

Subcutaneous and Sublingual Immunotherapy in Children: Complete Update on Controversies, Dosing, and Efficacy

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For this review, articles on immunotherapy dosing in pediatric respiratory allergy were identified via PubMed, through congressional abstracts for 2008, in reference lists of recent review articles, and via personal communication with experts. In pediatric subcutaneous immunotherapy (SCIT), doses shown to be effective, mostly in aluminium-adsorbed preparations administered every 6 weeks, contain 20 µg of group 5 major allergen, 12 µg Bet v 1, 15 µg Fel d 1, and 5 to 20 µg Der p 1. Evidence indicates that SCIT prevents new sensitizations and asthma onset 7 years after discontinuation and reduces symptoms 12 years after a 5-year SCIT course, even though skin reactivity returns. Consistent evidence of effect exists for sublingual immunotherapy in pediatric respiratory allergy with daily 15- to 25-µg grass group 5 major allergen and 6 µg Bet v 1. Der p/1 doses of 0.8/0.4 µg three times weekly (up to 27/57 µg daily) demonstrate inconsistent findings. Evidence of effect exists for SCIT in pediatric allergic rhinitis and asthma as treatment and preventive management. Evidence of effect exists for sublingual immunotherapy in pediatric allergic rhinoconjunctivitis and seasonal asthma. Similar results are doubtful for perennial asthma.

Introduction

For the past 10 years, the World Health Organization has recognized immunotherapy as the only causal treatment for allergic diseases. Repeated exposure of the allergic patient to the substance that causes the allergy, in high subcutaneous or sublingual doses, leads to changes

in effector and regulatory cells and cytokines. These changes result in a reduced tendency of the immune system to respond with a T-helper type 2 deviation to the allergen in question. Although the past decade has been marked by enormous improvements in the understanding of the immunologic mechanisms that comprise the basis of immunotherapy [1••,2,3], other aspects of this treatment modality are still not completely clear. One is the dosing of immunotherapy extracts. This has been especially complicated because allergens are biologic substances with varying composition. Immunotherapy studies have been carried out in different parts of the world with different allergens whose potencies have been expressed in local units without use of a unified language [4•]. In this article, we try to track doses used to the most universal expression of extract potency—micrograms of major allergen—although we know this method has certain drawbacks [5••].

Methods

A broad search was conducted to look for articles on immunotherapy in children—subcutaneous and sublingual—in which the dose of the administered allergen extract was mentioned.

Search strategy

Four search strategies were used to identify articles on allergen immunotherapy in children. For publications on subcutaneous immunotherapy (SCIT), a PubMed search was conducted using the keywords “immunotherapy,” “allergen,” “hyposensitization,” “child,” “children,” and “pediatric” to identify clinical trials published in the past 15 years. For the search for articles on sublingual immunotherapy (SLIT), the comprehensive review on SLIT published by the Joint Task Force on Sublingual Immunotherapy of the American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) [6], of

which the author is a member, was taken as a basis reference for articles up to October 2005. To find more recent publications on SLIT, an identical PubMed search was conducted adding the keyword "sublingual." Second, the search was augmented by scanning references of identical articles and reviews. Third, the most up-to-date information was added by searching the abstracts from the 2008 annual meeting of the AAAAI and from the 2008 annual meeting of the European Academy of Allergy and Clinical Immunology. Finally, some article and abstract authors were asked for more in-depth information, especially on the exact dosing used in the studies.

Types of patients in reviewed articles

In this review, we include original articles in which those recruited were exclusively allergic patients 18 years old or younger with a history of allergic rhinitis, conjunctivitis, and/or asthma in whom the causal allergen was identified and IgE sensitization was ascertained by prick test and/or study of specific IgE assays. Moreover, studies with a mixed pediatric/adult population were added if a pediatric subgroup analysis was included.

Types of intervention

We considered SCIT and SLIT. All appropriate aeroallergens were considered at all doses and all durations of treatment.

Study selection

All types of clinical trials were considered in this review: double-blind, placebo-controlled, randomized clinical trials (DBPCs); randomized, controlled trials (RCTs); open controlled trials; and retrospective and postmarketing studies. These latter studies were only analyzed if the allergen dose was specified.

