



Pros and cons on sublingual immunotherapy in children allergic to house dust mites

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Allergic asthma is a common pathology in children and house dust mites are the most frequent indoor allergens implicated 1. The Global Initiative for Asthma (GINA) guidelines has defined the management of allergic asthma, which recommends the association of allergen avoidance, pharmacologic treatment and allergen immunotherapy, when indicated 2.

Immunotherapy is a specific therapeutic approach in the treatment of allergic airway disease and insect venom allergy and has been utilized for decades: it is therefore recommended to start it as soon as possible in allergic children to modify the natural course of respiratory allergy. Specific immunotherapy (SIT) has been shown to be effective in reducing asthmatic symptoms, medication use and bronchial hyper-responsiveness 3-4. Additionally, it has been recently shown that specific immunotherapy can be also used to prevent the occurrence of new sensitizations to airborne allergens in children exclusively sensitized to house dust mites 5-6. However, subcutaneous administration of SIT is inconvenient, time and resource consuming and is occasionally associated with severe systemic side effects despite the guidelines developed for its use 7. On the other hand, sublingual immunotherapy (SLIT), which has been developed over the past 20 years, offers a better safety profile and ease of use. These advantages make it an attractive option for children 8-9.

The aim of this article is to review current knowledge related to SLIT in children allergic to mites and to identify needs for future research in this field.

Indications and contraindications for SLIT in children are not well established at present, anyway, as well as SCIT, the specific diagnosis of an immunoglobulin E-mediated allergic disorder is a necessary prerequisite. Immunotherapy is indicated as a supplement to allergen avoidance, to pharmacotherapy and to patient/parent education.

Efficacy and safety of SLIT have been demonstrated in adult, particularly in pollen-associated allergic rhinoconjunctivitis 10-11-12. Due to methodological problems, studies are not comparable as they were performed using different products, allergen concentrations, doses and duration of the treatment. Some studies in children have shown an effect in rhinitis and asthma in house dust mite sensitive children 13-14-15. Moreover, in paediatric patients affected by allergic rhinitis SLIT was found to be clinically effective with pollens but not with mites 11. Conversely, when administered to children suffering from allergic asthma, it was found that SLIT with mites extracts has a greater efficacy as compared to SLIT with pollens 16.

Nevertheless, the evidence in childhood is little less convincing and more data are needed, derived from large-population-based high quality studies. In fact the clinical relevance, long-term results and the size of the effect, as well as the dose, the treatment regimen and the duration have not been sufficiently elaborated.

Mechanisms of SLIT. The mucosal antigen presenting cells pick up the allergen in the oral mucosa 17. After the application of SLIT, a rise in serum IgG4 18-19, but lower than that observed in SCIT, and a down-regulation in Der-p-1-specific IgE production 20 and in ICAM-1 expression by nasal epithelial cells have been demonstrated 22. It has been also shown that SLIT is able to avoid the spontaneous increase in nasal IgE and in nasal tryptase after one year of treatment 21.

The induction of tolerance is thought to be mediated by T-reg cells and IL-10 23. A recent study reports that IL-18 and signalling lymphocytic activation molecule are up-regulated during SLIT suggesting that the Th2 type inflammatory response is down-regulated by an increase Th1 type response 24. According to this, Barberi et al. reported that 2-year SLIT is capable of inducing immunologic hyporeactivity to mites with a significant IL-10 increase and an important decrease of Th2-dependent pro-inflammatory cytokines 25. Another study showed that after 12 months of SLIT, mature dendritic cells derived from SLIT-treated patients showed a statistically significant defect of CD86 up-regulation, an increase of IL-10, and a reduction of IL-12 production. SLIT induces changes in DCs functions that might be responsible for an impairment of T cell activation or drive T cells towards a regulatory activity, thus restoring immune tolerance to allergens 26.

Efficacy in allergic rhinitis

Most of the data on the efficacy of SLIT has been generated in adults and safety and tolerability data seem to be convincing for grass pollen tablet. The efficacy for other allergens is not as well proven. A Cochrane review has been published on SLIT in patients with allergic rhinitis 12. It concluded that SLIT is a safe treatment, which significantly reduces symptoms and medication requirements in pollen-induced rhinitis, but there is less significant efficacy in house dust mites-induced rhinitis and the degree of this benefit compared to other available therapies such as SCIT is not clear. Two paediatric meta-analyses 11-27 suggest that SLIT is more effective than suggested by the previous Cochrane reviews, but in those analysis it was not possible to compare the effect of different allergens. Many other studies investigating SLIT and allergic rhinitis have not demonstrated a major effect, failing to show a benefit 14-15-28-29-30-31. Further trials have reported efficacy and tolerability of house dust mite SLIT also using high dose 32.

Efficacy in allergic asthma

Until recently only few studies 15-33 were performed with conflicting results. Two meta-analysis 27-34 demonstrated a clinical benefit of SLIT with significant reduction in symptoms and medication use. However, a third meta-analysis has demonstrated only a small improvement on asthma severity 34. Also two trials demonstrated improvement to bronchial challenge 35-36, but two did not 37-38. Another trial failed to show any effect in 92 mite-sensitive asthmatic children 39. In a recent meta-analysis on paediatric allergic

asthma it was concluded that SLIT reduces both symptom score and rescue medication use when compared to placebo 10. The effect was found particularly with house dust mite allergen extracts.

No relevant studies comparing SLIT and SCIT in children have been published.

Two studies, in which the combination of SLIT and SCIT have been analysed, concluded that this option may produce a better efficacy than SCIT alone in the improvement of symptoms and pulmonary function and it successfully combines the advantages of the 2 alternatives: rapid onset and potency in SCIT and safety and avoidance of injections in SLIT 40.

In the matter of preventive effects of SLIT in children sensitized to house dust mites, a recent non-randomized parallel group open study with SLIT for 5 years indicated a preventive effect of SLIT as regards development of new sensitivities 41.

Conclusion

Immunotherapy is indicated for patients with IgE-mediated allergy to house dust mites confirmed by a specific diagnosis such as Skin Prick Test and/or specific IgE dosage, because of its immunological influence demonstrated by deviation of the immunological response to allergens toward production of Treg-dependent cytokines, such as IL-10 and TGF- β . The relevance of IL-10 as an early marker of successful immunotherapy has been further highlighted. Safety of SLIT has been demonstrated in further studies, but also some case reports of adverse effects (oral mucosal symptoms, itching of the nose and the eyes, asthma or gastrointestinal symptoms and anaphylactic reaction) have been reported in recent literature. However, to date it is not possible to confirm the efficacy of SLIT in children population due to the modest level of methodological quality together with the publication bias, the high inter-study heterogeneity, the difference doses administered and the small sample size, represent the main interfering factors in this evaluation.

More data in children population are needed about SLIT's efficacy, before this treatment can be strongly recommended.

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