

Review

Evidence of effect of subcutaneous immunotherapy in children: complete and updated review from 2006 onward

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Objective: To update the scientific evidence of subcutaneous immunotherapy (SCIT) in children.

Data Sources: PubMed, EMBASE, and known articles.

Study Selection: All publications on SCIT in pediatric patients from January 2006 to April 2011. Study design was not a restriction. The articles were analyzed according to their outcomes and evaluated on their scientific quality using the Grading of Recommendations Assessment, Development, and Evaluation and Jadad tools. Clinical, safety, and immunologic data were gathered.

Results: The scientific evidence produced by the 31 articles analyzed showed that there is high-quality evidence that grass pollen SCIT causes a reduction in the combined symptom-medication score and increases the threshold of the conjunctival provocation test, immediately and 7 years after termination of SCIT, as well as the threshold of the specific bronchial provocation test and the skin prick test reactivity. *Alternaria* SCIT improves medication scores, combined symptom-medication scores, and quality of life. It augments the threshold in the nasal provocation test. High-quality evidence of house dust mite SCIT shows that asthma symptom and medication scores improve and emergency department visits and skin reactivity are reduced; moderate evidence indicates improvement in pulmonary function tests. Pollen SCIT prevents asthma (moderate evidence); evidence for long-term benefit of pollen SCIT (7-12 years after termination) is low to moderate. There is inconclusive evidence for SCIT reducing new sensitizations.

Conclusion: There is acceptable evidence that shows that grass pollen, *Alternaria*, and house dust mite SCIT is beneficial in allergic children.

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INTRODUCTION

Apart from elimination and avoidance of provoking factors where possible, the only cause-based treatment for allergic rhinoconjunctivitis and asthma is allergen specific immunotherapy. Several reviews on subcutaneous and sublingual immunotherapy have been published during the last few years, some of which are focused on pediatric patients.¹⁻⁷

The findings of these reviews vary in their evaluation from optimistic²⁻⁴ to a more moderate or even negative view on the usefulness of immunotherapy in children.¹ None of these reviews, however, included the most recent high-quality articles, and other possible explanations for those too positive or negative conclusions have been discussed by others.^{8,9} Three recent Cochrane meta-analyses¹⁰⁻¹² have provided clinical evidence for the usefulness of both sublingual and subcutaneous allergen specific immunotherapy.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool¹³ has been introduced as a method to evaluate the scientific quality and possible bias of trials, as published in articles and meta-analyses, in support of decision-making agencies. Since 2004, the GRADE system has been adapted by many specialties as a useful tool for the formulation of guidelines. The latest Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines were based on this instrument.^{14,15} Table 1 lists the parameters that define the quality of evidence in GRADE.

In this review on allergen specific subcutaneous immunotherapy (SCIT) in children, we selected articles published

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Table 1. Parameters That Define the Quality of Evidence in Grading of Recommendations Assessment, Development, and Evaluation^a

Quality of evidence	Study design	Reduce quality if . . .	Augment quality if . . .
High (4)	Randomized (4)	Study limitations ^b	Large effect ^d
Moderate (3)		–1 Serious	+1 Large
Low (2)	Observational (2)	–2 Very serious	+2 Very large
Very low (1)		Inconsistency	Dose response
		–1 Serious	+1 Evidence of a gradient
		–2 Very serious	All plausible confounding
		Indirectness	+1 Would reduce a demonstrated effect or
		–1 Serious	+1 Would suggest a spurious effect when results show no effect
		–2 Very serious	
		Imprecision ^c	
		–1 Serious	
		–2 Very serious	
		Publication bias	
		–1 Likely	
		–2 Very likely	

^a All plausible confounding would reduce a demonstrated effect: this means that confounding factors, if present, would reduce the effect of the treatment, but even so an effect is demonstrated. A good example is an underpowered study with too small sample sizes; this confounding factor might reduce the possibility to show an effect of the treatment. If, even so, a statistically significant effect can be demonstrated, this adds 1 point. The explanation would be the other way around for the second item.

^b Adequate sequence generation, allocation concealment, blinding, large percentage of dropouts, or early stopping.

^c Small sample size, rare events, or large confidence intervals.

^d Large effect: relative risk less than 0.5 or more than 1-SD differences; very large effect: relative risk less than 0.2 (grade working group).

since 2006. We evaluated their quality with the GRADE tool. Moreover, a second tool was applied, the Jadad system,¹⁶ which has been used by investigators of the Cochrane meta-analyses in the past to qualify the probability of bias in the publications.¹¹ Lastly, a summary table integrates all the evidence to draw conclusions on the effectiveness of SCIT in children with respiratory allergies. We evaluated clinical outcomes, safety issues, and immunologic findings.

METHODS

Search Strategy

One of the reviewers (D.E.S.L.-L.) searched MEDLINE and EMBASE, using the keywords [(immunotherap* OR desensit*)] AND [allerg*] AND [child* OR pediater*], with the time limits 2006 to April 2011. In addition, reference lists of recent reviews and published trials were searched. Newly identified articles were added to those already known to the investigators. Full texts and abstracts were also considered. Language was not restricted, as long as an English abstract was available.

Study Selection

Initial selection of trials on SCIT was based on title and abstract and refined by analysis of the corresponding full-text publications. We identified those that included exclusively participants between 3 and 18 years of age, with symptoms of respiratory allergy (seasonal or perennial allergic rhinitis or rhinoconjunctivitis and/or asthma) and proven allergen sensitivity. Study design was not a restriction. Only those trials were incorporated that reported clinical data and/or safety data and/or immunologic findings as outcome measures. Tri-

als recruiting both adults and children were only included if the pediatric data were presented separately and/or pediatric patients by far outweighed adults in number.

Data Collection and Analysis

For each study, data on design and outcomes were abstracted in a standard extraction sheet and into both quality assessment sheets: GRADE¹⁵ and Jadad.¹⁶ Facets of GRADE and how to assign a quality qualification are given in Table 1. Jadad scores ranged from 0 to 5; high scores are obtained by adequately randomized and masked trials, whose articles give a detailed description of the dropouts. Two of the authors independently performed quality assessment of the studies (D.E.S.L.-L. and D.R.P.-C.).

Information on safety and immunologic data were summarized in separate tables. The European Academy of Allergology and Clinical Immunology system¹⁷ was almost universally used in the articles for the classification of the severity of adverse events, although sometimes available data were limited. Briefly, mild symptoms of rhinitis or urticaria were classified as grade 1, moderate symptoms (including pulmonary symptoms) were graded 2, and more severe data (anaphylaxis or anaphylactic reaction) were classified as grade 3.

RESULTS

Retrieved Articles

One hundred nine articles were identified as possible candidates for review. Of these 31 were excluded because of publication date or age limits; one study was kept in the analysis because most patients were children.¹⁸ Forty-seven articles on sublingual immunotherapy will be analyzed in a

later article. The selected 31 articles form the basis of this review on SCIT in children (5 Chinese articles reviewed in abstract form).

Twenty-five articles reported clinical data as symptom and medication scores, pulmonary function tests, specific and nonspecific bronchial challenge tests, and/or skin prick tests. Twelve studies reported safety data and 17 immunologic outcomes of 16 different trials.^{19,20}

Design and Quality of the Studies

Six trials had a double-blind, placebo-controlled (DBPC) design, 5 were randomized controlled trials (RCTs), and 11 were open controlled trials (OCTs). The rest were open, postmarketing, and retrospective studies. The only pharmacoeconomic study²¹ used a retrospective, matched cohort design with cases and controls.