Results

Dose-response immunotherapy studies in children

Only a few dose-response studies have been published with SCIT, none in the pediatric age group. With SLIT, there is only one published double-blind, placebo-controlled dosing study [7••]. To make any further comments about the dose-effect relationship of immunotherapy in children, individual immunotherapy studies will have to be reviewed, with special attention paid to the doses used and the clinical efficacy reported (Table 1 [SCIT]). However, in most studies published more than a decade ago, the dosing is not mentioned or is expressed in nonuniversal units without reporting the microgram major allergen dose. That is why only some trials from more than 10 years ago are discussed in this review and more attention is paid to more recent studies that express doses.

We first review the efficacy of studies published on SCIT in children and then trials on SLIT in children with allergies. Finally, some trials studying safety are mentioned.

Clinical efficacy of studies for SCIT in children

Double-blind, placebo-controlled trials

Although the DBPC design offers the most valid information on efficacy, only a few trials on SCIT in children were DBPC because of the logical ethical drawbacks. One of the first DBPC trials of SCIT to recruit exclusively pediatric patients dated from the 1980s and investigated SCIT for *Cladosporium* spp [8].

A second DBPC trial [9] of SCIT in asthmatic children (12 active, 11 placebo) who were allergic to *Dermatophagoides pteronyssinus* showed an improvement in bronchial challenge tests—specific and nonspecific—in both groups. The confounder in this study was that the children were transferred for 12 months to the Italian Alps at the same time. The dose given was expressed in local units without referral to micrograms of major allergen. Another DBPC trial in 121 perennial asthmatic children with a mix of up to seven allergens showed no statistically significant difference between the active and placebo groups, as both improved [10].

Hedlin et al. [11] designed a partially DBPC trial in 29 children with polysensitization to perennial and seasonal allergens. All patients were given pollen immunotherapy, but only the randomized patients ($n = 15$) also received immunotherapy with a perennial allergen: cat or *D. pteronyssinus*. The dose administered at maintenance was 100,000 standard quality units (SQ-U) of a depot extract (Alurard SQ; ALK-Abelló, Hørsholm, Denmark) every 6 weeks, corresponding to 15 µg Fel d 1 or 7 µg Der p 1. Specific bronchial hyperreactivity improved in the active group ($P < 0.001$ vs placebo) after 3 years of SCIT. PC_{20} histamine also improved year by year but did not reach statistical significance in group-to-group comparison. All but one patient in the active group reported experiencing no more symptoms with cat exposure versus none in the placebo group.

A DBPC trial recently was undertaken in China [12] with SCIT for house dust mite in patients with allergic asthma. Of the 132 patients randomized, 85 were 6 to 16 years old, with 44 of them receiving active treatment. The authors found statistically significant improvement of symptoms and medication scores in the SCIT group and a statistically significant reduction in symptoms of verum compared with the placebo group during the maintenance phase of this 1-year trial. However, this improvement was not statistically significant in a subgroup analysis of the pediatric age group. All patients received 100,000 SQ-U (9.8 µg Der p 1 depot preparation [Alurard SQ]) every 6 weeks.

Randomized, controlled trials of SCIT in children

In an RCT of 15 actively treated asthmatic children (14 controls), SCIT with a dialyzed and chemically conjugated *D. pteronyssinus* extract showed efficacy [13]. The investigators demonstrated reduced asthma exacerbations ($P < 0.01$) and reduced use of bronchodilator and systemic corticosteroids ($P < 0.01$) in the active group compared with the control group. Moreover, PC_{20} methacholine

