Allergen Specific Immunotherapy in Children
When to start and what to expect

Moisés Calderón  MD PhD
Section of Allergy and Clinical Immunology

Allergy Summer School
Mykonos - June 29th 2009
# Specific Allergen Immunotherapy

<table>
<thead>
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<tbody>
<tr>
<td>SCIT</td>
<td>First RCT SCIT</td>
<td>SLIT</td>
<td>First RCT SLIT</td>
<td>WHO</td>
<td>ARIA</td>
<td>First Meta SLIT</td>
<td>Large RCT SCIT</td>
<td>First Meta SCIT</td>
<td>Large RCT SLIT</td>
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</tbody>
</table>

- **1st SCIT RCT in children:** Dreborg S et al. 1986
- **1st SLIT RCT in children:** Tari MG et al. 1990
Allergen Immunotherapy
WHO position paper

- Effective in IgE-mediated disease with a limited spectrum (1 or 2) of allergies
- Effective in allergic rhinitis/conjunctivitis allergic asthma and systemic reactions to wasp/bee venom
- Should be combined with allergen avoidance, pharmacotherapy and patient education

Specific Allergen Immunotherapy

Desensitisation treatment route

Europe: Finished products only

- France: 20% SLIT, 80% SCIT
- Germany: 42% SCIT, 25% Allergoids, 33% (other)
- Italy: 24% SLIT, 73% SCIT
- Spain: 19% SCIT, 25% Allergoids, 56% (other)

US: Bulk

- US: 100% SCIT
Specific Allergen Immunotherapy
Specific Immunotherapy
Children

- Clinical efficacy
- Safety
- Long-term effect
  - Prevention of new sensitisations
  - Prevention of asthma
- Practical issues
# Levels of Evidence

## Treatment

<table>
<thead>
<tr>
<th>Level</th>
<th>Study type</th>
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<tbody>
<tr>
<td>1a</td>
<td>Meta-analysis of RCT</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT</td>
</tr>
<tr>
<td>1c</td>
<td>All or none</td>
</tr>
<tr>
<td>2a</td>
<td>Meta-analysis of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or low quality RCT</td>
</tr>
<tr>
<td>2c</td>
<td>Ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Meta-analysis of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control Study</td>
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<tr>
<td>4</td>
<td>Case-series</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Oxford Centre for Evidence-based Medicine, 2001
Meta-analysis of RCT

Data Interpretation - Forest Plot

Standardised Mean Difference (SMD)

Study or sub-category | N | Treatment Mean (SD) | N | Control Mean (SD) | SMD (random) | Weight | SMD (random)
--- | --- | --- | --- | --- | --- | --- | ---
Ostuni 1994 | 0 | 2.01 (0.57) | 7 | 5.66 (1.40) | | | 
Ostuni 1994 | 18 | 0.81 (0.17) | 17 | 2.30 (0.98) | | | 
Bouquet 1990 | 20 | 0.65 (0.50) | 18 | 10.60 (33.20) | | | 
Mennet 1994 | 10 | 2.53 (1.97) | 10 | 9.49 (4.24) | | | 
Frew 1998 | 10 | 0.50 (0.50) | 6 | 12.40 (9.13) | | | 
Goddeer 2002 | 10 | 2.20 (1.00) | 8 | 1.20 (1.40) | | | 
Herrer 2005 | 22 | 0.44 (0.52) | 20 | 0.80 (0.54) | | | 
Jutel 2005 | 23 | 5.93 (3.28) | 23 | 5.82 (3.44) | | | 
Weiker 2001 | 17 | -112.06 (2632.00) | 13 | -11.50 (159.00) | | | 
Frew 2005 | 107 | 3.51 (2.45) | 89 | 4.59 (2.95) | 10.81 ≥ 0.49 [0.78, -0.24] | 0.56 | 0.61 [0.24, 0.23] | 
Vanney 1991 | 10 | 1.53 (1.00) | 16 | 2280.00 (656.00) | | | 
Herschtenberg 2001 | 74 | 0.26 (0.44) | 50 | 0.98 (0.41) | 6.14 ≥ 0.45 [-1.10, 0.52] | | 9.19 [0.45, 0.23] | 
Zener 1997 | 41 | 8.27 (5.98) | 40 | 11.58 (3.67) | 8.67 ≥ 0.45 [-0.89, -0.10] | | 9.19 [0.45, 0.23] | 
Corrigan 2005 | 77 | 166.50 (144.90) | 77 | 210.00 (155.90) | 10.12 ≥ 0.41 [-0.79, -0.09] | | 9.33 [0.41, 0.23] | 
Baldass 1996 | 49 | 6.58 (10.43) | 56 | 9.67 (8.19) | | | 