The possible bias and quality of the trials was analyzed with the Jadad and GRADE system (Table 2 and eTable 1). Four articles were assigned the maximum Jadad score of J5, 2 were scored J4, 3 were scored J3, 2 were scored J2, and 4 trials were rated J1; the rest had a score of 0.

Allergen Extracts

The allergen extracts were preparations from European allergen manufacturers in 23 of the 30 studies analyzed. In 1 RCT²² and in part of the patients of an OCT²³ an aqueous extract was used from a US manufacturer (AllerMed Laboratories, San Diego, California, and Greer Laboratories, Lenoir, North Carolina, respectively). Moreover, the pharmacoeconomic study was based on data of medication use by children undergoing immunotherapy who lived in Florida.²¹ Six studies administered extracts from Allergopharma (Hamburg, Germany), 5 extracts from ALK-Abelló (Hørsholm, Denmark), and 5 studies extracts from Stallergènes (Antony, France). A few administered extracts from Allergy Therapeutics (West Sussex, England), Leti Laboratories (Barcelona, Spain), ALK-Abelló (Madrid, Spain), and Bial-Aristegui (Bilbao, Spain) and a Croatian national standardized product.

Depot Extracts, Allergoids, and Adjuvants

Most European allergen extracts for SCIT are depot preparations: in 23 trials the natural allergen was adhered to aluminum hydroxide, glutaraldehyde, or calcium phosphate. Moreover, in 5 trials the allergen was chemically changed into a hypoallergenic formulation (allergoid).^{24–28} In 2 of these trials an adjuvant was added.^{27,28} In 4 trials a natural aqueous extract was administered. The type of extract in the Chinese trials was not specified.

Allergens

In most studies house dust mite (HDM) extract was administered. In 3 clinical studies and 1 safety study grass extracts were used, in 1 study grass and/or birch was used, and in 3 studies *Alternaria* extracts were used.

Clinical Outcomes

Table 1 gives details of all clinical trials selected between January 2006 and April 2011. In the right column, differences

found between active and placebo or control groups are stated, with the corresponding statistical significance. In some studies, only intragroup differences were reported, comparing data before and after SCIT. The study order is according to the allergen administered, according to the allergic disease primarily treated (rhinitis or asthma), and according to study design. Findings of the studies are discussed below, adding quality of evidence to them; for example, G2, J1 indicates GRADE score 2, Jadad score 1. Publications without clinical data are presented below under “safety” and “immunologic findings.”

Symptom and Medication Scores: Seasonal Allergens

For grass (and/or birch) immunotherapy Roberts et al showed improved symptom and medication scores in a high-quality DBPC trial (G4, J4). Long-term improvement of symptoms and reduction in medication and symptom-medication scores have been demonstrated for as long as 7 (Jacobsen et al; G4, J3)²⁹ and 12 (Eng et al; G2, J1)²⁴ years after finishing immunotherapy.

One DBPC clinical trial (G2, J5) of an *Alternaria alternata* extract, which incorporated 0.1 µg of the major allergen Alt a 1 administered monthly during maintenance therapy, showed no effect. The study was underpowered, but also the treatment might have been poorly effective in view of the very low maintenance dose of allergen included in the extract: of the variables analyzed some improved more in the active and others more in the placebo group.³⁰

Kuna et al (G4, J5)³¹ showed convincing improvement of asthma and rhinoconjunctivitis in a study that used a high-dose (8 µg of Alt a 1 for 6 weeks) *Alternaria* depot extract. After a baseline run-in season, symptom and medication scores reduced progressively during 3 years in favor of the active treatment group, accompanied by improved quality of life ($P < .05$).

A third study (G1, J1) of *Alternaria* immunotherapy was an open, observational trial of 99 patients who received a depot preparation of 0.2 µg of Alt a 1 every 4 to 6 weeks at maintenance. Asthma, rhinitis, and conjunctivitis scores were greatly improved from baseline, as well as the use of asthma medication,³² whereas the open design and low dose of allergen used question the reliability of this result.

Symptom and Medication Scores: Perennial Allergens and HDM

Only 1 selected trial reported on HDM SCIT in children with rhinitis. Wang et al³³ demonstrated a reduction in symptom and medication scores in favor of the active group (both $P < .01$) in a 1-year RCT. However, the analysis of the data is incomplete because the article is in Chinese.

All other selected HDM SCIT trials were in asthmatic children. In a large DBPC study in Chinese asthmatic children (G4, J4),¹⁸ the inhaled corticosteroid (ICS) dose was kept stable during the 12-month trial in all participants, with observed improved pulmonary function tests (unchallenged and challenged) in both the active and placebo groups. How-

Table 2. Evidence Table for Grass and/or Birch, *Alternaria*, and HDM

Statistically significant difference for active-placebo/control groups	No effect for active-placebo/control groups	Evidence ^a
AR symptoms Keskin et al, 2006 (G1) Jacobsen et al, 2007 (G2–3): long-term: +2 years, +7 years ^b Eng et al, 2006 (G2): long term: +6 years, +12 years	No studies without effect	Yes ^c : ●○○○ 7 years after ●●○○ 12 years after ●●○○
Medication Eng et al, 2006 (G2): long term: +6 years, +12 years	Inhaled corticosteroids: Roberts et al, 2006 (G4)	Yes: 12 years after ●●○○ No ^c : ●●●●
Symptoms and medication Roberts et al, 2006 (G4) Keskin et al, 2006 (G1): RC symptoms Eng 2006 (G2): long term: +6 years, +12 years	No studies without effect	Yes: ●●●● 12 years after ●●○○
Nasal provocation Pre-post: Keskin et al, 2006 (G1)	No studies without effect	Yes: ●○○○
Conjunctival provocation Roberts et al, 2006 (G4) Jacobsen et al, 2007 (G4): long term +2 years, +7 years ^b	No studies without effect	Yes: ●●●● 7 years after ●●●●
Prevention asthma Jacobsen et al, 2007 (G3–4): long term +2 years, +7 years ^b	No studies without effect	Yes: 7 years after ●●●○
Asthma symptoms Keskin et al, 2006 (G1) Eng et al, 2006 (G0): long term: +6 years, +12 years ($P = .08$)	No studies without effect	Yes: ●○○○ 12 years after ○○○○
Metacholine/specific bronchial provocation Roberts et al, 2006 (G4): specific	Keskin et al, 2006 (G1): methacholine Jacobsen et al, 2007 (G3–4): meta-choline, long term +7 years ^a	Yes, specific: ●●●● No, methacholine: ●○○○ No, methacholine 7 years after: ●●●○
SPT reactivity Roberts et al, 2006 (G4) Eng et al, 2006 (G2): long term: +6 years (only intragroup pre-post difference: Keskin et al, 2006 [G1])	Eng et al, 2006 (G2): long term: +12 years	Yes: ●●●● 6 years after: ●●○○ No: 12 years after ●●○○
New sensitizations Eng et al, 2006 (G2): long term: +6 years, +12 years	No studies without effect	Yes: 12 years after ●●○○
Improvement AR symptoms Improved active and placebo: Tabar et al, 2008 (G2) Active pre-post: Zapatero et al, 2011 (G1)	No studies without effect	Yes ^c : ●●○○
Improvement medication score Kuna et al, 2011 (G4)	Placebo more improved: Tabar et al, 2008 (G2)	Yes: ●●●●
Symptoms and medication First, second, and third year: Kuna et al, 2011 (G4) After up-dosing phase: Tabar et al, 2008 (G2)	After 12 months: placebo more improved: Tabar et al, 2008 (G2)	Yes: ●●●●
Nasal provocation Kuna et al, 2011 (G4)	No studies without effect	Yes: ●●●●
Conjunctival provocation Not studied	Not studied	No evidence
Prevention asthma Not studied	Not studied	No evidence
Asthma symptoms Tabar et al, 2008 (G2) PEF: active pre-post: Tabar et al, 2008 (G2) Active pre-post: Zapatero et al, 2011 (G1)	No studies without effect	Yes: ●●○○
Asthma medication Active pre-post: Zapatero et al, 2011 (G1)	No studies without effect	Yes: ●○○○ (only intragroup)

