

Expert Opinion

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Sublingual immunotherapy in children

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Sublingual immunotherapy (SLIT) is a safe and patient-friendly variant of allergen immunotherapy. These characteristics may provide physicians with a therapy, perfectly suited to the treatment of allergic children. To give an overview of currently published studies on SLIT in children Pubmed was searched for randomised clinical trials (RCTs). In addition available systematic reviews and long-term observational studies were analysed. Until now, 13 RCTs on allergic rhinitis, 22 studies on asthma (including eight studies involving only children) and one study on atopic dermatitis have been published. In addition, five systematic reviews on allergic rhinitis have been published and one is in press. One meta-analysis of adults and children with asthma has been reported. All studies report varying results. The effects and their magnitude differ between studies. Systematic reviews give inconsistent results. For allergic rhinitis three reviews appeared to be negative, two were positive and one analysis was inconsistent regarding children. In asthma a meta-analysis involving both adults and children concluded that SLIT is moderately effective. From observational studies effects of SLIT are suggested to persist after discontinuation. Randomised trials indicate that SLIT may prevent the onset of asthma and new sensitisations. As long as evidence for effectiveness is weak, SLIT cannot be firmly recommended in clinical practice. Nevertheless, the proven effectiveness of SLIT in adults supports the proof in principle of this therapy. In the near future immunotherapy trials in children may provide the required proof of effectiveness.

Keywords: allergic rhinitis, allergy, asthma, sublingual immunotherapy

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1. Introduction

The cornerstones of allergic rhinitis treatment are allergen avoidance, pharmacotherapy and specific immunotherapy. Introduced by Noon and Cantab in 1911 allergen-specific immunotherapy [1], that is the administration of gradually increasing amounts of allergen, is currently considered to be the only treatment that prevents symptoms by altering the natural course of the disease. Immunotherapy in the traditional subcutaneous form reduces both symptoms and medication requirements [2-4], and these effects persist after discontinuation of treatment [5]. Some studies suggest that subcutaneous immunotherapy might prevent the onset of asthma and the development of new sensitisations [6,7].

Although subcutaneous immunotherapy is effective in patients with allergic rhinitis and asthma it also has disadvantages [4]. First, injections can be inconvenient, in particular for children. Second, serious adverse events restrict this form of therapy to experienced physicians or specialised centres [4,8]. To overcome these drawbacks alternative routes of administration have been developed of

which sublingual immunotherapy (SLIT) have attracted the most attention. The evidence on the efficacy of SLIT in children is still inconclusive. Recent meta-analyses showed conflicting results [9-12], hampered by the significant heterogeneity in allergens, duration of treatment and outcome measures of the studies included. However, effective SLIT would clearly extend the therapeutic possibilities for allergic subjects, in particular for children. The absence of serious side effects enables the administration of SLIT not only in hospitals but also in primary care settings. Prescription of immunotherapy by general practitioners has the additional advantage of favouring introduction at an earlier stage of the disease, thereby potentially preventing the onset of asthma and the development of new sensitisations. From that perspective, SLIT is ideal for treating children seen in primary care.

2. Clinical trials

2.1 Randomised clinical trials and meta-analysis in allergic rhinitis

To date 12 double-blind placebo controlled (DBPC) randomised clinical trials (RCTs) with SLIT involving children with allergic rhinitis have been reported [13-24]. The smallest study comprised 15 patients [13], the largest involved 168 children [19]. In eight placebo-controlled studies [14,17-20,22-24] patients were treated with pollen extract (among of which four were grass pollen studies), whereas the other four placebo-controlled studies [13,15,16,21] involved treatment with house dust mite extract. In a thirteenth RCT SLIT with grass pollen was evaluated against symptomatic treatment [25]. Duration of treatment varied from 6 to 24 months. One study monitored children for 36 months, however, the placebo-controlled phase of this trial lasted for only 12 months [14]. Also the age of participants varied ranging from 3 – 14 to 7 – 18 years.

