Immunotherapy in the Pediatric Population

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Introduction

- Allergen immunotherapy is the only disease modifying treatment for allergic rhinitis, asthma, food allergy, and venom allergy
- Is immunotherapy truly efficacious and safe in children?
- Can immunotherapy in children stop the atopic march?

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

Désirée E. S. Larenas-Linnemann, MD**; Dino R. Pietropaolo-Cienfuegos, MD†; and Moisés A. Calderón, MD, PhD†‡

Ann Allergy Asthma Immunol. 2011;107:407–416.

Methods

- 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
- Clinical, safety, and immunologic data were gathered

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).

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
  - increases the threshold of the conjunctival provocation test, immediately and 7 years after termination of SCIT
  - Increases the threshold of the specific bronchial provocation test and the skin prick test reactivity

Results

- *Alternaria* SCIT
  - improves medication scores, combined symptom-medication scores, and quality of life
  - It augments the threshold in the nasal provocation test

Results

- High-quality evidence of house dust mite SCIT shows that
  - asthma symptom and medication scores improve
  - emergency department visits and skin reactivity are reduced
  - moderate evidence indicates improvement in pulmonary function tests

Results

- There is inconclusive evidence for SCIT reducing new sensitizations
- The bottom-line on SCIT in children: *There is acceptable evidence that shows that grass pollen, Alternaria, and house dust mite SCIT is beneficial in allergic children.*

Timothy Grass AIT

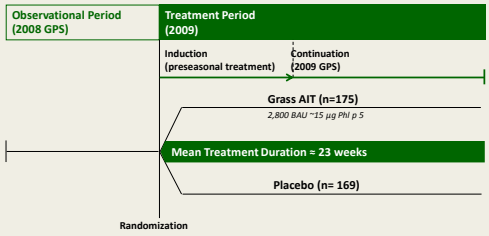
Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP.

Efficacy and Safety of Timothy Grass Allergy Immunotherapy Tablet Treatment in North American Children and Adolescents. JACI Jan 2011; 127(1):64-71

Study Objective

- To investigate the clinical efficacy and safety of Timothy grass AIT in North American children
- Timothy grass is cross-reactive
  - Rye
  - Meadow fescue
  - Bluegrass
  - Cocksfoot
  - Redtop
  - Sweet vernal
  - Partially reactive with Johnson grass

2-Year Double-Blinded Placebo-Controlled Randomized Multicenter Trial



CRITERIA FOR EVALUATION

- The primary efficacy endpoint is the *total combined score* of the daily symptom score (DSS) and daily medication score (DMS).
  - Subjects recorded symptoms and rescue medications daily in electronic diaries.
- DSS
- DMS
- Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).
- Specific immunoglobulin IgG_4
- Specific IgE-blocking factor
- Safety by adverse events (AEs)

Key Eligibility Criteria

- **Inclusion Criteria**
  - 5–17 years old
  - Clinical history of significant grass pollen-induced ARC, with or without asthma
  - Positive skin prick test against *Phleum pratense (*wheal diameter ≥5mm)
  - Positive specific IgE against *Phleum pratense* (≥ 0.7 kU/L)
  - FEV_1 ≥70% of predicted value at screening
- **Exclusion Criteria**
  - Symptomatic ARC requiring medication caused by ***overlapping*** allergens other than grass
  - Severe asthma
  - History of anaphylaxis
  - Immunosuppressive treatment
  - Receipt of immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years

Symptom and Medication Scoring

Daily Symptom Score (DSS; Maximum=18)

Individual Symptoms	Maximum Daily Score*
Runny nose	3
Blocked nose	3
Sneezing	3
Itchy nose	3
Red/itchy/gritty eyes	3
Watery eyes	3

*Symptoms: 0=none; 1=mild; 2=moderate; 3=severe

Daily Medication Score (DMS; Maximum=36)

Rescue Medication	Score/Dose Unit	Maximum Daily Score
Loratadine 10-mg tablet*	6 points/tablet	6
Olopatadine HCl 0.1% ophthalmic solution†	1.5 points/drop	6
Mometasone furoate nasal spray 50 µg‡	2 points/spray	8
Prednisone 5-mg tablet §	1.6 points/tablet	16

*One tablet per day ; †1 drop per affected eye twice daily; ‡2 sprays in each nostril once daily; § up to 10 tablets per day.

