

When to initiate immunotherapy in children with allergic disease? Lessons from the paediatric studies

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Purpose of review

Immunotherapy is the only treatment that may alter the natural course of disease. From that perspective, treatment in children might be very valuable. An overview of the recent literature is discussed.

Recent findings

The recent literature shows a shift from injectable immunotherapy to noninjectable routes of administration. A systematic review focussing on all forms of immunotherapy in children indicates that there is a lack of high-quality studies to provide evidence for the use of subcutaneous immunotherapy; moreover, evidence for the use of sublingual immunotherapy is still a matter of debate in spite of previous positive meta-analyses. New forthcoming studies may be promising. The 10 years follow-up of the Preventive Allergy Treatment study further underwrites the preventive properties of immunotherapy.

Summary

Taking the potential preventive action of immunotherapy into account, there is a case to start treatment early in life. However, evidence of the efficacy should be provided by large randomized controlled trials. The lack of high-quality studies with subcutaneous immunotherapy in children requires new studies to fill the gap. The current variation in clinical trials hampers the formulation of clear-cut recommendations on how to perform sublingual immunotherapy (SLIT) in terms of doses, doses schemes, target populations, allergens and specific products from manufacturers.

Keywords

allergy, immunotherapy, prevention

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Introduction

Introduced by Noon and Cantab in 1911 [1], allergen-specific immunotherapy is currently considered 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 sensitizations [6,7].

The potential preventive action and the alteration of the natural course at an early stage of the disease favour the use of this treatment in children. However, subcutaneous immunotherapy also has drawbacks [4]. Firstly, injections can be inconvenient, particularly for children. Secondly, serious adverse events restrict this form of therapy only to experienced physicians or specialized centres [4,8]. To overcome these issues, alternative and patient-friendly routes of administration have been developed, of which

sublingual immunotherapy (SLIT) has attracted the most attention. This review gives an overview of recent publications on different forms of immunotherapy in children.

Efficacy of immunotherapy in children, update 2007–2008

Medline and EMBASE were searched for those systematic reviews and randomized clinical trials (RCTs) in children with allergic rhinitis and asthma that studied the efficacy of all forms of immunotherapy and were published between 1 January 2007 and July 2008. In addition, the literature was searched for comparative and observational studies.

Allergic rhinitis

Few studies address the efficacy of subcutaneous immunotherapy in children with allergic rhinitis. A recent systematic review demonstrated that six studies only compared children undergoing subcutaneous immunotherapy with controls in a randomized design [9•]. From

these studies, four were placebo controlled. The last placebo-controlled randomized trial was published in 1986 [10]. One of the most striking findings of this review was that the methodological quality was low in five of six trials, whereas only two of six trials demonstrated efficacy. This is in line with a published meta-analysis addressing allergen injection therapy for seasonal allergic rhinitis [11]. In this systematic review, there were no accepted studies of allergen injection immunotherapy that were conducted exclusively in children. Furthermore, only nine studies extended the age range to include participants younger than 18 years of age; one study included patients between 6 and 56 years of age [12]; however, no data assessing specific outcomes were reported in the younger participants [11].

The recently published systematic review also addressed the efficacy of noninjectable routes of administration. Local nasal immunotherapy (LNIT) and oral immunotherapy (OIT) are not commonly used in the management of allergic rhinitis. Although three of four included LNIT trials demonstrated efficacy, only one provided evidence of high methodological quality. Two out of six OIT studies were of high quality; one provided evidence and one gave negative results.

The same study reviewed 11 SLIT trials published before June 2006. Five negative studies and one study with an outcome in favour of SLIT were of high methodological quality. For this reason, it was concluded that in spite of the accepted position of immunotherapy in guidelines, there is at present insufficient evidence that immunotherapy in any administrative form has a positive effect on symptoms or medication or both for use in children and adolescents with rhinoconjunctivitis.