Table 2. Continued

Statistically significant difference for active-placebo/control groups	No effect for active-placebo/control groups	Evidence ^a
Methacholine/specific Not studied	Not studied	No evidence
SPT reactivity Not studied	Not studied	No evidence
Quality of life Kuna et al, 2011 (G4) Active pre-post: Zapatero et al, 2011 (G1)	No studies without effect	Yes: ●●●●
New sensitizations Not studied	Not studied	No evidence
HDM		
AR symptoms Wang et al, 2011 (RCT, G?)	No studies without effect	Yes ^c : ●●○○(?)
Medication Wang et al, 2011 (RCT, G?)	No studies without effect	Yes: ●●○○(?)
Symptoms and medication Not studied	Not studied	No evidence
Nasal provocation Not studied	Not studied	No evidence
Conjunctival provocation Not studied	Not studied	No evidence
Prevention asthma Inal et al, 2007 (G0)	No studies without effect	No evidence
Asthma symptoms Wang et al, 2006 (G4) Tsai et al, 2010 (G4) Cevit et al, 2007 (G0) Zang et al, 2010 (retrospective, G?) Rosewich et al, 2010 (G0) Ibero et al, 2006 (G3): improved pre-post only in active Kim et al, 2009 (G0): improved pre-post only in active Adjuk et al, 2008 (G1): improved pre-post in active Majak et al, 2010 (G3): improved pre-post in both active and placebo as all on allergen specific IT]	Ibero et al, 2006 (G3): improved symptoms, but NS active-control Reha and Ebru, 2007 (G0): 5 years after specific IT both groups improved	Yes: ●●●●
Asthma medication Wang et al, 2006 (G4) Tsai et al, 2010 (G4) Zielen et al, 2010 (G4) Zang et al, 2010 (retrospective, G?) Rosewich et al, 2010 (G0) Majak et al, 2009 (G4): improved pre-post in both active and placebo as all on allergen specific IT] Majak et al, 2010 (G3): improved pre-post in both active and placebo as all on allergen specific IT]	Cevit et al, 2007 (G0): NS active-control Ibero et al, 2006 (G3): much improved medication, but NS active-control	Yes: ●●●●
Reduction frequency of emergency department visits Tsai et al, 2010 (G4) Chen et al, 2009 (G1)	No studies without effect	Yes: ●●●●
Pulmonary function tests Zielen et al, 2010 (G4): PEF Chen et al, 2009 (1): FEV ₁ , PEF Reha and Ebru, 2007 (G0): 5 years after specific IT: FVC, FEV ₁ , FEF _{25%-72%} Zang et al, 2010 (retrospective, G?): PEF pre-post Adjuk et al, 2008 (G1): improved pre-post in active: FEV ₁ , PEF	Chen et al, 2009 (G1): FVC Wang et al, 2006 (G4): PEF: improved pre-post in both active and placebo as all taking stable-dose ICS Majak et al, 2010 (G3): VEF1: improved pre-post in both active and placebo, but specific IT dose reduction ICS	Yes: when specific IT and control on ICS: for PEF ●●●○ for VEF1 ●○○○ After 5 years FEV ₁ : ○○○○ No improvement FVC: ●○○○

Table 2. Continued

Statistically significant difference for active-placebo/control groups	No effect for active-placebo/control groups	Evidence ^a
Metacholine/specific bronchial challenge Ibero et al, 2006 (G4): specific	Zielen et al, 2010 (G4): methacholine improved in both groups, but active more ICS reduction. Wang et al, 2006 (G4): as all taking stable-dose ICS Cevit et al, 2007 (G0): specific, active and controls improve	Yes: Specific ●●●● No, ^b when both on ICS specific/methacholine: ●●●●
SPT reactivity Wang et al, 2006 (G4) Ibero et al, 2006 (G3) Reha and Ebru, 2007 (G0): 5 years after specific IT Kim et al, 2009 (G0): improved pre-post only in active	Cevit et al, 2007 (G0): improved pre-post in specific IT, but specific IT control (NS)	Yes: ●●●●
New sensitizations Inal et al, 2007 (G0) Harmanci et al, 2010 (G1) Reha and Ebru, 2007 (G0): 5 years after specific IT	Gulen et al, 2007 (G0)	Yes: ●○○

Abbreviations: AR, allergic rhinitis; FEF_{25%–72%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HDM, house dust mite; ICS, inhaled corticosteroid; IT, immunotherapy; NS, nonsignificant; PEF, peak expiratory flow; RC, rhinoconjunctivitis; RCT, randomized controlled trial; SPT, skin prick test; VEF1, vascular endothelial factor 1.

^a ●●●● indicates high; ●●●○, moderate; ●●○○, low; ●○○○, very low; ○○○○, absent.

^b Years after termination of specific IT.

^c Yes/no: evidence supports the improvement (yes) or no improvement (no) of the item stated in the left column of each line.

ever, the investigators found an enhanced reduction in rescue medication use ($P < .016$) and symptoms in the active group.

Majak et al reported 2 high-quality studies with a comparable design in Polish children with moderate persistent asthma. Participants continued to need 400 to 800 μ g of budesonide daily to control their asthma at the end of a 6-month run-in phase in which a stepwise reduction of ICS dose was implemented.³⁴ After the up-dosing phase of SCIT again a further stepwise reduction of ICS dose was attempted. In the first study (G4, J5), the investigators analyzed the influence of oral prednisone and vitamin D₃ on the clinical and immunologic changes brought about by SCIT (Phostal; Stallergènes). Placebo, prednisone (steroid group), or prednisone and vitamin D₃ (steroid–vitamin D group) were added during a 3-month build-up phase of SCIT. Single doses of these agents were added only on the actual days of SCIT administration. The primary efficacy variable was the median daily ICS dose, which was reduced by 50% in the SCIT and the SCIT and steroid–vitamin D groups, but only by 25% in the SCIT and steroid group ($P = .027$) after 12 months of treatment. Asthma symptoms were reduced in all 3 groups ($P < .001$ vs baseline in intragroup comparisons; no intergroup differences). These results might suggest an inhibition of the effect of SCIT by prednisone.