Table 1. Trials with subcutaneous immunotherapy in children

Design	SCIT References & controls n	Allergen (manufacturer)	Dose	Duration	Positively influenced signs & symptoms	Negative outcomes	Comments
DBPC	Peroni et al. [9]	HDM (Alpare, by DHS)	800 alpare units	12 mo	SCIT: skin reactivity	SCIT and placebo: improved PC ₂₀ , MCh, PC ₂₀ , HDM	All children moved to Italian Alps for 1 y; both groups improved
DBPC	Adkinson et al. [10]	Allergen mix— maximum of 7	?	18–24 mo		No statistically significant reduction in medication use; days taking oral CS, PC ₂₀	Both groups improved; no intergroup differences
DBPC	Hedlin et al. [11]	Cat or HDM (Alucard, by ALK-Abelló)	15 µg Fel d 1 or 7 µg Der p 1	36 mo	PC ₂₀ allergen; symptoms of cat exposure; IgG4 rise	SCIT: PC ₂₀ histamine improved (non-stat- istically significant); medication	All children also received pollen SCIT
DBPC	Wang et al. [12]	HDM (Alucard, by ALK-Abelló)	7 µg Der p 1	12 mo (phase 1: 6 mo, build- up; phase 2: 6 mo, main- tenance)	Phase 2: symptoms, skin reactivity	No statistically significant reduction in medication use, morning and evening PEF, PC ₂₀ , histamine, IgE HDM, ECP, blood eosinophils	All patients on ICS; intragroup: significant reduction in symp- toms + medication; pediatric subgroup: non-statistically signifi- cant differences between SCIT and placebo groups
RCT	Pifferi et al. [13]	HDM; (Conjuvac, DHS and Bayer SpA [Milan, Italy])	? (in-house reference extract)	36 mo	Asthma exacerbations, use of bronchodilators and oral corticosteroids; PC ₂₀ MCh; new sensitizations	Medication score, lung function (non-statistically significant improvement), SPT	Mechanistic study (see text)
RCT	Tsai et al. [14]	HDM	?	12 mo	Asthma symptoms		
RCT	Jacobsen et al. [20]	Birch or grass (Alucard, by ALK-Abelló)	12 µg Bet v 1 or 20 µg Phl p 5	36 mo	7 y post-SCIT: asthma development, rhinocun- junctivitis symptoms, conjunctival provocation test; 2 y post-SCIT: same + PC ₂₀ , MCh, SPT	7 y post-SCIT: PC ₂₀ MCh, SPT	79/68 patients were studied at 7-y follow-up

Positive results are only those showing a statistically significant difference between SCIT and placebo. Only the children who were included in the primary analysis are shown. For details on the study design, see the text. SCIT = subcutaneous immunotherapy; SPT = skin prick test; ICS = inhaled corticosteroids; PEF = peak expiratory flow; MCh = methacholine; PC₂₀ = provocative concentration of 20% histamine; HDM = house dust mite; RCT = randomized, controlled trial; SCIT = subcutaneous immunotherapy; SPT = skin prick test; PC₂₀ = threshold for giving a new inhaler; ICS = inhaled corticosteroids.

Table 1. Trials with subcutaneous immunotherapy in children (continued)

Design	Reference	SCIT/ controls, n	Allergen (manufacturer)	Dose	Duration	Positive outcomes (SCIT vs controls) ^a	Negative outcomes	Comments
OCT	Eng et al, 1971	14/14 at start; 13/10 in 1997	Pollen (Allergovit, by Allergopharma)	Allergoid	Every 3 mo for 3 y	1997: eye, nose, chest, and total symptoms; SPT; percentage of patients with seasonal asthma symptoms; new sensitizations	No statistically significant reduction in medication use ($P = 0.08$), conjunctival provocation (non-statistically significant tendency)	SCIT given 1989-1991; patients prospectively observed during 1997 and 2003 pollen seasons
OCT	Eng et al, 1984	14/14 at start; 12/10 in 2003	Pollen (Allergovit, by Allergopharma)	Allergoid		2003: symptoms, medication, symptom and sensitizations	SPT, seasonal asthma ($P = 0.08$)	
OCT	Keskitalo et al, 1997	27/26 allergic rhinitis	Pollen (Allergovit, by Allergopharma)	20- μ g Phl p 5 equivalent (5000 TU)	30 mo	12 mo: rhinitis + asthma symptoms reduced (medication); seasonal reduction; PC ₂₀ MChA blunted; seasonal IgE rise; nasal provocation; IgE/IgG ratio reduced; IL-4 reduced	Reduced ECP rise in season (non-statistically significant); IL 19, TGF- β augmented in both groups	Allergoid; many seasonal immunologic alterations blunted with SCIT
OCT	Cevik et al, 1991	19/12 (asthma)	HDM (Allergovit, by Allergopharma)	5000 TU	12 mo	Symptoms	No statistically significant reduction in medication use; serum NO, ECP, and MCP T levels; PC ₂₀ HDM; SPT	SCIT group (baseline-12 mo): significant reduction in medication, NO, ECP, MCP-1, PC ₂₀ HDM
OCT	Inai et al, 1993	85/62 (allergic rhinitis, asthma)	HDM (Cieer Laboratorios, ALK-Abelló, Stallergenes, Allergopharma)	Approximately 5 y	5 y	SCIT: 75% no new sensitizations vs 47% for controls ($P = 0.002$)	Less medication (non-statistically significant); SPT, PC ₂₀ MCh	Patients with new sensitizations had higher atopy and medication scores
Retro-spectively	Cools et al, 1997	48/62 (asthma)	HDM, Grass (GIAI, Allergo)	5-20 μ g Der p 1 and Der p 2	61 mo	Asthma symptoms	Less medication (non-statistically significant); SPT, PC ₂₀ MCh	Evaluation 9.3 years after SCIT in childhood