The results of analysis of SLIT were at variance with the outcome of previous meta-analyses demonstrating clinical efficacy of SLIT in children. Two other groups aggregated studies into meta-analyses [13,14]. One meta-analysis found no significant effect on nasal symptoms [13], whereas the other study demonstrated significant reduction in both symptom and medication scores [14]. The meta-analyses, however, were hampered by significant heterogeneity. In case of statistical heterogeneity, one of the options is to perform a random-effect meta-analysis [14], as was done in these reviews. In a heterogeneous set of studies, a random-effect meta-analysis will award relatively more weight to smaller studies than such studies would receive in a fixed-effect meta-analysis [15]. But more importantly, a random-effect model does not eliminate the heterogeneity and is primarily intended for heterogeneity that cannot be explained [15]. However, the heterogeneity among SLIT trials can be explained in terms of type of allergen, allergen doses and duration of

treatment (see Fig. 1). For this reason, best evidence synthesis might be more appropriate [9^{••}].

Three SLIT studies in children with allergic rhinitis have been published after these reviews. A study with birch pollen included two dose regimes and one placebo arm. In this study with 88 children, the actively treated group appeared to have benefit in terms of symptoms and medication [16]. In a randomized double-blind, placebo-controlled (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 and overall evaluation of the treatment effect. Investigators from the department of Allergology, Erasmus MC recruited patients from primary care [17[•]]. Although the recruitment was performed in a primary-care setting, academic investigators selected and recruited using the inclusion and exclusion criteria in line with international guidelines. A striking observation was that also in patients with severe symptoms not even a trend in favour of SLIT was seen. These findings contrasted the results of a study among adults with the same extract [18]. In the latter study, an effect on symptoms, but not on medication use, was observed.

Another SLIT study comprising children and published after finalizing the analyses could not be evaluated easily as the age range is between 12 and 41 years and no separate data are available for children [19]. In this study, an effect was seen with post-hoc subgroup analysis. Patients with rhinitis, but without asthma, showed symptom improvement.

