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Review

Sublingual allergen immunotherapy in children: An evidence-based overview

Immunothérapie sublinguale chez l'enfant : revue générale

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Abstract

Although subcutaneous allergen immunotherapy (SCIT) is still considered the gold standard immunotherapy treatment for allergic diseases, due to the risk of severe adverse reactions and its limitations regarding practicality, allergen immunotherapy in the sublingual route (SLIT) has been suggested as an alternative to SCIT. In the last three decades an increasing number of studies assessing the efficacy and safety of SLIT have been published; however, not all of them bring the same degree of evidence. This paper aims to be a comprehensive review of the most outstanding and robust papers on SLIT in the paediatric population. We will discuss classical indications like rhinitis and asthma as well as novel possible indications like food allergy, conjunctivitis, latex allergy or atopic dermatitis. We used an evidence based medicine approach. We confirm that there is evidence supporting the efficacy and safety of SLIT mainly for allergic rhinitis, less for asthma and some other allergic conditions; there are still some pitfalls to go through, like immunologic mechanisms, optimal dosage, duration of treatment or long-term efficacy among others, before SLIT can be suggested as the first step in allergy treatment.

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Keywords: Sublingual immunotherapy; Children; Allergic rhinitis; Asthma

Résumé

Bien que l'immunothérapie sous-cutanée soit toujours considérée comme le traitement immunothérapeutique de référence, l'immunothérapie sublinguale est devenue une alternative sérieuse du fait du risque moindre d'effets secondaires et de sa pratique moins contraignante. Ces 30 dernières années, des études concernant son efficacité et sa sécurité ont été publiées, sans toutefois apporter le même niveau d'évidence. Cet article se propose de passer en revue les publications les meilleures, publiées chez l'enfant. Seront discutées les indications classiques que sont la rhinite et l'asthme, ainsi que les nouvelles indications que sont l'allergie alimentaire, la conjonctivite, l'allergie au latex et la dermatite atopique. Nous confirmons que les évidences sont fortes concernant l'efficacité et la sécurité de l'immunothérapie sublinguale principalement pour la rhinite allergique et moins pour l'asthme et les autres allergies. Certains points restent cependant à élucider, notamment ceux concernant le mécanisme d'action, la dose optimale, la durée du traitement et l'effet à long terme.

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1. Introduction

In 1911 the first publication of a successful trial on specific-allergen injection immunotherapy was done by Leonard Noon [1]. Since then, the medical community had put a lot of effort to establish the clinical efficacy and safety of injected immunotherapy by the subcutaneous route; known as subcutaneous immunotherapy (SCIT). Despite that, its use is limited by the possibility of severe systemic adverse reactions; this still is an issue of concern, specially in children. For this reason some other routes of treatment administration have been suggested. Nowadays, the most globally accepted alternative to SCIT is the sublingual route, known as sublingual allergen immunotherapy (SLIT). In this manuscript, we review the current status of SLIT in the paediatric population, addressing issues from an evidence-based approach.

2. Subcutaneous immunotherapy (SCIT) for allergic rhinitis

A recent update of a Cochrane review and meta-analysis on the effect of SLIT in allergic rhinitis selected 15 pediatric studies over the total of 60 randomised, double-blind, placebo-controlled trials (DBPC RCT) of SLIT selected by the authors [2]. A significant reduction in symptoms scores was found in the 15 selected pediatric studies (702 active/690 placebo patients) compared with the placebo group, the standard mean deviation (SMD) was -0.52 (95% confidence interval [CI] -0.94 to -0.10 , $P = 0.02$). A highly significant heterogeneity between studies was indicated ($\text{Chi}^2 = 177.60$, $P < 0.00001$, $I^2 = 92\%$). Twelve studies in children reported a significant reduction in the medication scores (569 active/575 placebo patients; the SMD was -0.16 (95% CI -0.32 to 0.00 , $P = 0.06$). Heterogeneity was non-significant ($\text{Chi}^2 = 17.31$, $P = 0.10$, $I^2 = 36\%$).

Due to the large interstudy clinical and methodological heterogeneity, results from large well-powered studies provide significant data to withdraw clearer conclusions [3]. These studies involved the use of two tablets with grass pollen extracts, one with a mixture of five different grasses [4] (Oralair, Stallergenes, Antony, France) and the other one with only one grass allergen [5] (Grazax, ALK-Abello, Horsholm, Denmark). It was demonstrated that SLIT using a fast dissolving tablet, was effective in children when treatment was started at least 8 weeks before the season. These two studies showed increased efficacy in symptom scores and in the use of rescue medication in children and adolescents from 5 to 18 years when therapy was performed pre- and co-seasonal for 1 year [4,5]. All this data led to registration of both tablets on the European market for children. More recently, a DBPC RCT study performed in North America, which included 345 children (5–17 years old) receiving the Grazax tablet, showed a significant improvement in the total combined symptoms and medication scores [6]. These three large studies in children have also shown significant increased levels of grass pollen specific IgG4 and other immunological markers in those patients receiving SLIT compared with placebo [4–6].