^aPost hoc results are only those showing a statistically significant difference between groups. Forty-five of the 112 patients were children. Forty-five patients were treated with depot preparations from ALK-Abelló, Stallergenes, or Allergopharma; and 40 patients were treated with aqueous extracts from Cieer Laboratorios. CS—corticosteroids; DBPC—double-blind, placebo-controlled trial; DHS—Dhyme-Hollister-Silver (Bridgeport, United Kingdom); ECP—eosinophil cationic protein; HDM—house dust mite; ICS—inhaled corticosteroids; IL—interleukin; MCh—methacholine; MCP-1—monocyte chemoattractant protein-1; NO—nitric oxide; OCT—open controlled trial; PC₂₀—peak expiratory flow; RCT—randomized, controlled trial; SCIT—subcutaneous immunotherapy; SPT—skin prick test; TGF- β —transforming growth factor- β ; TU—treatment units.

improved in the SCIT group. No microgram major allergen dose was stated.

Another RCT [14] with house dust mite SCIT for 12 months in asthmatic children showed reduced asthma symptoms ($P < 0.05$, active vs control), but again no dose was mentioned. Mechanistic assays were also carried out in this study.

Open controlled trials of SCIT in children

Long-term efficacy

The first publication on the long-term efficacy of hypo-sensitization therapy for bronchial asthma in children was the classic study by Johnstone and Dutton [15] in 1968, when as-yet unstandardized extracts were used.

Coois et al. [16] examined the effect of monthly injections of house dust mite or pollen over 5 years in asthmatic children. The house dust mite extract contained 5000 allergy units (AU) (Allerset, HAL, Allergy, Haarlem, The Netherlands [5000 AU = 5–20 µg of Der p 1 and Der p 2]). At re-evaluation almost 10 years later, the risk of frequent asthmatic symptoms was three times higher in the control group than in the SCIT-treated group (prevalence ratio, 3.43; $P = 0.0006$). The frequent use of antiasthmatic medication was also more pronounced in the control group, although the difference was not statistically significant ($P = 0.38$). Lung function parameters and results of skin prick tests with house dust mite were comparable in the two groups.

Eng et al. [17,18•] recently demonstrated the long-term benefit of SCIT, 6 and 12 years after termination. From 1989 to 1991, preseasonal SCIT was given with a depot allergoid pollen preparation (Allergovit; Allergopharma, Rheinbeck, Germany) for 3 consecutive years. Fourteen children with severe seasonal allergic rhinitis (mean age, 9.3 years) were recruited, and 14 matched controls, who refused SCIT, were sought. Six and 12 years after termination of SCIT, 12 actively treated patients and 10 controls were found for the follow-up study. Between-group comparisons showed a continued reduction in seasonal rhinitis symptoms ($P < 0.03$), medication use ($P = 0.05$), and new sensitizations ($P = 0.05$). Moreover, at 6 years, a reduction in skin prick sensitivity was seen, but this reduction was lost after 12 years. The same pattern was shown for seasonal asthma: still reduced at 6 years but with only a trend toward reduction at 12 years post-SCIT ($P = 0.087$, asthma was still present in 33% of the active group vs 70% of the controls). No precise dose of the allergoid extract was stated in this publication, but the same product 12 years later was reported to have 20 µg group 5 major allergen equivalents in the last measurable production step before the extracts were formed into an allergoid [19].