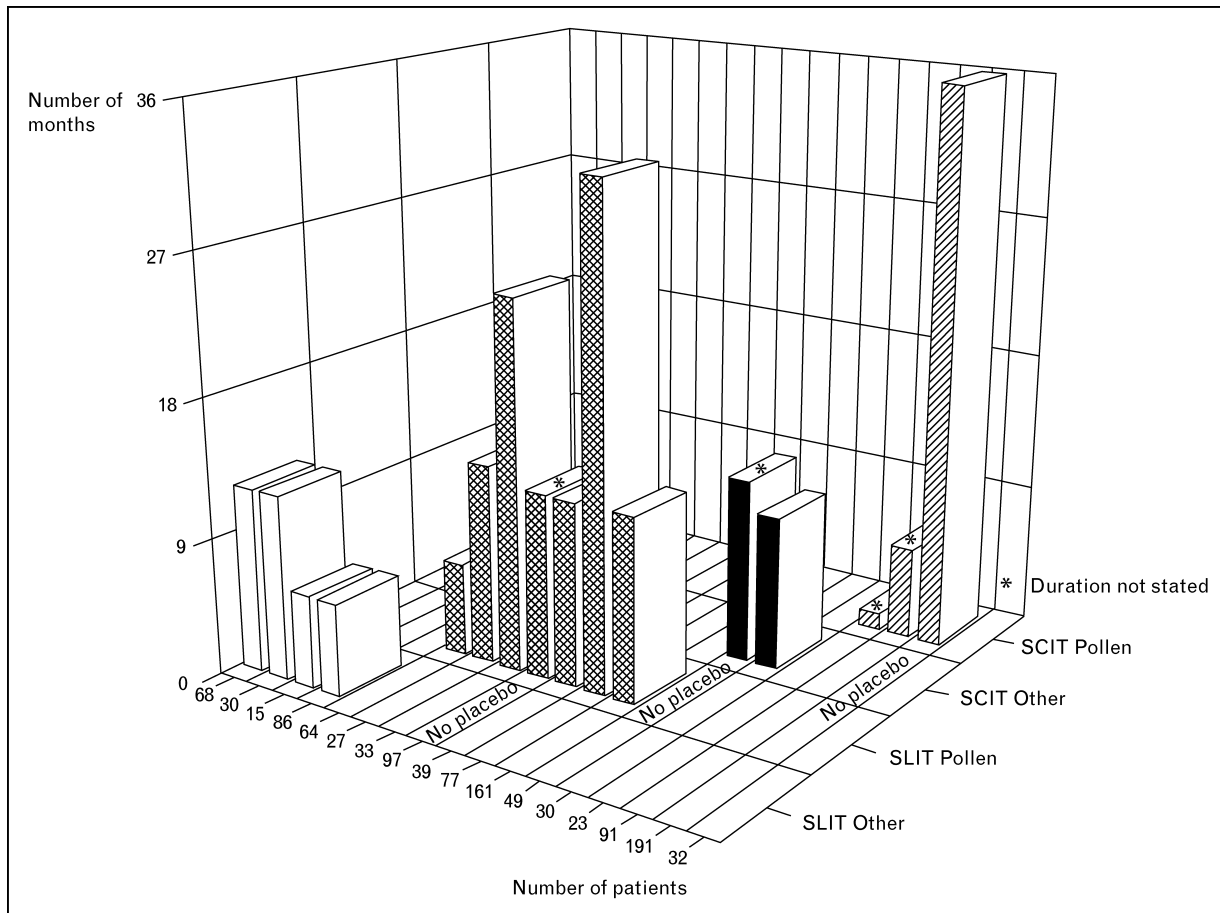
Allergic asthma

No recent RCTs with subcutaneous immunotherapy (SCIT) in asthma have been published. In the past, a study using mixtures of allergens showed no efficacy of SCIT in children [20]; however, the use of mixtures has been abandoned in European clinical practice, as the low amount of allergens in mixtures may be responsible for the lack of effect.

Recent studies on the efficacy of SLIT in asthmatic children comprise a meta-analysis [21] and a RCT [22[•]].

In the meta-analysis, nine studies, all published after 1990, fulfilled the selection criteria [21]. A total of 441 patients had a final assessment and were included in the analysis. Two hundred and thirty-two patients received SLIT and 209 received placebo. Overall, there was a significant reduction in both symptoms and medication use following SLIT. There was, however, a substantial heterogeneity characterized by an I^2 index of 94.4% (symptoms) and 95.4% (medication scores), which means that about 95% of the total variability among effect sizes is caused not by sampling error but by true heterogeneity between studies.

Figure 1 Heterogeneity in trials: variation in duration (1–36 months), allergens (grass, birch, ragweed, parietalia, olive pollen, house dust mite, cladosporium), administration [perennial, pre-seasonal or co-seasonal (denoted by asterisk)], placebo-controlled versus symptomatic treatment and heterogeneity in outcome measures



SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy. Reproduced from [9**].

This observation warrants an approach of investigating the sources of heterogeneity instead of pooling data in a meta-analysis.

A recent double-blind, placebo-controlled trial was published after completing the meta-analysis. This study comprised 111 children with house dust mite (HDM) induced mild-to-moderate asthma [22*]. After 18 months of treatment, there was no significant difference between diurnal and nocturnal asthma symptom scores between SLIT and placebo groups. Inhaled corticosteroids and inhaled β_2 -agonists' use was reduced in both groups without significant differences between groups. There were no significant differences in lung function (FEV1 and peak flow rate variations) between the groups. Rhinitis symptom score decreased in both groups, with no difference between the two groups. SLIT induced a significant reduction in skin sensitivity to HDM ($P < 0.01$) and a significant increase in HDM-specific IgE and IgG4 antibodies ($P < 0.001$) in the SLIT group compared with

the placebo group. It was concluded that in mild-to-moderate asthmatic children optimally controlled by pharmacological treatment and HDM avoidance, SLIT did not provide any additional benefit, despite a significant reduction in the allergic response to HDM.