SLIT dose-response relationship [7]. in the pediatric population has been evaluated only in one DBPC RCT with two different doses of SLIT drops for tree-pollen allergy in 88 children suffering seasonal allergic rhinitis, confirmed by skin prick test, specific serum IgE, and conjunctival allergen challenge. This study showed that 18 months treatment using SLIT with tree pollen extract provided dose-dependent benefits in terms of significantly reduced symptoms and medication use [8].

Interestingly, a pediatric study of SLIT in a “primary care setting” did not show any differences at all for symptoms, rescue medication-free days, and disease-specific quality of life (QoL) between active and placebo groups, not even when subgroup analysis was carried out. This study, had several important limitations, and suggested that SLIT is effective for the management of rhinitis in children selected and followed up by specialists [9].

3. Subcutaneous immunotherapy (SCIT) for asthma

Despite the clinical efficacy shown in some studies in asthmatic children using SCIT [10], the risk of important side-effects such as irreversible bronchial obstruction after the use of mite extracts in asthmatics has questioned its use in asthmatics, specially in the children population [3].

A systematic review and meta-analysis of nine DBPC RCT in asthmatic children (232 SLIT/209 placebo) showed a significant reduction in both symptom scores (SMD -1.14 ; 95% CI, -2.10 to -0.18 ; $P = 0.02$) and in the medication use (SMD, -1.63 ; 95% CI, -2.83 to -0.44 ; $P = 0.007$) following SLIT treatment [11]. However, a relevant heterogeneity due to widely differing scoring systems was reported by the authors [11].

In a DBPC RCT of 24 children (age range 8–15 years), suffering from mild to moderate asthma, with single sensitization to mite allergens, Pajno et al. showed that after 2 years treatment with SLIT to house dust mite (HDM), there was a significant decrease in asthmatic symptoms ($P = 0.0001$) and medication use ($P = 0.0001$) in the active group compared to the placebo group [11]. This study showed no changes of the immunologic parameters.

Interestingly, in a recent large trial on SLIT grass-tablet used for rhinoconjunctivitis in children 5–16 years of age, their asthma symptoms (coughing, wheezing, shortness of breath and exercise-induced symptoms) were significantly reduced, whereas the use of rescue medication for asthma was reduced, but not significantly [5].

Because of lack of sufficient data, there is still no clear consensus regarding the use of SLIT in allergic children with asthma symptoms, particularly those with pollen allergy and concomitant allergic rhinitis [12,13]. According to the WHO position paper on allergen immunotherapy, age under 5 years is a relative contraindication for allergen-specific immunotherapy [14]. However, a more recent asthma expert panel recommends that SLIT can be considered for patients with persistent symptoms and in patients whose asthma is not well controlled by pharmacotherapy, or in whom multiple medications are required [15]. Although efficacy of SCIT has been shown for the treatment of allergic asthma, there is a risk of an acute

asthma exacerbation in patients with severe asthma when this treatment is administered. Thus, severe or uncontrolled asthma is a contraindication for SLIT [15].

4. Long-term effect and prevention of new sensitizations and asthma

It has been suggested that the use of SCIT in well-selected patients, can prevent the development of asthma in allergic rhinitis patients and new sensitivities in monosensitized children. At present, few well-designed studies have investigated the long-term effect of SLIT. There is no double-blind study with SLIT specifically designed to study the preventive effect on the development of new allergen sensitizations. However, some randomised controlled open trials have suggested this preventive effect with SLIT.

Di Rienzo et al. [16], in a prospective controlled open study, followed 60 children (mean age 8.5 years) with asthma/rhinitis due to dust mites for 10 years. They were subdivided into two matched groups with 35 subjects undergoing 4–5 years of SLIT and 25 subjects receiving only drug therapy. The patients were evaluated at baseline, at the end of SLIT and 4–5 years after SLIT discontinuation. In the SLIT group there was a significant difference compared with baseline for the presence of asthma ($P = 0.001$), whereas no difference was observed in the control group. This difference was also seen 5 years after the SLIT discontinuation.