The second trial (G3, J5) analyzed the effect of montelukast on clinical and immunologic changes after allergen specific immunotherapy. Forced expiratory volume in 1 second (FEV₁) increased and symptoms reduced similarly with no significant difference-between groups. There was a 17% greater reduction

in ICS dose in favor of the SIT only group in comparison with the SIT and montelukast group, suggesting that also montelukast reduces SCIT efficacy. Immunologic results of both studies are discussed under “immunologic findings.”³⁵

In an RCT (G4, J3) of Chinese asthmatic children, the maximum tolerated dose of an aqueous HDM extract (Allermed) was added to usual antiasthma pharmacotherapy. The addition of SCIT resulted in a reduction in symptom and medication scores ($P < .01$ for both), as well as a trend toward reduction in emergency department visits when compared with pharmacotherapy alone.²²

In a multicenter, multinational RCT (G4, J3) of SCIT with an allergoid depot HDM, active treatment resulted in a 54% reduction in the use of ICS after 2 years compared with a 29% reduction in the control group ($P < .05$). During the trial asthma control was maintained concomitantly, whereas nonspecific bronchial hyperreactivity (BHR) even improved slightly.²⁶

In a 4-month RCT (G3 [symptoms] to G4 [BHR], J2) of a modified HDM extract, there was a trend toward a reduction in symptom and medication scores that was not statistically significant, possibly because of the low numbers studied. In this study the provocation concentration that caused a decrease in FEV₁ of 20% showed a 12.8-fold increase in the mean quantity of allergen, with no improvement in the controls ($P = .002$).³⁶

In a 1-year open trial of a depot HDM extract (G0, J1), there was a reduction in symptoms, medication use, and pulmonary function, including specific BHR in both the SCIT-treated and medication-only groups,³⁷ whereas only the

reduction in symptoms reached statistical significance in favor of the active group ($P = .039$). In an OCT with a depot HDM extract that involved a rush build-up phase, there was a reduction in symptoms within 8 weeks ($P < .05$) that was maintained for 12 months, whereas no intergroup differences in medication scores were observed (G0, J0).³⁸ In a 1-year OCT (G1, J0) in Chinese asthmatic children, HDM SCIT resulted in a reduction in emergency department visits in the active group ($P < .05$), as well as an increase in FEV₁ and peak expiratory flow (PEF) in favor of the immunotherapy group ($P < .05$).³⁹ A subsequent article on the same study also showed an increase in lung function (forced vital capacity, pre-FEV₁, and pre-PEF) in the active group ($P < 0.05$) vs placebo.⁴⁰ An immunologic study performed by Ajduk et al (G1, J0) also included clinical evaluations before and after 1 year of SCIT with a locally produced standardized Der p extract.⁴¹ The total symptom score ($P = 0.005$), FEV₁, and PEF ($P < .05$) increased in comparison to pretreatment values. An OCT 5 years after discontinuation of a 4-year treatment with a calcium-phosphate extract of HDM or grass demonstrated a maintained improvement in the spirometric values in favor of the active group ($P < .05$) (G0, J0).⁴² A postmarketing study of 422 children and adolescents receiving preseasonal SCIT of 4 injections with a allergoid-depot extract enhanced by monophosphoryl lipid A showed a marked reduction in medication and symptom scores, as evaluated by the prescribing physician and by the patients (G0, J0).²⁸ However, these last studies with very low GRADE and Jadad scores are virtually uninterpretable in view of the absence of masking and/or a control group for comparison, particularly in view of the known large placebo effects that are observed in clinical trials of immunotherapy.

Provocation Testing

In an RCT of SCIT with a depigmented depot *Dermatophagoides pteronyssinus* extract (G4, J3), 4-month treatment was accompanied by a 12-fold reduction in specific BHR in the active group compared with no change in the control group ($P = .002$).³⁶

Skin Prick Testing

In an RCT (G4, J4) of a subcutaneous high-dose depot HDM extract during 18 months, there was a reduction in skin allergen sensitivity ($P < .004$).¹⁸ In another RCT (G4, J2) with a depigmented *D pteronyssinus* depot extract, the same effect was already seen within 4 months of starting immunotherapy.³⁶ In 1 of 2 OCTs (G1, J0) skin sensitivity was already reduced at 8 weeks of a rush build-up schedule ($P < .05$ compared with baseline) and remained low for 12 months. Another OCT (G0, J0) investigated skin prick testing 5 years after discontinuation of SCIT ($P < .005$).^{38,42} One OCT found no statistical difference in skin reactivity between groups.³⁷ Thus, despite the variable quality of these studies, a reduction in immediate cutaneous allergen sensitivity after SCIT has been a consistent finding.

Two RCTs reported that 4 to 5 years of SCIT significantly reduced the onset of new allergic sensitizations on skin testing,^{23,42} whereas 2 found no difference⁴³ or even a difference in favor of nontreated control children.⁴⁴ Whereas the evidence in favor of suppression of immediate sensitivity to the relevant allergen used for treatment is convincing, current evidence of whether new sensitizations are prevented is inconclusive and further studies are needed.

Prevention of Asthma

An RCT (G3.5, J3)²⁹ with grass and/or birch pollen SCIT for 3 years demonstrated a reduced development of clearly defined asthma symptoms in children with rhinitis only at study start. The number of patients who developed asthma 7 years after immunotherapy among controls was 24 of 53 and 16 of 64 in the actively treated group. The final statistical model that included treatment, baseline bronchial hyperresponsiveness, and asthma status showed an odds ratio for no asthma of 4.6 (95% confidence interval, 1.5–13.7). The results of an OCT of 5 years SCIT with a HDM extract seemed promising, but no clear asthma definition was given and only medication use was reported (G0, J0).²³

Cost-effectiveness

These studies are complex to perform but of high priority. One study used a retrospective matched cohort design to demonstrate that SCIT reduces health care utilization and costs among all children enrolled in Florida Medicaid between 1997 and 2007. The total health care cost included total inpatient stays, outpatient visits (inclusive and exclusive of immunotherapy-related care), total pharmacy fills, and total health care use. A statistically significant cost reduction was reported within 18 months of SCIT treatment in 2771 children newly diagnosed as having AR, compared with symptomatic drug treatment alone.²¹

Clinical Efficacy

eTable 2 summarizes the evidence concerning clinical efficacy of immunotherapy with grass, *Alternaria*, and HDM.

SCIT: Safety Issues

eTable 3 summarizes data for adverse reactions reported in the DBPC trials and in all trials together. There was great variety in the methods and the extent to which adverse reactions were reported. Inevitably, because many variables were not universally included, there is considerable variation in the n values of the data in the table. There were 4 DBPC trials in which specific immunotherapy was only given to the active group.^{18,30,31,45} Two involved *Alternaria* extracts, one of high (8 µg of Alt a 1)³¹ and one of low allergen content (0.1 µg of Alt a 1),³⁰ although no difference in the number of systemic reactions was observed; no conclusions can be drawn in view of the low numbers. The other 2 DBPC trials reported a higher rate of adverse events. Both of them involved high-dose depot preparations. In a study of an alum-based grass pollen extract containing 20 µg of Ph p 5 (Roberts et al), there were 18 patients in the active and 17

patients in the placebo group. After 18 months of treatment, a total of 21 systemic reactions were reported in 13 patients (72% of patients), 4 of which were asthma exacerbations vs 9 (3 asthma) in 7 patients (41%) in the placebo group. Similar numbers were published for an adult study with this product.⁴⁶