The only RCT on the long-term efficacy of SCIT and prevention of asthma is the preventive allergy treatment (PAT) study [20••]. Between 1992 and 1994, 205 children 6 to 14 years old with seasonal allergic rhinitis to birch and/or grass pollen were stratified and randomized to the SCIT or control group. The maintenance SCIT treatment

consisted of injections of a depot preparation (100,000 SQ-U/mL) with 20 µg Phl p 5 and/or 12 µg of Bet v 1 every 6 weeks for 3 years. At the beginning of the trial, 117 children had no seasonal asthma symptoms. Significantly fewer actively treated patients had developed asthma 7 years post-SCIT as evaluated by clinical symptoms (odds ratio, 2.5 [1.1–5.9]). Rhinitis and conjunctivitis symptoms and conjunctival provocation test still favored the actively treated individuals, showing a statistically significant difference compared with the control group. However, skin reactivity had returned.

New sensitizations

The first publication to report on the reduction in new sensitizations in children with SCIT treatment dates from 1997 [21]. Forty-four asthmatic children were included in this open controlled study and received house dust mite SCIT (Stallergènes, Antony, France, dose not stated) for 3 years. New sensitizations developed in 12 of 27 of the actively treated children and in the entire control group.

Pajno et al. [22] reported similar findings in asthmatic children at 6-year follow-up after SCIT with a house dust mite extract started circa 1993 to 1994 (ALK-Abelló, Milan, Italy, dose not stated).

A more recent open controlled study on the same subject [23] was carried out in 147 children (45 depot preparation SCIT, 40 aqueous solution SCIT, 62 controls). At the end of 5 years of SCIT, 75.3% of the patients in the SCIT groups showed no new sensitization, compared with 46.7% in the control group ($P = 0.002$). No differences were observed between the aqueous and depot SCIT subgroups. The patients developing new sensitizations had higher atopy ($P = 0.002$) and medication scores for rhinitis ($P = 0.008$) and asthma ($P = 0.013$) compared with patients not developing new sensitizations after 5 years of SCIT. Extracts from various manufacturers were used in the depot preparation group (ALK-Abelló, Stallergènes, Allergopharma), which resulted in doses varying from approximately 0.5 to 5 µg Der p 1. In the aqueous SCIT group, doses were adjusted individually from a 5000 AU/mL *D. pteronyssinus* extract (Greer Laboratories, Lenoir, NC).

The open controlled study by Keskin et al. [19] was very comprehensive, measuring clinical and immunologic outcomes. The extract used was an allergoid with major allergen equivalent in the last measurable production step (before allergoidization) of 20 µg Phl p 5 per maintenance dose (aluminium-adsorbed Allergovit). Rhinitis and asthma symptoms and medication scores were significantly better in the active group (27 children) than in the control group (26 children) after 2.5 years of SCIT. Moreover, immunologic parameters improved.

Immunologic mechanisms and provocation tests with SCIT treatment in children

Tsai et al. [14] studied apoptosis of certain cell lines in an RCT of SCIT with a house dust mite extract (dose and

manufacturer nor stated) in 60 asthmatic children. Using the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling) method, the investigators showed, after 12 months of SCIT, an augmented apoptosis of CD4⁺ interleukin (IL) 4⁺ T-helper type 2 cells ($P = 0.001$) and of CD45⁺ R0 cells ($P < 0.05$) in comparison with the control group, whereas the apoptosis of CD4⁺ interferon (IFN)- γ T-helper type 1 cells was unchanged. Moreover, specific serum IgE was reduced, and IFN- γ was augmented with statistical significance.

Another 12-month, open controlled study [24] of house dust mite SCIT (5000 treatment units/ml of Dpt/D), no microgram dose stated) in 31 asthmatic children showed a reduction of eosinophil cationic protein (ECP), nitric oxide, monocyte chemoattractant protein-1, and skin prick test reactivity in the treated group. However, specific bronchial hyperreactivity (PC₂₀ allergen) did not show any difference, as it improved in both groups.