Total N = 957
Test for heterogeneity: CH² = 36.05, df = 14 (P = 0.0005), η² = 63.2%
Test for overall effect: S = 5.10 (P = 0.0005)

Effect size
- Poor: ≤ 0.20
- Medium: = 0.50
- High: > 0.80

Heterogeneity
- Low: η² 25%
- Moderate: η² 50%
- High: η² 75%

MA Calderon 2009
Specific Immunotherapy
Children

• Clinical efficacy
  • Safety
  • Long-term effect
    - Prevention of new sensitisations
    - Prevention of asthma
• Practical issues
Clinical Efficacy - SCIT
SCIT for Seasonal Allergic Rhinitis
Systematic Review and Meta-analysis

- 51 DB PC RC studies were included (1950-2006)
- Patients with SAR due to grass, tree or weed pollen
- Participants: n=2,871 (1,645 active; 1,226 placebo)
- Adults

## SCIT in children - DB PC RCT

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>SCIT/placebo</td>
<td>12/11</td>
<td>121</td>
<td>15/14</td>
<td>44/41</td>
</tr>
<tr>
<td>Age</td>
<td>7-14 yrs</td>
<td>7-16 yrs</td>
<td>6-45</td>
<td></td>
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<tr>
<td>Disease</td>
<td>asthma</td>
<td>Asthma mod-severe</td>
<td>asthma</td>
<td>asthma</td>
</tr>
<tr>
<td>Allergen</td>
<td>HDM</td>
<td>Allergen mix</td>
<td>Cat or HDM</td>
<td>HDM</td>
</tr>
<tr>
<td>Dose</td>
<td>800 alpare units</td>
<td>?</td>
<td>15 ug Fed d 1</td>
<td>7 ug Der p 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 ug Der p 1</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>12 mo</td>
<td>18-24 mo</td>
<td>36 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Positive outcomes</td>
<td>SCIT: skin reactivity</td>
<td>None</td>
<td>PC$_{20}$ allergen; Sx of cat exposure IgG$_4$ rise</td>
<td>Phase 2: Sx, medication and skin reactivity</td>
</tr>
<tr>
<td>Comments</td>
<td>All children moved to Italian Alpes for 1 yr, both groups improved</td>
<td>Both groups improved, no intergroup differences</td>
<td>All ptes also received pollen SCIT</td>
<td>All patients on ICS</td>
</tr>
</tbody>
</table>
SCIT in children with grass pollen seasonal allergic asthma

- RCT, 3-16 yr age
- Seasonal asthma: at least 200ug ICS
- SCIT n=18; placebo n=17
- SCIT for 2 years

Clinical Efficacy - SLIT
SLIT - Vaccine Presentation

Vials

Pump Doseuse

Disposable single dose

Soluble tablets
## SLIT for Allergic Rhinitis

**Meta-analysis: Symptom Score - Radulovic S et al. AAAAI 2009**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>N</th>
<th>% 95% CI</th>
<th>% 95% CI</th>
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<td>10.00 (1.00)</td>
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<td>10.00 (1.00)</td>
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<tr>
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<tr>
<td>Falsani 1995</td>
<td>10</td>
<td>10</td>
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<td>Cosen 1994</td>
<td>10</td>
<td>10</td>
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<td>10.00 (1.00)</td>
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<td>Diaz 2001</td>
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<td>10</td>
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<td>10.00 (1.00)</td>
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<td>10</td>
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<td>Hoard 1999</td>
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<td>10.00 (1.00)</td>
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<td>Dei 2001</td>
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<td>10</td>
<td>10.00 (1.00)</td>
<td>10.00 (1.00)</td>
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<td>Velzore 1989</td>
<td>10</td>
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<td>10.00 (1.00)</td>
<td>10.00 (1.00)</td>
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<td>Ande 2003</td>
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<td>Ceffrazi 2000</td>
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<td>Brown 2004</td>
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<td>Dubaelen 2003</td>
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<td>Gutz 2000</td>
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<td>Morgan 1989</td>
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<td>La Rosa 1990</td>
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<td>Menouc 2002</td>
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**Total (95% CI)**

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<tr>
<th></th>
<th>1351</th>
<th></th>
<th>1350</th>
<th></th>
<th>4.42</th>
<th>[−0.56, 0.23]</th>
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<tr>
<td></td>
<td>1351</td>
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<td>1350</td>
<td></td>
<td>4.42</td>
<td>[−0.56, 0.23]</td>
</tr>
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</table>