In the 12-month DBPC trial of Wang et al (eTable 1) with a HDM extract containing 9.8 μg of Der p 1, there were 7 grade 1 (0.4% of all injections), 71 grade 2 (4.8% of injections), and 7 grade 3 reactions (0.5% of injections) in the SCIT group and 2 grade 1 (0.1%) and 25 grade 2 reactions (1.7%) in the placebo group ($P < .001$) (reactions were graded according to European Academy of Allergology and Clinical Immunology 1993 classification⁴⁷). None of the reactions resulted in hospitalization. Five (all <12 years old) of a total of 64 patients failed to reach maintenance dose on account of systemic adverse effects.¹⁸

In a RCT that used an HDM depot extract in a cluster (20 children) and a conventional (10 children) up-dosing schedule, there was a lower rate of systemic adverse effects in the cluster up-dosing group (nonsignificant) Schubert et al concluded that cluster SCIT is safe in children.⁴⁸

SCIT: Immunologic Findings

Seventeen studies evaluated immunologic outcome measures. Only statistically significant differences between active and placebo or control groups are mentioned in eTable 3. Investigators of most pediatric SCIT trials within the scope of this analysis found no change in total or serum specific IgE after 3 to 18 months of treatment. In 1 study the seasonal increase in specific IgE was blunted already after 7 weeks of build-up²⁵; however, after cluster SCIT specific IgE was augmented.⁴⁸ Serum specific IgG and IgG4 levels increased after 8 weeks of a cluster up-dosing schedule, 16 weeks of a conventional up-dosing,⁴⁸ and a second cycle of preseasonal pollen allergoid SCIT.²⁸ The IgG changes went hand-in-hand with an increase in the inhibitory activity of patients' serum measured by the cellular antigen stimulation test.

Various investigators reported an increase in peripheral T-regulatory (Treg) cell or peripheral blood mononuclear cell production of interleukin 10 (IL-10), interferon γ (IFN- γ) and the IFN- γ :IL-4 or IFN- γ :IL-5 ratio^{19,39}; others found reductions in IL-13 and IL-4 produced by Tregs or in serum, serum nitric oxide, serum and nasal eosinophil cationic protein, and monocyte chemotactic protein 1,^{18,20,25,37,39} together with a reduction in the cellular proliferation index, already from 8 weeks on.³⁸

Several investigators studied peripheral T-cell responses, including Tregs. In comparison to nontreated asthmatic patients, after SCIT both adaptive and inducible Tregs increased in the circulation in number and activity²⁰; Tregs secrete and induce secretion of transforming growth factor β (TGF- β) and IL-10. Also, in one study cytotoxic T-lymphocyte-associated protein 4-mediated signals were necessary for inhibitory activity. Compared with baseline values, the percentage of cytotoxic T-lymphocyte-associated protein 4-positive

cells expressing CD4⁺CD25⁺ increased significantly at 3 months after SCIT but decreased significantly at 12 months. At that point there was a significant increase in TGF- β ₁.⁴¹ In one well-conducted assay that isolated highly purified T cells, no difference was reported in the expression of Foxp3, GATA-3, or t-bet.⁴⁸

In the studies by Majak et al, which were described earlier, the following immunologic data were reported. In the first study prednisone reduced the clinical benefit of SCIT while decreasing the induction of CD4⁺CD25⁺Foxp3⁺ cells at 3 and 12 months; moreover, TGF- β , IL-10, and IL-13 were less reduced after 12 months. Adding vitamin D annulled this negative effect. Also, some immunologic differences were found between specific immunotherapy responders and nonresponders, the former having higher levels of IL-10, IL-5, and IL-13 in the supernatant ($P = .048$ to $P = .001$).³⁴ In the second study montelukast decreased the induction of regulatory activity by suppressing the increase in Foxp3 and TGF- β .³⁵

DISCUSSION

Generally, only RCTs are included in reviews on immunotherapy. However, critical analysis of publications of clinical trials has shown that the quality of the trials depends not only on their design but also on other factors.^{49–51} The GRADE system was introduced to evaluate the scientific quality of trials and their strength in supporting recommendations on a regulatory level.^{15,52} We decided to include all trials reported since January 2006, irrespective of their design, and to use the GRADE and Jadad system to evaluate their quality. It has become clear that the trials on allergen immunotherapy have certain characteristics that make them different from trials of conventional medication.⁵⁰ That is why we accepted an outcome analysis close to, but not strictly following, the intent-to-treat principle, without resting quality points. From January 2006 to April 2011 we detected only 4 clinical trials on grass SCIT in children. Even so, there is high-quality evidence that grass pollen SCIT causes a reduction in the combined symptom-medication score and raises the threshold of specific provocation tests and skin prick test reactivity, for some parameters even 7 years after immunotherapy. There is moderate evidence that pollen specific immunotherapy may reduce the onset of asthma. Also for SCIT with another seasonal allergen, *Alternaria*, the high quality of the 3 selected trials resulted in evidence in favor of efficacy, which contrasts to the low evidence of efficacy for mold extracts that has traditionally existed. The only perennial allergen studied in pediatric clinical trials during the last 5 years is HDM. All but 1 trial were in asthmatic children. High-quality evidence shows asthma symptom and medication-scores improve and emergency department visits and skin reactivity are reduced. There is moderate evidence for an improvement in pulmonary function tests. Improvement in BHR varies and depends on the study designs. In the earlier studies^{18,36,37} free use of medication was allowed, resulting generally in a reduction in medica-

tion use in the active group,^{18,36,37} sometimes accompanied by an increase in medication use in the control group.³⁶ As a consequence in almost all selected trials bronchial hyperreactivity improved in both groups.³⁶ A study design that enhanced the demonstration of clinical efficacy of SCIT was applied in a recent high-quality study: the dose of ICS was kept well under control and gradually reduced in both groups, reaching a significantly greater reduction in the active group, without deterioration in BHR.²⁶

The reporting of the safety data of a trial varies. Some investigators provide information on adverse events per patient, others per injection. Some report local reactions, whereas others just report systemic reactions probably related to the treatment. A more uniform method of reporting safety data of immunotherapy trials should be followed in the future to facilitate the analysis of data grouped together of several trials. The publication of the World Allergy Organization grading systems is a step in the right direction.⁵³

The immunologic basis of SCIT has been broadened with publications throughout the last years. The assays in allergic children presented have shown humoral and cellular immunologic responses evolving over time according to the progression of SCIT, similar to what has been seen in adult studies. Good-quality clinical and immunologic data on SCIT have been produced by new investigators from countries in different parts of the world. It is of interest to also analyze reports from these regions.⁵⁴

Currently, there is acceptable scientific evidence for the beneficial effect of specific allergen SCIT for grass pollen, *Alternaria*, and HDM in children. Immune mechanisms are better understood. Evidence for long-term (sustained) benefit of SCIT (7–12 years after termination) is still low to moderate, and evidence for the preventive effect is already of moderate scientific quality for pollen SCIT. Evidence for the reduction of new sensitizations in the articles of clinical trials published between January 2006 and April 2011 is inconclusive.

To enhance the demonstration of treatment effect for clinical trials of immunotherapy in asthma, rather than use symptom reduction as the primary end point, a reduction in medication, while symptoms do not exacerbate and lung function is maintained, may be a more realistic variable to study.