Observational, comparative and other studies

Other recent studies have an observational character. It has been suggested in an open-controlled study that immunotherapy ameliorates otitis media [23]. In a retrospective but not controlled study, patients were followed 3 years after discontinuation of SLIT. Remission of asthma and rhinitis was obtained in 95 and 83%, respectively [24]. In another controlled but not randomized study, improvement in asthma symptoms, medication and late phase skin reaction was observed in children treated with SLIT with HDM extract [25]. These improvements were accompanied by decrease in nitric oxide (NO), eosinophil cationic protein (ECP) and membrane-associated placental tissue (MP) 1 in serum.

Several other studies underline the anti-inflammatory effects of immunotherapy. In one study of children with asthma, the absence of worsening of symptoms was attributed to an increase in transforming growth factor (TGF) β positive T cells [26]. In another study, decrease in bronchial hyperresponsiveness was associated with a decrease in serum TNF- α [27]. During SLIT, signalling lymphocytic activation molecule (SLAM) and IL-18 that induce IFN- γ production are upregulated [28].

Anti-IgE has an additional clinical effect when administered in combination with subcutaneous immunotherapy in adults [29,30]. In children, a randomized controlled trial demonstrated that combined anti-IgE treatment and immunotherapy leads to decreased release of sulphido-leukotrienes from leucocytes after allergen stimulation [31].

Implications for the future

An important observation is that the evidence for the efficacy of subcutaneous immunotherapy in children is less than optimal. From a guideline point of view, one might argue that there is sufficient evidence for a status of Ib (one or more randomized controlled trials showing efficacy) [32^{••}]; however, this status cannot be confirmed by a formal systematic review of rhinitis studies [17[•]]. As all placebo-controlled trials in children with rhinitis have been published before 1987, it is understandable that these studies do not match with the CONSORT criteria, formulated and published in 1996 [33]. Accepting the drawbacks of older studies, one has to acknowledge that neither the efficacy nor the ineffectiveness of subcutaneous immunotherapy in children has been proven. All assumptions about the efficacy have been based on successful trials in adults. In one study, immunotherapy in 22 children with rhinitis has been compared with that in 16 matched children with asthma. No differences in immunological parameters, skin-test sensitivity and bronchial hyperresponsiveness could be found [34]. For registration authorities, this might not be sufficient. Thus, there is still a need for RCTs in this area.

From all noninjectable routes of administration, SLIT is the most promising therapeutic modality. The proven effectiveness of sublingual immunotherapy in adults [35], particularly when sublingual tablets containing high doses of allergen are used [36–39], underwrites the proof of principle of this therapy. Theoretically, there is no ground to believe that immunotherapy being effective in adults will not work in children. However, reviewing the literature up to July 2008, there are still inconsistencies between the outcomes of studies and systematic reviews. One of the major barriers to the introduction of sublingual immunotherapy into daily clinical practice is the heterogeneity of studies. Not only

the results of the meta-analysis are difficult to interpret, but also the variation in clinical trials hampers the formulation of clear-cut recommendations on how to perform SLIT in terms of doses, doses schemes, target populations, allergens and specific products from manufacturers.

The preliminary results from studies with sublingual tablets suggest clinical efficacy of SLIT in children [40]. Large immunotherapy trials with these products used in children, currently under way, may provide the required proof for effectiveness.

Immunotherapy in atopic dermatitis

It has been hypothesized that systemic immunotherapy may have some clinical benefit in atopic dermatitis. A recent review on this topic reports positive results [41]. Many studies, however, are open, observational or performed on adults. Success has been achieved in a recent double-blind placebo-controlled study with subcutaneous immunotherapy [42]. In analogy to these findings, a randomized placebo-controlled study using SLIT with HDM extract in children with atopic dermatitis has been published recently [43[•]].