The effect of 3 years co-seasonal SLIT in reducing hay fever symptoms and the development of asthma in children with hay fever was evaluated in 113 children aged 5 to 14 years in an open randomised study [17]. Standard symptomatic therapy was used as control. The actively treated children used less medication in the second and third years of therapy, and their symptom scores tended to be lower. From the second year of immunotherapy, subjective evaluation of overall allergy symptoms was better in the actively treated children. Development of asthma after 3 years was 3.8 times more frequent (95% confidence limits, 1.5–10.0) in the control subjects.

It has recently been demonstrated that the grass tablet Grazax has a long-term efficacy in adults over 2 years following a 3-year therapy [18]. It can be speculated that because the immune response of children during the first year of SLIT strongly correlates with that of adults, then, the long-term efficacy data for adults can be extrapolated to children [19]. The long-term effect of the grass-tablet Grazax in terms of reducing the development of asthma in children with hay fever is now under-investigation in the GAP study [20].

5. Safety

The sublingual route was introduced as an alternative to the injection subcutaneous route with the aim of reducing side effects and increasing the safety of immunotherapy. There is no difference in the incidence of SLIT related adverse reactions between children and adults [21].

In well-conducted systematic reviews on the effect of SLIT the most frequently reported adverse reactions are localized to

the oral mucosa, such as itching and swelling. Most of these reactions are mild in severity and mostly self-limited. None of the trials included in these reviews reported severe systemic reactions or anaphylaxis, and none of the systemic reactions reported required the use of adrenaline [22,23].

The safety profile of the SLIT grass allergen tablet Grazax was evaluated in an exclusively designed DBCP RCT including 60 children aged 5 to 12 years age with rhinoconjunctivitis and/or asthma [24]. Treatment was given for 28 days outside the grass pollen season. The majority of the reported reactions were localized to the mouth or throat and were mostly mild (71%) to moderate (27%) in severity. The most frequently reported treatment-related adverse events were oral pruritus (62%), throat irritation (36%), mouth oedema (31%) and ear pruritus (22%). All participants recovered completely from the events within days [24].

At present, eight cases of anaphylaxis associated to SLIT have been reported [25–31]; three of these cases were in adolescents of 11 [27], 16 [28] and 13 [29] years of age. Risk factors could be multiple allergens, previous anaphylaxis due to SCIT and very high dosages. Despite these reported cases of anaphylaxis, SLIT is generally considered to have a better safety profile than SCIT [3].

No fatalities have been reported due to SLIT.

6. Other indications

6.1. Food allergy

Due to an unacceptable high rate of systemic reactions in previous reports with the use of SCIT in food allergy [32], research has suggested the oral route as a better way to treat food allergy. Both oral immunotherapy and SLIT are promising options mainly differentiated in the amount of allergen used, large or small respectively and, in the case of SLIT, the standardization of the extracts used in this treatment [33,34].

In a recent publication [35], 18 children allergic to peanut aged 1 to 11 years of age, were randomized 1:1 to receive either placebo or SLIT treatment in a regimen of 6 months of dose escalation and 6 months of maintenance dose (monthly dose of 60 000 µg, Ara h 2 content approximately 3600 µg). After treatment, the active group tolerated the oral challenges 20 times more peanut protein than placebo group. A parallel change in immunological markers in SLIT treated patients was observed with an increase in IgG4 and a decrease in specific IgE and IL-5 levels. Adverse events were mainly local and occurred in 11.5 and 8.6% administered doses in active and placebo groups respectively.

There are ongoing promising projects to perform SLIT to fish and fruit allergy with recombinant major allergens [36] that represent the future in food allergy treatment.

6.2. Ocular allergy

In a recently published Cochrane systematic review and meta-analysis [37] of DB PC RCT an improvement in the individual and total symptom ocular scores was detected for

SLIT compared to placebo. In the sub-analysis of the nine-paediatric studies included (children between 4 to 17 years of age), a significant reduction in total ocular symptom score with a SMD of -0.27 (95%CI -0.46 to -0.07 ; $P = 0.007$; $I^2 = 39\%$) was obtained. In two single but large well-powered paediatric studies using SLIT with the tablets [4,5], an improvement in ocular pruritus and watery eyes was also observed in the SLIT group compared to placebo.

6.3. Atopic dermatitis

Atopic dermatitis (AD), especially in the paediatric population, coexists with sensitization to food and airborne allergens [38] in 80% of the patients. The link between different sensitizations and the AD course is controversial, but there is evidence towards a relevant association with HDM allergy [39]. Assuming there is a pathogenesis role of dust mites in AD, it could be hypothesized that allergen immunotherapy with dust mite is a therapeutically acceptable option in AD dust mite sensitized patients.