Lately the evidence for the efficacy of SCIT in asthma has increased, reinforced by positive conclusions from the Cochrane meta-analyses.^{12,55} During the last decades the benefit of SCIT in asthmatic children has been questioned, especially based on a negative result from a large randomized DBPC trial of a multiple allergen extract in children with perennial asthma (Adkinson et al).⁵⁶ Our review presents recent data that provide clear evidence in support of the use of SCIT in children with bronchial asthma.

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eTable 1. Adverse Reactions in Clinical Trials With Subcutaneous Immunotherapy in Children, 2006–2011^a

	Systemic reaction per patient-year	Systemic reaction in group 1 per patient-year	Systemic reaction in group 2 per patient-year	Systemic reaction in group 3 per patient-year	Systemic reaction per injection	Local reaction per injection
Double-Blind, Placebo-Controlled Trials (Kuna et al, Tabar et al, Roberts et al, and Wang et al)						
Active, No. (%)	16 (12.2)	12 (9.1)	4 (3.1)	7 (3.6)	109 (3.3)	24 (1.3)
Active, No. ^b	131	131	131	195	3293	1793 injections
Placebo, %	9.0	6.0	3.0	0	1.3	
Placebo, No.	99.5	99.5	99.5	164.5	2983	
All Trials^c						
Active, No. (%)	63 (6.0)	47 (4.4)	14 (1.3)	9 (0.65) ^d	159 (1.3)	438 (6.4)
Active No.	1,057	1,057	1,076	1,388	12,522	6,870

^a Local reactions per patient-year, 111/607 = 18.3%.

^b Number is different in each calculation because in many trials not all detailed data were given. In the calculation of each variable, only those trials reporting the variable were taken into account.

^c Approximately 16,764 injections of active immunotherapy were given in total in all trials.

^d This was 9 of 1,000 patients (0.9% of all patients).

eTable 2. Quality of Evidence of Pediatric SCIT Studies Published in 2006–2011, According to the Grading of Recommendations Assessment, Development, and Evaluation Approach

Study	Design (starting score)	Large effect	Confound annulated ^a	Dose response gradient	Total
Seasonal Allergic Rhinitis and Asthma Studies					
Eng et al, 2006 (SAR [mild asthma], 12 SCIT, 10 control; 5–16 years old; allergoid-ALOH grass [and tree] preseason for 3 years, 12 years after IT)	OCT (2) AR symptoms + medication reduction	No	$P < .03$, even though groups are small	No	+1
	Seasonal asthma symptoms	No	No	No	0
	New sensitizations	No	$P < .05$, even though groups are small	No	+1
Keskin et al, 2006 (SAR [mild asthma]; 27 SCIT, 26 control; 6–18 years old; allergoid-ALOH grass, 20 μ g of Phl p 5 [eq] every 6 weeks; duration, 27 months)	OCT (2)	No	No	No	0
Jacobsen et al, 2007 (SAR [mild asthma]; 79 SCIT, 68 control; 6–14 years old; ALOH grass or birch SCIT, 20 μ g of Phl p 5 or 12 Bet v 1 [eq] every 6 weeks; duration, 3 years; 7 years after IT)	RCT (4) AR symptoms and medication	No	No	No	0
	New asthma	OR at 7 years after IT, 4.6 (95% CI, 1.5–13.7)	No	No	+1
Roberts et al, 2006 (asthma and AR; 18 SCIT, 17 placebo; 3–16 years old; ALOH grass SCIT, 20 μ g of Phl p 5 [eq] every 6 weeks; duration, 18 months)	DBPC (4)	No	No	No	0
Kuna et al, 2009 (AR/asthma mild-moderate persistent; 30 SCIT, 20 placebo; 5–18 years old; ALOH <i>Alternaria</i> , 8 μ g of Alt a 1 every 4–6 weeks for 36 months)	DBPC (4) rhinoconjunctivitis	No	No	Time per dose gradient first, second, and third year	+1
	Asthma	No	No		+1
Tabar et al, 2008 (asthma mild-moderate persistent AR; 14 SCIT, 14 placebo; mean age, 12 years; <i>Alternaria</i> , 0.1 μ g of Alt a 1 every 4 weeks for 12 months)	DBPC (4) rhinoconjunctivitis	No	No	No	0
	Asthma	No	No	No	0
Zapatero et al, 2011 (asthma mild-moderate persistent AR; 99 SCIT, 4–16 years old; ALOH <i>Alternaria</i> , 0.2 μ g of Alt a 1 every 4 weeks for 12 months)	Open (2) rhinoconjunctivitis	No	No	No	0
	Asthma	ICS reduction $P < .001$, ACT $P < .001$	No	No	+1
Perennial Allergic Rhinitis and Asthma Studies					
Wang et al, 2011 (allergic rhinitis; 32 SCIT, 32 controls; children; <i>Dermatophagoides pteronyssinus</i> SCIT for 12 months)	RCT (4)	No	No	No	0
Wang et al, 2006 (asthma; 64 SCIT, 65 placebo, 6–45 ^a years old; ALOH <i>Dermatophagoides</i> SCIT; 9.8 μ g of Der p 1 every 6 weeks for 12 months)	DBPC (4)	No	No	No	0

eTable 2. Continued

Limitations in design and execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publication bias	Total	Quality of evidence
No sample size calculations	No	No	No	No	−1	2, low
	No	Asthma only measured by subjective symptoms	No	No	−2	0, very low
	No	No	No	No	−1	2, low
Second season 18 extra controls added, no calculation sample size	No	No	No	No	−1	1, very low
Dropout in controls 33% (at 7 years after IT: deduction 0.5)	No	RC symptoms only evaluated with VAS	No	No	−1.5	2–3, moderate
	No difference Bronchial provocation test	No	No	No	−1.5	3–4, moderate-high
No	No	No	No	No	0	High
No	No	No	No	No	0	High
No	No	No	No	No	0	High
Sample size not reached.	Medication score improved in placebo	No	No	No	−2	Low
		No	No	No	−2	Low
No	No	No	No	No	0	Low
No objective measures of asthma control	No	No	No	No	−1	Low
Only abstract available in English					?	
No	No	No	No	No	0	High