Fifty-six children aged 5 years or older 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 ninth month. 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-to-moderate disease, whereas only a marginal benefit was observed in patients with severe disease. The authors concluded that sublingual immunotherapy might represent an additional therapeutic tool for the treatment of extrinsic atopic dermatitis in properly selected children.

Prevention and immunotherapy

Against the background of the high prevalence of allergic sensitization and allergic disorders, a treatment that may prevent the onset of allergic disease or development of new sensitizations would push out frontiers. Several studies suggest that immunotherapy has preventive capacities. The well known Preventive Allergy Treatment (PAT) study demonstrates that 10 years after the initiation of a 3-year course of subcutaneous immunotherapy, the odds ratio for not developing asthma was 4.6 at 95% confidence interval (CI) (1.5–13.7) in favour of immunotherapy [44^{••}]. A controlled, but not randomized, study published in 1997 demonstrated that subcutaneous immunotherapy prevents the onset of new sensitizations in children [7]. Two recent studies were able to replicate

these findings [45,46]. Studies with SLIT also underwrite the preventive capacities of immunotherapy. A 3-year open study among 113 grass-pollen allergic children demonstrated that in the control group not receiving SLIT, development of asthma after three years was 3.8 times more frequent (95% CI 1.5–10.0) compared with those receiving SLIT [47]. In a recent study with a comparable design, SLIT appeared to reduce the onset of new sensitizations [48]. New sensitizations appeared in 34.8% of controls and in 3.1% of SLIT patients (odds ratio, 16.85; 95% CI 5.73–49.13).

When to initiate immunotherapy in children with allergic disease?

According to the updated Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, indications for immunotherapy are the same for children over 5 years of age as for adults. The indications for subcutaneous immunotherapy are as follows [31,32^{••}]:

- (1) Patients with symptoms induced predominantly by allergen exposure.
- (2) Patients with a prolonged season or with symptoms induced by succeeding pollen season.
- (3) Patients with rhinitis and symptoms from the lower airways during peak allergen exposure.
- (4) Patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms.
- (5) Patients who do not want to be on constant or long-term pharmacotherapy.
- (6) Patients in whom pharmacotherapy induces undesirable side-effects.

The indications for sublingual immunotherapy are as follows [31]:

- (1) Carefully selected patients with rhinitis, conjunctivitis or asthma or both caused by pollen and mite allergy.
- (2) Patients insufficiently controlled by conventional pharmacotherapy.
- (3) Patients who have presented with systemic reactions during injection-specific immunotherapy.
- (4) Patients showing poor compliance with or refusing injections.

Although these indications are valid, the guidelines position immunotherapy as a therapeutic modality for better control of symptoms if pharmacotherapy fails or is not desired. The main advantage of immunotherapy, however, is not symptom control, but alteration of the natural course of disease. From that point of view also, well controlled patients may be eligible for immunotherapy. Taking the potential preventive action of immunother-

apy into account, there is a case to start treatment early in life. Therefore, one may argue that we should focus on immunotherapy in children. Consequently, we should look for safe and patient-friendly modifications of immunotherapy. 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 and peptides) or combined administration with anti-IgE antibodies. From the alternative routes of administration, sublingual immunotherapy is the most promising, provided that evidence will come from large-scale studies using high doses of allergens. Such trials should also be the basis to guide the clinician in daily practice. In addition, conventional subcutaneous immunotherapy should also be backed up by well designed and well powered studies.

Conclusion

There are indications that immunotherapy prevents the development of asthma in children with rhinitis and the development of new sensitizations. These findings favour a policy of early introduction of systemic immunotherapy, even in children well controlled with pharmacotherapy. However, evidence of the efficacy should be provided by large RCTs. The lack of high-quality placebo-controlled studies with subcutaneous immunotherapy in children requires new studies to fill the gap. In SLIT, large RCT will provide more guidance than meta-analyses do. The current variation in clinical trials hampers the formulation of clear-cut recommendations on how to perform SLIT in terms of doses, doses schemes, target populations, allergens and specific products from manufacturers.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 594).

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