Outcome measures of the studies were symptoms, rescue medication and combined symptom-medication scores. Studies with pollen generated varying results. In one study of 161 children with a grass pollen allergy allergen-specific IgE and IgG-subclass antibodies increased significantly in patients treated with SLIT, indicating an activation of the immune response induced by the locally applied grass pollen extract [14]. After one year of SLIT no significant differences in a clinical score index between treatment and placebo were observed. Although the authors stated that subgroup analysis in a repeated measures model revealed a significant improvement of symptoms after three years in patients treated with SLIT who had severe symptoms before the beginning of treatment, this improvement was seen two years after the end of the placebo-controlled phase and the introduction of SLIT for all patients. Moreover, patients receiving 2 years of SLIT had been compared with subjects receiving 3 years of SLIT. In another grass pollen study with 97 children a

multiple-symptom-medication score was significantly reduced in the SLIT group mainly due to an effect on medication [20]. However, the medication scores of the SLIT group after one year of treatment were much higher than the scores of the placebo group and a correction for this discrepancy should have been incorporated in the analysis. Reanalysis of the medication scores after three years of treatment demonstrated no statistically significant difference between the two treatment groups ($p = 0.72$) [26]. In a randomised DBPC study of 168 youngsters with grass pollen allergy no treatment effect was seen on symptoms, rescue medication-free days, disease specific quality of life or overall evaluation of the treatment effect. Patients were recruited from primary care [19].

A study with birch pollen comprised two dose regimes and one placebo arm. In this study with 88 children the actively treated group appeared to obtain a benefit in terms of symptoms but not in terms of medication [22]. An open randomised trial with 113 children comparing standard therapy with standard treatment plus short-term co-seasonal grass pollen SLIT demonstrated lower medication scores after three years for the SLIT group without effects on symptom scores or symptom-medication scores. Four smaller placebo controlled trials in 39, 41, 30 and 66 children reported beneficial effects in two studies [17,24]. From the four studies focused on patients with allergic rhinitis due to house dust mite allergy one study reported a positive effect on nasal symptoms [21], one study showed reduction in use of nasal steroids [13] and one study was clearly negative [15]. Another study concluded that rhinitis symptom scores decreased significantly [16]. However, only intra-group p-values for the symptom scores were presented. No measure of variability was stated, making it impossible to calculate the inter-group p-value (SLIT versus placebo) or to draw a conclusion on the effect of the intervention.

Several reviews of SLIT studies in children have been published. Sopo *et al.* performed a qualitative analysis. No clinically relevant results were shown using SLIT for respiratory allergies due to seasonal allergens or house dust mites in children [11]. In another review Passalacqua *et al.* concluded that SLIT had proven to be effective and safe in adults and children [27]. Due to the limited number of studies in children at that time a Cochrane analysis published in 2003 was not able to make conclusions on the efficacy of SLIT in children [12]. In contrast, two other groups aggregated studies into meta-analyses [10,28]. One meta-analysis found no significant effect on nasal symptoms [10], whereas the other study demonstrated significant reduction in both symptom and medication scores [28]. The three meta-analyses however were hampered by significant heterogeneity. In the case of statistical heterogeneity, one of the options is to perform a random-effect meta-analysis [28], as was done in these three reviews. A random-effect model does not eliminate the heterogeneity and is primarily intended for heterogeneity that cannot be

explained [28]. However, the heterogeneity among SLIT trials can be explained. For instance, Penagos *et al.* showed that the type of allergen and the duration of treatment influenced the clinical effect. SLIT with pollen was found to be effective in contrast to SLIT with mites and trials lasting for more than 18 months showed efficacy as opposed to trials with a shorter duration [28]. Apart from the heterogeneity, the differences in approach (qualitative or systematic), selection of publications [10,12,28] and age range [10] hampers comparison of the reviews. All reviews concluded that the results look promising but that, due to the inadequate study design and/or lack of power in most trials, more research is needed.