**Test for overall effect:** $Z = 5.88$ ($P < 0.00001$)

**Favour SLIT**

**Favour Placebo**

MA Calderon 2009
Meta-analysis of the efficacy of SLIT in the treatment of allergic rhinitis pediatric patients, 3 to 18 years of age

Meta-analysis of the efficacy of SLIT in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>SLIT Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>SMD (random) 95% CI</th>
<th>Weight %</th>
<th>SMD (random) 95% CI</th>
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<tr>
<td>Caffarelli</td>
<td>23</td>
<td>2.39 (0.50)</td>
<td>4.60 (0.73)</td>
<td>10.64 [-3.51, -2.53]</td>
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<tr>
<td>Ipolti</td>
<td>47</td>
<td>1.28 (0.77)</td>
<td>3.15 (0.66)</td>
<td>11.47 [-2.57, -1.99]</td>
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<td>Torni</td>
<td>39</td>
<td>6.00 (1.62)</td>
<td>9.44 (0.96)</td>
<td>11.25 [-2.53, -1.03]</td>
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<tr>
<td>Niu</td>
<td>49</td>
<td>0.04 (0.01)</td>
<td>0.06 (0.02)</td>
<td>11.63 [-1.26, -0.82]</td>
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<td>Pagno</td>
<td>12</td>
<td>2.50 (0.14)</td>
<td>6.60 (4.88)</td>
<td>10.69 [-1.24, -0.23]</td>
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<td>Hirsch</td>
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<td>0.17 (0.30)</td>
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<td>10.89 [-1.46, 0.35]</td>
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<td>Rolinck-Verninghaus</td>
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<td>2.54 (5.00)</td>
<td>2.50 (5.06)</td>
<td>11.33 [-0.52, 0.64]</td>
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<td>Baezeciller</td>
<td>3</td>
<td>0.42 (0.45)</td>
<td>0.29 (0.26)</td>
<td>10.46 [0.33, 1.59]</td>
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<tr>
<td>Vouglas</td>
<td>33</td>
<td>0.11 (0.60)</td>
<td>0.06 (0.02)</td>
<td>11.85 [0.46, 1.52]</td>
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</table>

Total (95% CI) 232 209

Test for heterogeneity: Chi² = 144.10, df = 8 (P < 0.00001), P = 94.4%
Test for overall effect: Z = 2.32 (P = 0.02)

Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy

Albrecht Bufe, PhD, MD, a Peter Eberle, MD, b Eivy Franke-Beckmann, MD, b Jürgen Funck, MD, b Martin Kimmig, MD, b Ludger Klimek, MD, c Roland Knecht, MD, b Volker Stephan, MD, d Bente Tholstrup, MSc, e Christian Weißhaar, MD, b and Friedrich Kaiser, MD b

Bochum, Hamburg, and Wiesbaden, Germany, and Hørsholm, Denmark


<table>
<thead>
<tr>
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<th>75,000SQ-T</th>
<th>Placebo</th>
<th>Total</th>
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<tr>
<td></td>
<td>(n=126)</td>
<td>(n=127)</td>
<td>(n=253)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>MonoS</td>
<td>24</td>
<td>21</td>
<td>45</td>
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<tr>
<td>PolyS</td>
<td>102</td>
<td>106</td>
<td>208</td>
</tr>
</tbody>
</table>
SLIT Grass Pollen Tablet in Children

Symptom Score

RCT, Germany

- Active n=114, Placebo n=120

-24% reduction in symptoms score

-35% reduction in medication score

SLIT Grass Pollen Tablet in Children
Immunological results

## SLIT Grass Pollen Tablet in Children

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of Asthma</td>
<td>37%</td>
</tr>
<tr>
<td>Grazax</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Significant improvement in asthma symptoms**

Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis

Ulrich Wahn, MD, a Ana Tabar, MD, b Piotr Kuna, MD, c Susanne Halken, MD, DMSc, d Armelle Montagut, PhD, e Olivier de Beaumont, MD, f Martine Le Gall, f on behalf of the SLIT Study Group Berlin, Germany, Pamplona, Spain, Lodz, Poland, Odense, Denmark, and Meylan and Antony, France


<table>
<thead>
<tr>
<th></th>
<th>300 IR (n=131)</th>
<th>Placebo (n=135)</th>
<th>Total (n=266)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>MonoS</td>
<td>54</td>
<td>41.2</td>
<td>55</td>
</tr>
<tr>
<td>PolyS</td>
<td>77</td>
<td>58.8</td>
<td>80</td>
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</table>
SLIT Tablet in Children
Efficacy by sub-group of age

