studies included children younger than 5 years.
- Several randomized trials have shown that SLIT is safe when used in preschool children, showing a rate of side effects equal to SLIT in older children, reversible with the reduction of the dose.
- As far as efficacy of SLIT in preschool children is concerned, this topic is still a matter of debate as clinical evaluation of efficacy is difficult in preschool children when spirometry is rarely possible to perform. Moreover, the lack of data on this topic is linked to the fact that it would be desirable to obtain reliable data on the safety before planning double-blind controlled studies to evaluate the efficacy in this age range.
- Further studies should be encouraged on the efficacy of SLIT in preschool children.
- When SLIT is started in preschool children, compliance should be a matter of particular attention for the physician.

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