As we have not been able to pool the data from all RCTs we recently performed a best evidence synthesis, a rating system with levels of evidence based on the overall quality and the outcome of the trials with all forms of immunotherapy to assess efficacy. Analysis of the SLIT group showed no therapeutic effect [26].

2.2 Randomised clinical trials and meta-analysis in asthma

Although 22 studies on the efficacy of SLIT in asthma have included children, only 8 studies involve children, whereas the other 14 RCTs included both adults and children [9]. In a small study with 15 patients higher peak flow and fewer asthma exacerbations were seen in the actively treated group [13]. In another small study of 30 children with asthma SLIT with house dust mite extract resulted in a decrease of pulmonary symptoms without affecting bronchial hyper-reactivity [15]. SLIT with house dust mites influenced daily, nighttime and daytime asthmatic scores after 24 weeks of treatment in a study with 97 children [29]. Patients receiving SLIT improved their forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and peak expiratory flow (PEF) as compared to baseline values. For pollen allergy it has been shown that SLIT abrogates seasonal bronchial hyper-reactivity in children with asthma [30]. In the same study population symptoms were also assessed [18]. Pulmonary symptoms however did not differ between SLIT and placebo groups, probably because both groups had been treated with fluticasone during the first season. Abrogation of bronchial hyper-responsiveness was demonstrated in the second season, a period without fluticasone co-medication [30].

Two studies, focussed on allergic rhinitis and previously discussed [20,24] also involved children with asthma. Lack of effect on asthma symptoms suggested that SLIT is not useful in the treatment of seasonal asthma.

The question as to whether SLIT is effective in asthma in children cannot be answered by meta-analysis. One meta-analysis is available involving both adults and children [9]. RCTs on SLIT in asthma treatment were selected. From 119 citations, 25 studies with 1706 patients were included in this meta-analysis. Immunotherapy was

seen to significantly reduce asthma severity when parameter compositions were all analysed by categorical outcomes. There was a non-significant reduction in asthma symptoms when analysed using standardised mean differences. The authors concluded from this analysis that SLIT is beneficial for asthma treatment, albeit the magnitude of the effect is not very large.

2.3 Effectiveness in atopic dermatitis

It has been hypothesised that systemic immunotherapy may have some clinical benefit in atopic dermatitis. A recent review on this topic reports positive results [31]. Many studies, however, are open, observational or performed in adults. Success has been achieved in a recent DBPC study with subcutaneous immunotherapy [32]. In analogy to these findings a randomised placebo-controlled study using SLIT with house dust mite extract in children with atopic dermatitis has been published recently [33].

A total of 56 children aged ≥ 5 years were enrolled, and 28 were allocated to SLIT. The difference from baseline in the SCORAD, an eczema scoring system, was significant between the two groups starting from month nine. Similarly, there was a significant reduction in the use of medications only in the active group. A significant difference in the considered parameters was found only in patients with a mild – moderate disease, whereas severely affected patients displayed only a marginal benefit. The authors concluded that SLIT might represent an additional therapeutic tool for the treatment of extrinsic atopic dermatitis in properly selected children.

3. Safety aspects

One of the main advantages of SLIT is its safety profile. According to the recent Allergic Rhinitis and its Impact on Asthma (ARIA) update on subcutaneous and SLIT in all reported DBPC trials, SLIT was well tolerated [34]. Side effects are mainly local (oral itching or swelling) or gastrointestinal (nausea, vomiting, diarrhea and 'stomach ache'). These side effects appeared to be mild and well managed by a temporary dose reduction. A comprehensive review addressed the issue of safety [35]. A total of 25 studies were evaluated. Although the review was not focused on children 16 studies included children. Studies were divided into high-dose and low-dose treatment categories. Thirteen studies belonged to the low-dose group, 12 belonged to the high-dose group. All patients with at least one adverse reaction were considered. The rate of all adverse events was reported to be 17 – 60% of patients in the SLIT-treated groups and 8 – 14% in the placebo-treated groups. Systemic reactions were, respectively, 17 and 12%. Severe systemic reactions were never reported. Local reactions were significantly more frequent in the low-dose group than in the high-dose group ($p < 0.0001$), while there was no