eTable 2. Continued

Study	Design (starting score)	Large effect	Confound annulated ^a	Dose response gradient	Total
Majak et al, 2009 (asthma; all SCIT: 18 + prednisone and Vit D, 18 + prednisone, 18+ placebo; 6–12 years olds; CaPOH <i>Dermatophagoides</i> SCIT; 59 µg of major allergens every 4 weeks for 12 months + prednisone [and VitD] on build-up injection days)	DBPC (4) (all receiving SCIT)	No	No	No	0
Majak et al, 2010 (asthma; 6–12 years old; all SCIT: 18 + montelukast, 18 + placebo; CaPOH <i>Dermatophagoides</i> SCIT; 59 µg of major allergens every 4 weeks for 12 months [and montelukast daily during build-up])	DBPC (4) (all receiving SCIT)	No	No	No	0
Tsai et al, 2010 (asthma; 20 SCIT, 20 controls; 5–14 years old; HDM aqueous extract; highest tolerated dose, 15 days for 6 months)	RCT (4)	No	$P < .01$ for medication and symptoms, even though groups are small	No	+1
Zielen et al, 2010 (asthma; 33 SCIT + fluticasone, 32 fluticasone; 6–17 years old; ALOH <i>D pteronyssinus</i> allergoid; 7 µg of Der p 1 and 6 µg of Der p 2 every 6 weeks for 24 months)	RCT (4) reduction of ICS use	No	$P < .05$, even though underpowered	No	+1
Ibero et al, 2006 (asthma; 15 SCIT, 15 controls; 8–16 years; <i>Dermatophagoides</i> patients SCIT depigmented-glutaldehyde depot 0.8 + 0.5 µg of Der p 1 + 2 eq/ mo for 4 months)	RCT (4) asthma symptoms + medication Specific bronchial sensitivity	No Active resists 12 times more <i>D pteronyssinus</i> in bronchial challenge after treatment	No $P = .002$, even though groups are small; dropout in control because of poor asthma control	No No	0 +2
Inal et al, 2007 (AR and/or asthma; 6–16 years old; 45 depot, 40 aqueous, 62 control; ALOH or CaPOH every 4 weeks or aqueous every week HDM SCIT for 5 years)	OCT (2) new sensitizations. asthma prevention	No	No	No	0
Cevit et al, 2007 (asthma; 19 SCIT, 12 controls; mean age, 6–16 years; ALOH SCIT HDM; 4000 TU every 4 weeks for 12 months)	OCT (2)	No	No	No	0
Chen et al, 2009 (asthma; 35 SCIT, 23 controls; 5–14 years old; ALOH HDM SCIT; 100,000 U every week for 12 months)	OCT (2)	No	No	No	0
Chen et al, 2009 (asthma; 42 SCIT, 23 controls; children; HDM SCIT for 1 year)	OCT (2)	No	No	No	0
Kim et al, 2009 (asthma; 15 SCIT, 10 controls; 7–13 years old; ALOH HDM SCIT, rush build-up; 5000 TU every 4 weeks for 12 months)	OCT (2) symptoms	No	No	No	0

eTable 2. Continued

Limitations in design and execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publication bias	Total	Quality of evidence
No	No	No	No	No	0	High
5 Dropouts in placebo group during build-up phase because they did not reach maintenance	No	No	No	No	−1	Moderate
No sample size calculation.	No	No	No	No	−1	4, high
No. according to power calculation not met. (ITT analysis for second year using 3 patients last-observation-carried forward)	No	No	No	No	−1	4, high
Randomization method not specified; no environmental control.	No	No	No	No	−1	3, moderate
Underpowered	No	Specific bronchial challenge test	No	No	−2	4, high
Atopy score used not validated; no investigator masking mentioned	No	Asthma indicates use of inhaled β -agonists	No symptom scores measured	No dropouts described	−4	0, very low
No sample calculation (ITT); no masking of investigators mentioned	Lung function (NS) more improved in controls	No	No	No	−2	0, very low
No investigator masking stated; no medication scores	No	No	No	No	−1	1, very low

eTable 2. Continued

Study	Design (starting score)	Large effect	Confound annulated ^a	Dose response gradient	Total
	Immunology	No	Immunology: statistically significant difference though small groups	No	+1
Gulen et al, 2007 (asthma; 70 SCIT, 59 controls; 6–10 years old; CaPOH HDM SCIT; 5000 TU every 4 weeks for 48 months; Analysis 24 months after SCIT)	OCT (2) new sensitizations	45% vs 18% in active vs controls	No	No	+1
Harmanci et al, 2010 (AR and/or asthma; 62 SCIT, 60 controls; 8–18 years old; CaPOH HDM SCIT; 8 IR every 4 weeks for 48 months)	OCT (2) new sensitizations	No	No	No	0
Adjuk et al, 2008 (asthma; 16 SCIT, 10 healthy controls; 5–12 years old; SCIT standardized HDM extract every 4 weeks for 12 months)	OCT (2) (immunologic study) quality of clinical evaluation	No	No	No	0
Reha and Ebru, 2007 (asthma; 56 SCIT, 51 fluticasone, 400 µg/d; 4–15 years old; CaPOH SCIT with HDM or grass; 800 U (8 IR) every 4–6 weeks for 48 months; analysis 5 years after SCIT)	OCT (2)	No	No	No	0
Rosewich et al, 2010 (AR and/or asthma; 422 SCIT, 6–18 years old; allergoid + monophosphoryl lipid A depot preparation of 1 to 3 allergens; 4 preseasonal injections for 1–3 years)	Postmark (2)	No	No	No	0
Safety^b					
Hernández et al, 2010 (asthma [5% allergic rhinitis]; 77 cluster SCIT; 2–5 years old; depigmented, depot HDM; 0.86–0.5 µg of Der p 1–2 every 4 weeks for 18 months)	Obser-vational (2) safety	No	No	No	0
Schubert et al, 2009 (22 cluster, 12 conventional SCIT; 6–18 years old; ALOH depot HDM in cluster or conventional build-up for 4 months)	RCT (4)	No	No	Time gradient: cluster changes at 8 weeks, conventional at 16 weeks	+1
Rosewich et al, 2010 (AR and/or asthma; 6–17 years old; 34 SCIT: 10 one cycle, 24 two cycles; analysis on 20 first and 24 second cycles; allergoid + monophosphoryl lipid A depot grass preparation; 4 preseasonal for 1–2 cycles)	Open (2) immunology	No	No	Time- and cycle-related dose response	+1

Abbreviations: ACT, ; ALOH, aluminum hydroxide; AR, allergic rhinitis; CaPOH, calcium phosphate; CI, confidence interval; DBPC, double-blind placebo-controlled; eq, equivalent; HDM, house dust mite; ICS, inhaled corticosteroid; IT, immunotherapy; ITT, intent to treat; IR, index of reactivity; OCT, open controlled trial; OR, odds ratio; PFT, pulmonary function test; RC, rhinoconjunctivitis; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis; SCIT, subcutaneous immunotherapy; spBPT, specific bronchial provocation test; TU, treatment units; VAS, visual analog scale; VitD, vitamin D.

^a All plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.

^b In many other studies safety was recorded as well.

eTable 2. Continued

Limitations in design and execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publication bias	Total	Quality of evidence
? (abstract only)	No	No symptom nor medication score, only PFT + immunology	No	No	−1	1, very low
No investigator masking mentioned, no sample size calculation	No	No medication score	No results reported of intergroup comparisons	No	−3	0, very low
	No	No		No	−2	1, very low
No investigator masking stated	Controls did much better	No	No	IgE studied but not reported	−3	0, very low
No investigator masking stated	No	No	No		1	1, very low
Investigator masking not stated; no comparisons between groups, only pre-post	No	No	No medication score, because very little medication was taken		−1	1, very low
Investigator masking not stated	No	No	Adverse events not stated	Reason for dropout no stated	−2	0, very low
2 of 3 outcome measures are unmasked evaluations of the prescribing physician	No	No medication scores, only percentage of patients using medication	No	No	−2	0, very low
Retrospective medical record review	No	No	No	No	0	1, very low
Investigator masking not mentioned (no calculation sample size, but differences did reach significance)	No	No	No	Neither PFT nor spBPT reported	−2	3, moderate
No controls.	No	No	No	No	−1	2, low

eTable 3. Immunologic Changes With SCIT in Children (Publications 2006–2011)