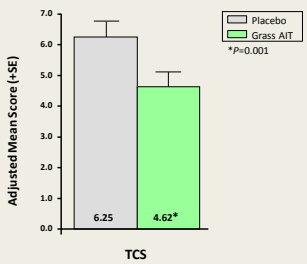
Overall Subject Characteristics

	Grass AIT* (n=175)	Placebo (n=169)
Sex (%)		
Male	67	62
Age, y		
Mean	12.1	12.6
Range	6–17	5–18
Race (%)		
White	87	88
Sensitive to non-grass allergens (%)	87	91
Positive asthma status (%)	26	26
Grass Sensitivity		
Mean Wheal	11 mm	11 mm
Specific IgE	32 kU/L	35 kU/L

*75,000 SQ-T/2,800 BAU *Phleum pratense*

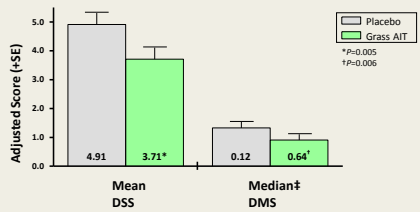
Total Combined Symptom and Medication Scores: All Sensitization Types Grouped

26% relative reduction in mean total combined score (TCS)



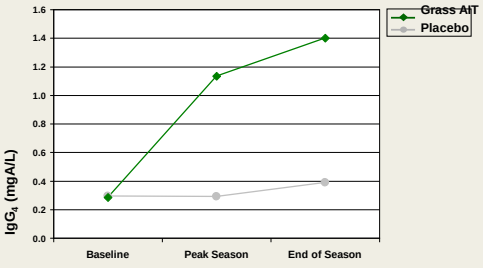
Daily Symptom and Medication Score Results: All Sensitization Types Grouped

25% relative reduction in mean daily symptom score (DSS)
66% relative reduction in median daily medication score (DMS)



‡ Median values were analyzed because data were not normally distributed.

IGG$_4$ LEVELS AGAINST *PHLEUM PRATENSE*

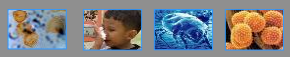


Pediatric

2% Incidence of Treatment Related AEs

AE	Grass AIT (%)	Placebo (%)
Oral Pruritus	38.9	3.6
Throat Irritation	37.1	3.0
Stomatitis	14.9	1.2
Ear Pruritus	11.4	0.6
Mouth edema	10.3	0.6
Oral pharyngeal pain	8.0	2.4
Pharyngeal erythema	7.4	1.8
Eye pruritus	6.3	1.8
Lip swelling	7.4	0
Headache	4.0	2.4
Dry throat	4.0	1.2
Oral Paraesthesia	4.0	1.2
Nasal congestion	4.0	0.6
Pharyngeal edema	4.0	0
Pruritus	3.4	3.6
Sneezing	3.4	0.6
Cough	3.4	0
Nausea	2.3	1.2
Dysphagia	2.9	0
Nasal discomfort	2.9	0
Swollen tongue	2.9	0
Oral pain	2.3	0

Efficacy of sublingual immunotherapy in allergic rhinitis in pediatric patients 4 to 18 years



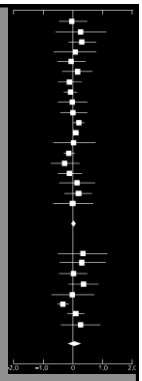
Meta-analysis of RCT

Penagos M., Compalati E., Tarantini F.,Baena Cagnani R., Huerta Lopez J., Passalacqua G., & Canonica G.W.

Annals of Allergy Asthma and Immunology 2006

Purpose: To assess the efficacy of Immunotherapy delivered by the sublingual route, whether or not the allergen was subsequently swallowed in the treatment of allergic rhinitis in children.

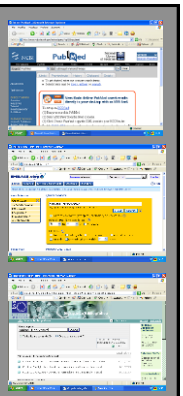
Study Selection: Randomized, placebo-controlled and double-blind trials that studied SLIT in pediatric patients (4 to 18 years) with allergic rhinitis.



Penagos et al. Annals of Allergy Asthma and Immunology 2006

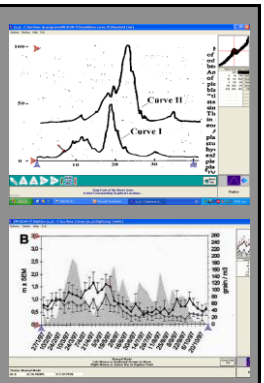
Data Sources:

Comprehensive searches of the EMBASE, LILACS, OVID and MEDLINE databases from 1966 to November 2005 and references of identified articles and reviews.