difference in the rate of systemic reactions. According to another extensive review 17 serious adverse events (mainly asthma) were reported in the literature [36]. Until now two cases of anaphylaxis have been reported. One patient was treated with a mixture of seven allergens [37], one patient underwent a rush immunotherapy with latex extract [38]. Three observational surveys among children have been published [39-41]. Between 3 and 17% experienced side effects, none of them sufficiently serious to discontinue therapy. Interestingly, in one study children under 5 years of age were included, suggesting that SLIT is feasible and safe in very young children [40].

4. Compliance

Compliance with SLIT is a matter of debate. In contrast to subcutaneous immunotherapy, preparations for SLIT can be administered at home without medical supervision. While this may be convenient for the patient, the lack of control may negatively affect compliance. A way to examine compliance is to evaluate clinical trials. Data on compliance with medication however are sparse. In some articles compliance is mentioned, but the results do not refer to medication intake, but to the number of drop-outs [14,16,18] or it is not clear what the results represent [22]. In four randomised placebo-controlled trials in children with allergic rhinitis, participants recorded their medication intake on a diary card. Bahçeciler *et al.* did not present the results [13]. Rolinck-Werninghaus *et al.* reported the number of drop-outs due to non-compliance, but it was not clear how compliance was defined [20]. Hirsch *et al.* presented a detailed report on the medication intake and showed that 53 (8/15) and 67% (10/15) of the participants (6 – 15 years of age) in the SLIT and placebo group respectively reported complete regular intake [15]. Roder *et al.* reported compliance, defined as a medication intake of $\geq 80\%$, in 80% of the patients treated with grass pollen and in 71% of subjects treated with placebo [19].

In a non-controlled study participants were called unannounced after 3 and 6 months of treatment and asked to count the left-over mono-dose vials [42]. Passalacqua *et al.* reported that 69 (49/71) and 66% (37/56) of the participants (2 – 13 years of age) used more than 90% of the prescribed doses after 3 and 6 months, respectively.

One has to bear in mind that compliance achieved and reported in a study may not reflect the real-world situation of daily clinical practice.

5. Long-term aspects

The question arises as to whether SLIT has a long-lasting effect after discontinuation of treatment. For subcutaneous immunotherapy this issue has been addressed in a 7-year prospective placebo-controlled RCT [5].

For SLIT only data from a 10-year matched case-control study are available [43]. In the SLIT group there was a significant difference versus the baseline for the presence of asthma and the use of asthma medications, whereas no difference was observed in the control group.

A prospective but non-randomised study has suggested that subcutaneous immunotherapy is able to prevent new sensitisations [7]. In addition, two large but retrospective trials also indicated that subcutaneous immunotherapy might prevent the onset of new sensitisations [44,45]. Regarding SLIT in one open randomised trial, immunotherapy appeared to prevent the onset of new sensitisations as measured by the skin-prick test [46]. In this study new skin sensitisations appeared in 38% of the controls and in 5.9% of the SLIT patients ($p = 0.01$). Children were included. The ages of the patients ranged from 5 to 60 years. In the case-control study by Di Rienzo *et al.* no change was seen as far as new sensitisations were concerned [43].

It has been suggested that immunotherapy may reduce the risk of asthma. In a large multicenter randomised but open trial, it appeared that subcutaneous immunotherapy reduced the risk of developing asthma in children with rhinitis only [6]. This effect persisted during 10 years of follow-up. Regarding SLIT Novembre *et al.* found that in an open trial that after three years of SLIT, 8 of 45 actively treated subjects and 18 of 44 controls developed asthma, with a relative risk for untreated patients of developing asthma of 3.8 [25].