In a DBPC RCT in 56 children (5 to 16 years of age) with active AD and mono-sensitized to HDM without respiratory symptoms, receiving SLIT treatment for 2 years, it was observed an improvement in their symptoms using the SCORAD score [40]. This positive effect was mainly observed in the group of patients with mild-moderate symptoms (SCORAD < 8 points) than in the severe AD group (SCORAD > 8 points) [40]. Moreover, 2 patients with active treatment were dropped out because of worsening of their disease.

Although these studies represent an encouraging treatment option, so far, SLIT is not indicated in AD without associated respiratory symptoms.

6.4. Latex allergy

Natural rubber latex (NRL) allergy is common among healthcare professionals but it can also affect paediatric population, especially those who had multiple surgeries or procedures, where the mucous membranes are extensively exposed to latex.

In the first DBPC RCT with SLIT in NRL allergic adult patients using a maintenance dose of $1500 \mu\text{g/monthly}$ for 12 months, Nettis et al. showed a decrease in symptom scores, rescue medication and bronchial and glove provocation tests in active group compared to placebo [41].

At present, the only DBPC RCT in paediatric population using SLIT for latex allergy [42] shows a good safety and efficacy profile for SLIT treatment with a maintenance dose of $1200 \mu\text{g/monthly}$ for 1 year. In this study, 23 children (4 to 15 years of age) with urticaria, rhinoconjunctivitis and/or asthma due to latex were randomized to active or placebo. This treatment was well tolerated with no local or systemic symptoms. At the end of the treatment all patients in the active group showed a reduction of 50% or more in the symptom score in the glove and rubbing test compared with 37% subjects in the placebo group. No changes in SPT or specific IgE to latex were reported.

Two adult cases of anaphylaxis in the course of a DBPC RCT with SLIT latex in the build up phase with 5 and $1000 \mu\text{g}$ doses of latex protein [30].

6.5. Hymenoptera venom

Venom immunotherapy is always given by the subcutaneous route [43]. However, new recent studies have suggested SLIT as an alternative for venom allergy. A proof of concept treatment in this field has been published in a DBPC RCT with SLIT venom treating 30 honeybee monosensitized patients who suffered large local reactions after honeybee sting [44]. After 6 months in maintenance regimen with $525 \mu\text{g/monthly}$, 57% patients from the active group showed a reduction in local reactions after a controlled sting challenge of more than 50%, with no significant changes in placebo group. No adverse events were reported. No studies have been conducted in children.

6.6. Mechanisms

SLIT exhibits some mechanisms comparable to SCIT concerning the switch from a T-helper (Th) 1 into a Th2 immune response [45]. These common changes include rapid increases in specific immunoglobulin (Ig)E and specific IgG4 with a long term decrease of IgE (despite these changes are less marked in SLIT than SCIT), decreases in effector cells in target organs, up regulation of T-regulatory (Treg) cell responses mirrored in an increase of interleukin (IL)-10 and TGF beta. Some of these biomarkers, for instance IL-10, have been detected in SLIT treated patients as early as after 4 weeks treatment with birch pollen [46]. Biological markers changes may be accompanied by clinical improvements but not necessarily, which is the cornerstone of the current lack of immunological markers for SIT follow-up.

The good safety profile of SLIT may be explained by the important difference in the tolerogenic milieu of the gut system and especially the oral mucosa. In the mouth, the ratio between antigen presenting cells (ACP), called Langerhans cells (LC), and mast cells is imbalanced in favour of LC, making from it the perfect location to administer the allergen assuring an immunologic tolerance induction via APC but a low IgE mediated reactions because of the low concentration of effectors cells like Mast cells [47]. LC plays a central role in SLIT mechanism inducing local tolerance through direct IL-10 and in a second stage, once in the lymphoid tissue, through Th3, Th1 and Treg stimulation and Th2 cell suppression [48]. More research needs to be done to confirm the mechanisms involved in SLIT.

7. Conclusions

Recent meta-analyses and well-powered studies have indicated that SLIT has a significant effect in reducing symptoms and the need of medication use in allergic rhinitis and conjunctivitis in the paediatric population. Evidence is positive, although weaker for asthma. Some other medical indications for the use of SLIT such as atopic dermatitis, latex,

food and venom allergy need further research to achieve sufficient clinical evidence to become a competitive treatment option. In general, SLIT has proven to be safe and well tolerated. No doubt that SLIT is a good alternative to SCIT.

There are still some important unmet needs regarding SLIT in children such as determination of: the optimal dose and dosing frequency of allergen administration; efficacy in patients unresponsive to pharmacotherapy; duration of treatment and the long-term efficacy and preventive capacity in the development of new sensitizations and asthma.

Disclosure of interest

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Pascal Demoly is a consultant and a speaker for Stallergenes, ALK and Therabel and was a speaker for Schering-Plough-MSD, Astra Zeneca and GlaxoSmithKline.

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