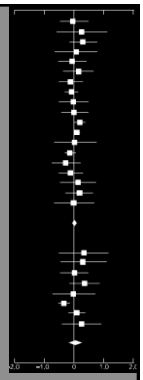
Penagos et al. Annals of Allergy Asthma and Immunology 2006

- Outcomes were extracted from original articles.
- When this information was not available, authors of each trial were contacted.
- Some graphics were digitalized.



Penagos et al. Annals of Allergy Asthma and Immunology 2006

- Results: The initial scanning identified 102 articles, 60 of which were potentially relevant trials on SLIT use in pediatric patients with allergic rhinitis.
- 16 studies were randomized. 10 met inclusion criteria for the meta-analysis.
- All randomized clinical trials included 491 participants, 251 allocated to SLIT group and 240 to placebo group.



Penagos et al. Annals of Allergy Asthma and Immunology 2006

Symptom Score

Review Manager 4.2.7
Version date: 27 May 2004
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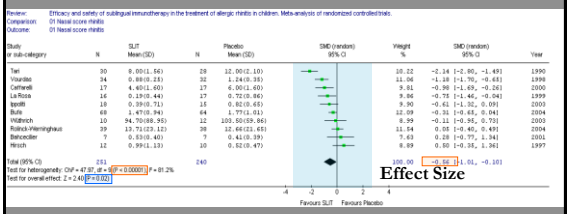

Penagos et al. Annals of Allergy Asthma and Immunology 2006

Medication score

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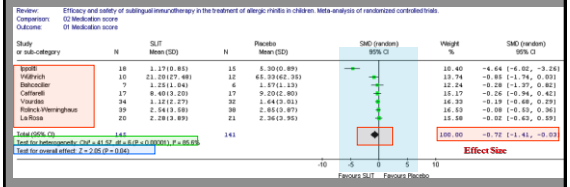
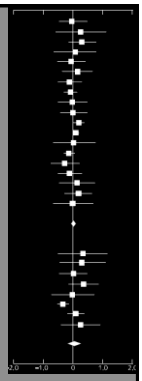


Penagos et al. Annals of Allergy Asthma and Immunology 2006

Conclusion:

SLIT reduces both symptom and medication scores in pediatric patients with

allergic rhinitis.



Penagos et al. Annals of Allergy Asthma and Immunology 2006

Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children

- A prospective nonrandomized study was carried out in a population of asthmatic children younger than 6 years of age whose only allergic sensitivity was to house dust mites
- The study was designed to determine whether specific immunotherapy with standardized allergen extracts could prevent the development of new sensitizations over a 3-year follow-up survey
- Ten of 22 children monosensitized to HDM who were receiving SIT did not have new sensitivities compared with zero of 22 children in the control group (p = 0.001, chi square test)

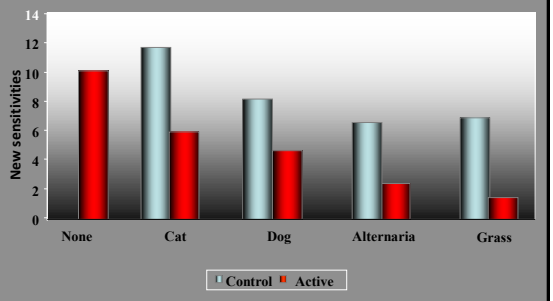
Des Roches et al. JACI 1997

Prevention of new sensitivities after HDM immunotherapy in children

	No. of patients	New sensitivities after IT	No new sensitivities after IT
HDM immuno-therapy group	22	12	10
Control group	22	22	0

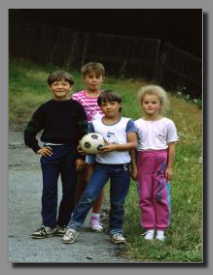
Des Roches A. *et al*. JACI 1997;99:450-53

Prevention of New Sensitivities After Treatment of 3 Years



Source:Des Roches et al. *JACI. 1997*

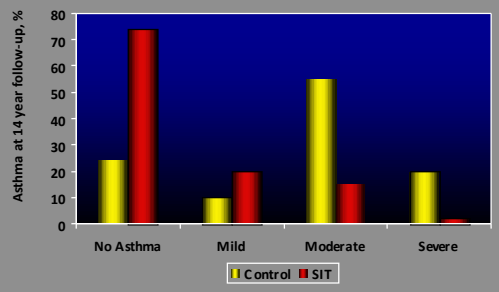
Long-Term Study on Children



- 14-year study on preventive effects of immunotherapy published in *Pediatrics*
- Allergy shots reduced number of children who developed asthma