6. Conclusion

In the last 5 – 10 years an increasing number of clinical trials on SLIT in children have been published. It appeared that the efficacy of SLIT varies between the different studies. Some large studies do not provide evidence for efficacy of SLIT in children. Systematic reviews are much hampered by heterogeneity in terms of size, duration, allergen content and dosage regimes. Therefore, it is difficult to draw overall conclusions about efficacy. In contrast, all studies emphasise the safety of SLIT, which is one of the most important motives for the search for an effective form of SLIT in children. Also, compliance, if measured, appears to be acceptable, thereby taking into account that compliance reported in a study does not necessarily reflect compliance in a real-world situation. To evaluate the long-term effects of SLIT, in particular the clinical effects after discontinuation of treatment, controlled studies are required. No data are available about the desired duration of treatment. Altogether, based on the current literature SLIT cannot be firmly recommended for the treatment of children with allergic disease. Dose-finding studies, new large RCTs and studies of the optimal duration and of long-lasting effects may facilitate the introduction of SLIT in the future.

7. Expert opinion

To manage allergic diseases three approaches are possible. First, allergen avoidance is considered to be the basis and the first step. However, although the reasoning behind allergen avoidance is sound, that is allergen exposure elicits an allergic reaction, thus allergen avoidance should diminish allergic systems, evidence for the effectiveness of allergen avoidance in daily practice is not convincingly available [47]. Second, pharmacotherapy may control allergic symptoms. According to international guidelines allergic rhinitis and asthma may be treated with antihistamines, nasal and bronchial steroids, anti-cholinergic drugs, bronchodilators and antileukotriene antagonists. However, effective pharmacotherapy only controls allergic inflammation and clinical symptoms as long as medication is administered. The restrictions of allergen avoidance and pharmacotherapy, warrant the search for ways to alter the natural course of allergic disease. Immunotherapy in all its forms has been considered as the only therapeutic option able to modify the natural course of allergic disease. However, particular in children, there is a need to overcome the disadvantages of classical immunotherapy by injection. Approaches to meet this need have been focused on alternative routes of administration, or alternative variants of allergens (modified allergens, recombinant allergens, DNA-based conjugates, peptides) or combined administration with anti-IgE antibodies.

SLIT can be considered to be an attempt to combine the effects of classical immunotherapy and the comfort and safety of drops or tablets. From that point of view SLIT should be compared with conventional injection therapy. To date, three comparative studies in adults have been published on sublingual and subcutaneous immunotherapy [48-50]. Two studies have been hampered by study design deficiencies such as lack of power, absence of a placebo arm or absence of a double-blind, double-dummy design [48,49]. One study that used an optimal double blind placebo

controlled double dummy randomised design was difficult to interpret as the result of a large drop-out and an insufficient exposure to pollen in the second year, resulting in almost no symptoms [50]. Thus, large well-designed studies are needed to address the question whether SLIT is equally effective as subcutaneous immunotherapy. Other routes of administration are either not accepted in clinical practice (inhal immunotherapy) or ineffective (oral and bronchial immunotherapy) [26]. To sum up, the question remains as to whether SLIT will develop into an effective and well-accepted therapeutic modality in allergic children. As long as evidence for effectiveness is weak and the magnitude of the effect cannot be clearly established SLIT cannot be firmly recommended in clinical practice. Nevertheless, the proven effectiveness of SLIT in adults [12], in particular when sublingual tablets containing high doses of allergen are used [51-54], supports the proof of the principle of this therapy. Theoretically, there are no grounds to believe that immunotherapy, being effective in adults, will not work in children. Large immunotherapy trials with children, currently under way, may provide the required proof of effectiveness.

Alternative approaches to introduce safer and better variants of immunotherapy are to modify allergenic extracts [55], to use recombinant allergens [56], allergen peptides [57], DNA based conjugates [58] or concomitant administration of anti-IgE [59-61]. All these forms of immunotherapy aim at more effective and safer treatment. Convenience is not only achieved by alternative routes of administration but also by a lower number of required injections or fewer adverse effects. It is expected that in the coming years more therapeutic options will become available.

Declaration of interest

R Gerth van Wijk has been involved in a SLIT study sponsored by Artu Biologicals.

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