In the open controlled study by Keskin et al. [19] (20 μ g Phl p 5 allergoid, see above), a statistically significant improvement was demonstrated in the seasonal reduction of PC₂₀ methacholine, skin test reactivity, seasonal nasal reactivity (nasal provocation testing for grass pollen), and nasal lavage ECP levels in the active group compared with the controls. Changes were recorded after the first year of immunotherapy but were more pronounced after the second year. The seasonal increase in IgE decreased ($P < 0.05$), and grass-specific IgG, IgG1, and IgG4 already had increased significantly at the end of the seven-injection build-up therapy ($P < 0.001$ for all). IL-4 levels in the culture supernatants showed a steady decline from baseline at first and second year of immunotherapy ($P < 0.001$).

Another open controlled SCIT study also showed a rise in specific serum IgG and a reduction in specific serum IgE in 56 children with seasonal asthma, but again no dose was stated [25].

Clinical efficacy studies for SLIT in children

All randomized efficacy studies up to now have been conducted in children over the age of 5 years.

Double-blind, placebo-controlled and randomized controlled trials with SLIT in children

SLIT studies have been published since 1986 [26], with the first on SLIT to children in 1990 [27]. The first pediatric study to mention dose used in micrograms of major allergen was the DBPC study published in 1997 by Hirsch et al. [28].

Various meta-analyses on SLIT have been conducted since, two of them in children. However, the SLIT studies carried out in children vary greatly in many parameters. This makes the heterogeneity in the meta-analyses too high [29]—with an I² of 85% to 95%—which strongly reduces the validity of the results obtained.

As a solution for the heterogeneity in meta-analytic reviews can be carried out. Some on SLIT in children have been published recently [30,31], one of them complete being the systematic review by Röder et al. as both DBPC trials and RCTs on SLIT for allergic rhinitis were included and a solid quality assessment was made.

Röder et al. [30] concluded that there was no evidence for effect of SLIT in children, which may be a valid conclusion based on their data. However, the authors do not include articles published after June 2006. Moreover, a closer look at the individual studies in their systematic review shows us interesting data that may explain the negative outcomes in some SLIT studies.

From June 2006, when the Röder et al. [30] review ended, until June 2008, various trials on SLIT in children have been published. Three large, high-quality (> 6 points on the Delphi list [32]) DBPC RCTs have been conducted in children, two with grass pollen SLIT tablets [33••,34••] and one DBPC, multiple-dose study with birch SLIT [7••]. In the first DBPC trial [33••], 75.1 standard quality tablets (SQ-T)-[®](Graxax; ALK-Abelló, Horsholm, Denmark, 15 μ g Phl p 5) were given daily in a pre-seasonal protocol, started 17 weeks pre-seasonally. Results were given for 114 SCIT-treated and 120 placebo patients (5–16 years old). Statistically significant reductions in the symptoms and medication scores were demonstrated (22% and 34%, respectively; 28% and 65% in peak pollen season), together with a 64% reduction in asthma symptoms.

In the second DBPC trial [34••], 278 children (5–16 years old) with seasonal allergic rhinoconjunctivitis were recruited. A total of 227 patients could be included in the per-protocol analyses (115 SLIT, 112 placebo). Daily 30 mg index of reactivity (IR) tablets of five grasses were administered (Oralair; Stallergenes, Antony, France, 25- μ g group major allergen), with a 2-day run in period of 100 IR (day 1) and 200 IR (day 2). After a pre-seasonal treatment started 4 months before the pollen season, a statistically significant improvement was documented in the primary efficacy variables: symptoms and medication score.

The only dose-effect study of immunotherapy in children [7••] was done with two different doses of birch pollen extract (Aquagen SQ; ALK-Abelló, Hørsholm, Denmark). The 32 children in the low-dose group (1.6 μ g Bet v 1, 5 d/wk) showed statistically significant reduction only in symptoms, whereas the 27 children in the high-dose group (13 μ g Bet v 1, 5 d/wk) improved in symptoms and medication scores compared with placebo.