Source: Johnstone DE, Dutton A. *Pediatrics* 1968

Prevention of Asthma 14 Years Later



Source: Johnston & Dutton 1968

Preventive Allergy Treatment (PAT) Study

- Multi-center prospective European study
- 205 children, ages 7-15, with seasonal allergic rhinitis:
  - 191 followed for 5 years
- Control group vs. active treatment group

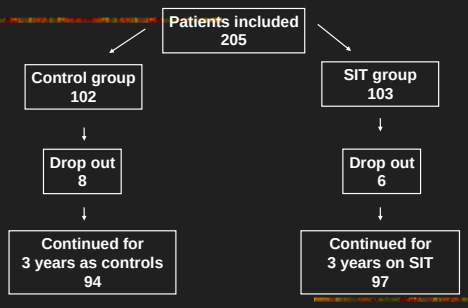
SIT and Long-Term Prevention of Asthma in Children

- **5-y follow-up on PAT study**
  - 3-y course of SIT in children with seasonal rhinoconjunctivitis caused by allergy to grass and/or birch pollen
  - Children underwent testing 2 y after discontinuation of SIT

PAT = preventive allergy treatment; SIT = specific immunotherapy

Niggemann B, et al. *Allergy.* 2006;61:855-859.

Patient flow:

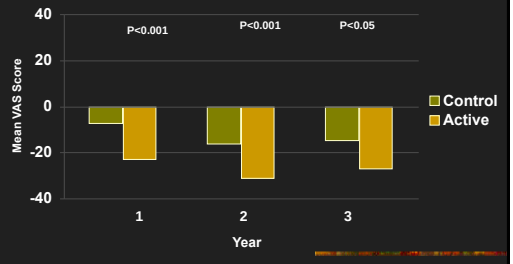


RHINITIS: CHANGE FROM BASELINE

(VISUAL ANALOGUE SCORES)

CONJUNCTIVITIS: CHANGE FROM BASELINE

(VISUAL ANALOGUE SCORES)



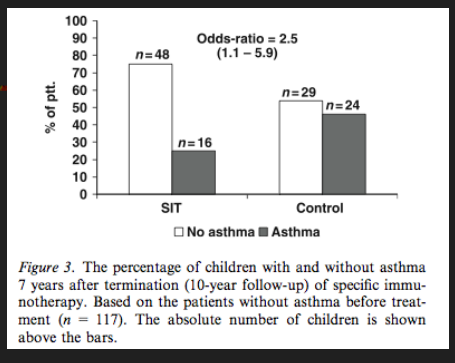


Figure 3. The percentage of children with and without asthma 7 years after termination (10-year follow-up) of specific immunotherapy. Based on the patients without asthma before treatment (n = 117). The absolute number of children is shown above the bars.

Jacobsen et al. Allergy 2007, 62:943-948

SIT and Long-Term Prevention of Asthma in Children

- Children who had undergone SIT had less asthma after 5 y (as evaluated by clinical symptoms)
- There were 2.5 times less likely to develop asthma
- Three years of SIT had long-term clinical effect and prevented development of asthma in children with seasonal rhinoconjunctivitis

SIT = specific immunotherapy

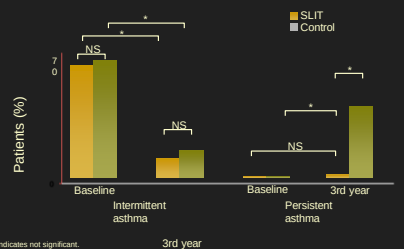
Niggemann B, et al. *Allergy.* 2006;61:855-859.

Preventive Effects of SLIT in Childhood

- A total of 216 children with AR with/without intermittent asthma were evaluated with drugs alone or drugs plus SLIT openly for 3 years
- PFTs, methacholine challenge, and skin prick tests beginning and end of study

Marogna et al. *Ann Allergy Asthma Immunol.* 2008;101:206–211.

Asthma Prevalence at Baseline and After 3 Years of Sublingual Immunotherapy (SLIT)



*P<0.001. NS indicates not significant.

Marogna et al. *Ann Allergy Asthma Immunol.* 2008;101:206-211.

SLIT Results

- Mild persistent asthma was less frequent in SLIT children
- Significant decrease in clinical scores in SLIT children
- Number of children with a positive methacholine challenge decreased significantly after 3 years only in the SLIT group

Marogna et al. *Ann Allergy Asthma Immunol.* 2008;101:206-211.

Conclusions

- Both SCIT and SLIT are efficacious in the pediatric population for ARC and possibly asthma
- Immunotherapy may prevent new sensitizations
- Immunotherapy may decrease or stop the atopic march (ARC to asthma)