Study	Extract	Allergen	Design	AR/asthma	Dosing	Duration, mo	Active	Placebo/control	Immunologic data
Kuna et al, 2011	ALOH	<i>Alternaria</i>	DBPC	AR/asthma	High	36	30	20	Significant decrease in specific IgE after 3 years. IgG4 rise in active vs placebo 300 times ($P < .001$) at 3 years
Keskin et al, 2006	Allergoid-ALOH	Grass	OCT	AR (mild asthma)	High	27	27	26	Only in active: IL-4 reduction, reduced seasonal increase in ECP in nasal fluid and serum specific IgE ($P < .05$) already after build-up of 7 weeks. Increase in IgG, IgG1, and IgG4 ($P < .001$)
Rosewich et al, 2010	Allergoid and MPL	Grass	Open	AR/asthma	Pollinex	3 mo 1 or 2 preseason	34	0	Only after second year immunologic changes: specific IgG and IgG4 (24 times) increase ($P < .001$), Treg increase and leukotrienes in supernatant after basophil stimulation reduction ($P < .05$).
Wang et al, 2006	ALOH	HDM	DBPC	Asthma	High	12	64	65	Specific IgE without changes. Serum ECP reduced in both (both: $P < .001$)
Majak et al, 2009	Phostal	HDM	DBPC (all SCIT)	Asthma	Medium	12	18: IT and prednisone and VitD/ 18: IT NS prednisone	18 IT	Steroid group divided in SIT responders/non-according to accomplished ICS reduction: PBMCs from responders had higher levels of IL-10, IL-13, and IL-5 and higher percentage of Foxp3 cells at baseline. At 3 months: all groups showed increase in TGF- β and no change in Foxp3 cells. Steroid group less IL-5. At 12 months: specific IT and prednisone group less reduction in TGF- β and IL-10 and IL-13 and much less increase in Foxp3 than other 2 ($P = .006$).

eTable 3. Continued

Study	Extract	Allergen	Design	AR/asthma	Dosing	Duration, mo	Active	Placebo/control	Immunologic data
Majak et al, 2010	Phostal	HDM	DBPC (all SCIT)	Asthma	Medium	12	18: IT and montelukast	18: IT	PBMCs at 3 months: a rise in Foxp3 and TGF- β in IT, but not in IT-montelukast. Both groups rise in IL-10 and IL-13 production from PBMC. At 12 months: lower Foxp3 expression and percentage of Foxp3-positive cells in IT-montelukast vs IT. IL-10, IL-13, and TGF- β expression reduced in all but less so in IT-montelukast. Patients from the control group excluded from per protocol analysis because of uncontrolled asthma mostly showed Foxp3 and TGF- β levels below the lower 95% confidence interval at 3 and 12 months.
Wang et al, 2011 (abstract)		HDM	RCT	AR	?	12	32	32	IgE total and specific no changes. IgG4 increased significantly only in active.
Schubert et al, 2011	ALOH	HDM	RCT, 2 active groups	Asthma	Cluster/conventional	4	Cluster 22	Conventional 12	Immunology: more rapid tolerance induction with cluster: specific IgE rise since week 8 onward ($P < .05$), IgG (mite) ($P < .001$) and specific IgG4 ($P < .001$) increased already after 8 weeks. Classic specific IT: increase till 16 weeks. Same picture for blocking CD63 expression and release of cysteinyl leukotrienes after in vitro basophil stimulation.
Cevit et al, 2007	ALOH	HDM	OCT	Asthma	?	12	19	12	Compared with baseline after 12 months: serum MCP-1 reduced in both groups ($P = .009$ and $.04$). Reduction from baseline in serum ECP and Nitric oxide in specific IT group. Total and specific IgE unchanged in both groups.

eTable 3. Continued

Study	Extract	Allergen	Design	AR/asthma	Dosing	Duration, mo	Active	Placebo/control	Immunologic data
Chen et al, 2009	ALOH	HDM	OCT	Asthma	High	12	35 (IT and ICS)	23 (ICS)	Compared with baseline after 12 months: serum IL-13 and IL-4 reduced $P < .05$, IFN- γ and IFN- γ : IL-4 ratio augmented ($P < .05$ all)
Chen et al, 2009 (abstract)		HDM	OCT	Asthma	?	12	42	23	Compared with baseline after 12 months: serum IL-4 reduced only in active. In both IFN- γ and IFN- γ : IL4 incremented ($P < .05$).
Kim et al, 2009	Rush induction phase	HDM	OCT	Asthma	?	12	15	10	Cellular proliferative responses (stimulation index) reduced after 8 weeks and maintained reduce at 12 months ($P < .05$) only in specific IT group. IFN- γ : IL-5 index increased at 8 weeks and maintained elevated. CD4 ⁺ cells augmented at 8 weeks, but not after 12 months. No change in controls.
Ajduk et al, 2008		HDM	OCT	Asthma	Local product	12	16	10	% Tregs unchanged. T-cell TGF- β_1 production augments after specific IT in children without need for ICS compared with children who need ICSs for asthma exacerbation who show no increase ($P < .005$); Treg IL-10 production decreased after 3 months. No change in serum specific IgE at 3 + 12 months. Reduction eosinophils in active pre-post specific IT ($P < .05$).
Zhang et al, 2010		HDM	Retrospective	Asthma	Medium	10	35 (IT and ICS)	50 (ICS)	Total and specific IgE no change.

eTable 3. Continued

Study	Extract	Allergen	Design	AR/asthma	Dosing	Duration, mo	Active	Placebo/control	Immunologic data
Wang et al, 2010	ALOH	HDM	Not apply	Asthma	Not stated	18–24	27	27	PBMCs from asthma patients after 18–24 months SCIT and from asthmatic controls: Inducible (CD4 ⁺ CD25 ⁺ Foxp3 ⁺ IL-10 ⁺) and adapted (CD4 ⁺ CD25 ⁺ IL-10 ⁺ Foxp3 ^{+/−}) Tregs in PBMCs were elevated after SCIT, more so after stimulation with HDM. Adapted (CD4 ⁺ CD25 ⁺ IL-10 ⁺ Foxp3 ^{+/−}) Tregs augmented only after stimulation. nTreg cells no difference SCIT vs controls or after stimulation. Specific IgG4 30 times higher in SCIT. Specific IgE no difference.
Wei et al, 2010	ALOH	HDM	Not apply	Asthma	Not stated	18–24	27	27	Stimulation of Tregs from SCIT patients with HDM produced an increase in IL-10 and reduced proliferation, IL-4 and TGF- β were lower and IFN- γ higher than the asthmatic controls.
Zielen et al, 2010	Allergoid-ALOH	HDM (Dpt)	RCT	Asthma	High	24	33 (IT and fluticasone)	32 (fluticasone)	IgE decrease more in active at 12 months (NS) and 24 months ($P = .02$). IgG1 (2 times) and 4 (11 times) augmented ($P =$ and $<.0001$, respectively)

Abbreviations: ALOH, aluminum hydroxide; AR, allergic rhinitis; DBPC, double-blind, placebo-controlled; ECP, eosinophil cationic protein; Foxp-3, fork head box protein 3; HDM, house dust mite; ICS, inhaled corticosteroid; IL, interleukin; IFN- γ , interferon γ ; IT, immunotherapy; MCP-1, monocyte chemotactic protein 1; MPL, monophosphoryl lipid A; nTreg, naturally occurring regulatory T cells; NS, not significant; OCT, open controlled trial; PBMCs, peripheral blood mononuclear cells; PP, per protocol; P95, the lower 95 % confidence interval; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; TGF, transforming growth factor β ; Tregs, regulatory T cells; VitD, vitamin D.