Trials with SLIT for allergic asthma in children

Apart from the presented trials on SLIT for allergic rhinitis, there are some DBPC trials on SLIT with house dust mite extract in children with asthma [22,35,36,37•,38]. In these studies, the relative dose in monthly micrograms of Der p 1/2 varied from 1.5 to 120 times the recommended SCIT dose. No clear relationship was found

between dose and effectiveness of SLIT in these studies, as some low-dose trials showed improvement and some high-dose studies were negative.

Finally, there was one more negative study of SLIT for allergic respiratory symptoms in a primary care setting. This study is not mentioned any further, as children were not selected on the basis of a positive skin prick test or treated by specialists.

More details of individual studies on SLIT in pediatric allergic rhinitis and asthma can be found in a previous issue of this journal [39•].

Immunologic mechanisms and provocation tests with SLIT treatment in children

Just as in the adult studies on immunologic changes with SLIT, increases in serum-specific IgE, IgG4, IL-10, and transforming growth factor- β have been demonstrated in children, as has been a reduction in eosinophils and mRNA for IL-5 in stimulated peripheral blood mononuclear cells [40]. Recently, an upregulation of various IL- γ -stimulating cytokines, such as IL-18 and signaling lymphocytic activation molecule, was detected. Some of these changes have been shown to be dose- and efficacy-related [40,41]. In low-dose SLIT studies, changes are not seen [42,43] or are not statistically significant [44].

Safety of immunotherapy in children

SCIT safety

Akcakaya et al. [45] reviewed all records of 88 patients 6 to 15 years old who had been treated with SCIT from 1989 to 1997. Of a total of 5760 injections given, 206 injections (3.57%) caused local reactions, and 12 patients presented with systemic reactions (0.2%), one of which was classified as anaphylaxis with a drop in blood pressure and respiratory distress leading to intubation. Four patients received epinephrine. Seven of the 12 patients (58.3%) experienced no local reactions before a systemic reaction, and in this study, all systemic reactions occurred less than 30 minutes after the injection. Doses were usually increased weekly. The typical maximum dose was 0.8 mL of 0.01 weight/volume extract of Stallergenes and 1 mL of 0.01 weight/volume extract of Novo-Helena (Allergopharma, Rheinbeck, Germany), Alutard, and Bencard (Bencard Laboratories, Brentford, England). Once the patient reached the maintenance dose or the maximum tolerated dose, the injection schedule was changed to every 2 and then to every 4 weeks.

Keskin et al. [46] investigated the safety of SCIT in asthmatic children, looking at nonspecific bronchial hyperactivity 1 hour after an immunotherapy injection. The authors found no reduction in the PC₂₀ with methacholine after SCIT administration (dose not stated).

SLIT safety

In general, SLIT is considered to have less systemic adverse events than SCIT. Even so, systemic adverse events have

been reported to occur in the trials on SLIT, sometimes leading to treatment discontinuation [6]. In adults, a dose-response relationship in adverse events has been shown with SLIT grass tablets with doses up to 1,000,000 SQ-I, which contain approximately 200 μ g Phl p 5 (13 times the dose given normally) [47]. In a 1-month safety study of the grass tablet with 15 μ g Phl p 5, of 60 patients 5 to 16 years old, one child presented with a serious adverse event—an asthma attack—and another presented with various systemic, nonserious adverse events. Both were withdrawn from the study [48•].

With ever-increasing use of this treatment modality, the first serious adverse events in the open population have been published, two in the pediatric age group [49,50••]. The second pediatric case was a 16-year-old female, who after a 3 week break in maintenance treatment in the third year of SLIT decided to take six times her normal dose (normal dose was 10 drops of 100 IR/mL, total dose = 51 μ g Der p/1). An anaphylactic reaction started at 5 minutes and evolved into shock, but with a good final outcome.

Conclusions

In all pediatric immunotherapy studies reviewed, the same dose is used as in adults (in SCIT and SLIT). Studies with varying design have been presented in this review on SCIT in children. In some, the dose administered is stated in micrograms of major allergen. Almost all SCIT studies have been carried out with depot preparations (different from the preparations used in the United States). Aluminium-adsorbed preparations permit applications at maintenance every 6 to 8 weeks. Moreover, this is a slightly T helper type 1-deviating adjuvant. All SCIT studies use similar doses per application: for grass SCIT, 20 μ g group 5 major allergen; for birch SCIT, 12 μ g Bet v 1; for cat, 15 μ g Fel d 1. For house dust mite, the doses reported vary from 0.5 μ g Der p 1 in one study to 5 to 20 μ g Der p 1 in all other SCIT trials. Mixes of up to seven allergens do not seem to be effective. The long-term studies conducted many years after SCIT discontinuation are very promising. An interesting issue is that although the skin prick tests' positivity seems to return 5 to 6 years after discontinuation of SCIT in these two trials, clinical efficacy partially remains.

