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?

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

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.

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

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

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
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 IgG4
• 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 (wheat diameter ≥5mm)
  – Positive specific IgE against Phleum pratense (≥ 0.7 kU/L)
  – FEV1, ≥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)

<table>
<thead>
<tr>
<th>Individual Symptoms</th>
<th>Maximum Daily Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itchy nose</td>
<td>3</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>3</td>
</tr>
<tr>
<td>Sneezing</td>
<td>3</td>
</tr>
<tr>
<td>Red/itchy/gritty eyes</td>
<td>3</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>3</td>
</tr>
</tbody>
</table>

Daily Medication Score (DMS; Maximum=36)

<table>
<thead>
<tr>
<th>Rescue Medication</th>
<th>Rescued Dose Unit</th>
<th>Maximum Daily Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine 10 mg tablet</td>
<td>*</td>
<td>6 points/tablet</td>
</tr>
<tr>
<td>Olopatadine HCl 0.1% ophthalmic solution</td>
<td>†</td>
<td>1.5 points/drop</td>
</tr>
<tr>
<td>Mometasone furoate nasal spray 50 µg</td>
<td>‡</td>
<td>2 points/spray</td>
</tr>
<tr>
<td>Prednisone 5 mg tablet</td>
<td>§</td>
<td>1.6 points/tablet</td>
</tr>
</tbody>
</table>

*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) vs Placebo (n=169)

<table>
<thead>
<tr>
<th>Sex (%)</th>
<th>Male</th>
<th>67</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean</td>
<td>12.1</td>
<td>12.6</td>
</tr>
<tr>
<td>Range</td>
<td>5–18</td>
<td>6–17</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td>White</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Sensitive to non-grass allergens (%)</td>
<td>87</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Positive asthma status (%)</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

Grass Sensitivity

<table>
<thead>
<tr>
<th>Mean Wheal</th>
<th>Specific IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 mm</td>
<td>32 kU/L</td>
</tr>
<tr>
<td>11 mm</td>
<td>35 kU/L</td>
</tr>
</tbody>
</table>

Total Combined Symptom and Medication Scores: All Sensitization Types Grouped

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

Adjusted Mean Score (+SE)

Placebo | Grass AIT
--------|---------
6.25    | 4.62*   

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)

Adjusted Score (+SE)

Placebo vs Grass AIT

Mean DSS: 4.91 vs 3.70*  
Median DMS: 0.12 vs 0.06*  
† Median values were analyzed because data were not normally distributed.
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

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

<table>
<thead>
<tr>
<th>Pediatric</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2% Incidence of Treatment Related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grass AIT (%)</td>
<td>Placebo (%)</td>
</tr>
<tr>
<td>Oral Pruritus</td>
<td>38.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>27.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>16.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>11.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Rhinitis symptoms</td>
<td>16.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>9.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
<td>7.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>6.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Lip swelling</td>
<td>7.4</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Dry throat</td>
<td>4.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Oral Parthenyi</td>
<td>4.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Head congestion</td>
<td>4.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
<td>4.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Sneezing</td>
<td>3.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Cough</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Ear pain</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Swollen tongue</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Oral pain</td>
<td>2.3</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Outcomes were extracted from original articles.

When this information was not available, authors of each trial were contacted.

Some graphics were digitalized.
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.

**Conclusion:**
SLIT reduces both symptom and medication scores in pediatric patients with allergic rhinitis.

**Prevention of new sensitivities after HDM immunotherapy in children**

<table>
<thead>
<tr>
<th>HDM immunotherapy group</th>
<th>No. of patients</th>
<th>New sensitivities after IT</th>
<th>No new sensitivities after IT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

Prevention of New Sensitivities After Treatment of 3 Years

Control vs. Active

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

Prevention of Asthma 14 Years Later

Control vs. SIT

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

Patient flow:

Patients included

Control group 102
- Drop out 8
- Continued for 3 years as controls 94

SIT group 103
- Drop out 6
- Continued for 3 years on SIT 97

**RHINITIS:** CHANGE FROM BASELINE (VISUAL ANALOGUE SCORES)  

![RHINITIS Graph](image1.png)

**CONJUNCTIVITIS:** CHANGE FROM BASELINE (VISUAL ANALOGUE SCORES)  

![CONJUNCTIVITIS Graph](image2.png)

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**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

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**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

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

![Asthma Graph](image3.png)
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


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)