The situation is different for SLIT. Since the first SLIT publication more than 20 years ago, the field has been marked by dose searching, in quantity and in frequency and formulation. Some good trials published from 2006 to the present make certain aspects of dosing clearer. This is pointed out as we go through the negative studies in the Röder et al. [30] review below:

1. Dose. The most recent SLIT studies in adults [51••,52••] and children [7••] demonstrate a clear dose-response relationship.

2. Dosing frequency. Daily dosing tends to be more effective than dosing with lower frequency [51••,52••,53].
3. Preseasonal dosing. Commencing SLIT at least 4 months before the start of the pollen season augments its efficacy [54]. This was not the case in three of the eight seasonal studies.
4. Patient selection, asthma. Two of the studies focused on asthma. In these studies, rhinitis symptoms were secondary (or exploratory) end points, likely with insufficient power to detect a statistically significant difference between groups.
5. Duration of treatment. Four of 12 studies had interrupted treatment. In the latest Cochrane review on SLIT, the best effect was seen in studies with at least 1 year of continuous treatment [55•].
6. Patient selection, polysensitization. In the study conducted by Vourdas et al. [56], polysensitized children were included. In the SLIT group, 30 of 34 children were polysensitized, 23 of them to grass. The olive pollen season starts in May, showing important overlap with the grass pollen season that starts just 1 month earlier in Greece. Of the placebo patients, only 15 of 32 were sensitized to grass. Taking a closer look at the figures on symptom scores, it becomes clear that during the first year, the SLIT group showed more symptoms than the placebo group, whereas during the second year, this relationship was reversed. Although statistics did not show a difference between groups, with these reservations, a beneficial treatment effect seems likely.
7. Number of patients with allergic rhinitis included. More than one half of the studies were underpowered, with less than 20 allergic rhinitis patients in the actively treated group.
8. Possible confounding by drug effects. In one study, all patients received maintenance inhaled fluticasone during the pollen season in addition to SLIT/placebo, which may have resulted in marked improvement in SLIT and placebo groups, thereby reducing intergroup differences for symptoms ($P = 0.059$ for nasal symptoms).

When these points are all overcome, SLIT does show clinical efficacy, as has been demonstrated in the recent DBPC pollen SLIT studies [7••,33••,34••]. These studies are consistent and present a high level of evidence for SLIT's effect in pollen-induced rhinoconjunctivitis in children.

The evidence for SLIT's effect in perennial asthmatic children with house dust mite allergy is still not so straightforward, as two of four recent, high-quality studies were negative [37•,57]. One problem in this pathology is likely the multifactorial cause of asthma. Especially in perennial asthma, sensitization to house dust mite may

be found without it being the causal factor. Asthma has many faces, one of them being an alteration in the repair mechanisms of the bronchial epithelium that will not improve with immunotherapy. Here, the patient selection will have to be more specific, eliciting only those patients in whom asthma is mainly caused by their allergy. Moreover, the use of inhaled corticosteroids in treatment and control groups in all SLIT asthma studies may mask a rise in symptoms in the placebo group. Randomized, long-term studies in SLIT are still awaited.

With doses that are too high, systemic and even serious adverse reactions do occur in SLIT, making safety a determining factor for the maximum dose. This maximum tolerated dose does not seem to be lower for small children in comparison with older ones [58,59•].

In conclusion, positive and negative clinical trials with immunotherapy in children have taught us to come closer to an optimal dose, improving efficacy, but the last word has not yet been spoken, especially in regard to SLIT for asthma and SLIT's long-term efficacy. Moreover, SLIT has to be a specialist's treatment given that the patient's selection is crucial to obtain efficacy, and adverse events, although rare, do occur.

Disclosure

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