Median improvement vs placebo - ITT population

Placebo (n=64) vs 300 IR (n=49)

Placebo (n=71) vs 300 IR (n=82)

5-11 years:
- Placebo: 39.4%*
- 300 IR: 35.0%*

12-17 years:
- Placebo: 39.4%*
- 300 IR: 35.0%*

RCT
- 278 children
- 5-17 yr age
- 300 IR (25 mcg)
- 4mo pre-season co-seasonal

5-Grass Pollen Tablet for SAR in Children

Significant efficacy on nasal congestion and on ocular symptoms

5-Grass Pollen Tablet for SAR in Children

Immunological response

IgG4 (μg/L)

Visit 1 | End point
---|---
0 | 200
1000 | 1200

IgE (kU/L)

Visit 1 | End point
---|---
0 | 10
50 | 60

SLIT With Tree Pollen Extract In Children

- DB PC RCT
- n=88
- Children 5-15 yrs
- SLIT for 18 months

Mean Symptom Score


Mean Medication Score

- Placebo
- 24,000 SQ-U/week (3.6 μg major allergen)
- 200,000 SQ-U/week (30 μg major allergen)

MA Calderon 2009
SLIT in children modulates allergen induced \textit{in vitro} expression of cytokine mRNA in PBMC

Savolainen J. Allergy 2006; 61: 1184-90.
SLIT with grass pollen mix in youngsters in primary care

Randomised

6-18 years age

2 years
- Grass pollen mix (n=91)
- Placebo (n=77)

ITT analysis

### Clinical Efficacy of SLIT vs SCIT

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>n</th>
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<tbody>
<tr>
<td>Piazza I</td>
<td>1993</td>
<td>Open controlled</td>
<td>43</td>
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<tr>
<td>Bernardis P</td>
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<tr>
<td>Quirino T</td>
<td>1996</td>
<td>RCT double-dummy</td>
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<td>Mungan D</td>
<td>1999</td>
<td>RCT single blind</td>
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<td>Herrscher RF</td>
<td>2006</td>
<td>Retrospective cohort</td>
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<td>Mauro M</td>
<td>2007</td>
<td>RCT</td>
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No studies in Children
Specific Immunotherapy
Children

- Clinical efficacy
- Safety
  - Long-term effect
    - Prevention of new sensitisations
    - Prevention of asthma
- Practical issues
Safety - SIT in Children
SCIT in Children – Adverse Events

Akcakaya E at al. 2000
- HDM extracts
- n= 88 (6-15 yo); 1989-1997
- Local reactions = 3.6%
- Systemic reactions = 0.2 %
  1 anaphylaxis
  All < 30 min after injection

Keskin O et al. 2005
- HDM in asthmatic children
- No reduction in MCh PC_{20}

Roberts G et al 2006
- SCIT = 72%
- Placebo = 41%
- Local: 55% SCIT
  45% placebo
- Systemic: 70% SCIT
  30% placebo
- Time: 65% up-dosing
  35% maintenance
- No adrenaline
## SLIT - Adverse Reactions

<table>
<thead>
<tr>
<th>Local</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labial oedema</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Buccal pruritus</td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Bucco-lingual oedema</td>
<td>Rhino-conjunctivitis</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>Asthma/ Wheezing</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
</tr>
<tr>
<td></td>
<td>Pruritus/ Rush</td>
</tr>
<tr>
<td></td>
<td>Gastro- intestinal</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>No anaphylaxis</td>
</tr>
</tbody>
</table>

Radulovic S et al. AAAAI 2009
# SLIT Safety in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Fiocchi A.¹</th>
<th>Di Rienzo V.²</th>
<th>Agostinis F.³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>3 to 7 years (n=68)</td>
<td>3 to 5 years (n=126)</td>
<td>2 to 4 years (n=33)</td>
</tr>
<tr>
<td>Disease</td>
<td>AR +/- A</td>
<td>AR +/- A</td>
<td>AR +/- A</td>
</tr>
<tr>
<td>Study design</td>
<td>Observational</td>
<td>Post-marketing</td>
<td>Observational</td>
</tr>
<tr>
<td>Allergen</td>
<td>Grasses and dust Extract</td>
<td>Grasses, mites, olive. Extract</td>
<td>Various allergen Allergoid</td>
</tr>
<tr>
<td>Duration</td>
<td>246 days</td>
<td>2 years</td>
<td>22.3 months</td>
</tr>
<tr>
<td>Local AE</td>
<td>Oral itching</td>
<td>Oral itching</td>
<td>Oral itching</td>
</tr>
<tr>
<td>Systemic AE</td>
<td>Urticaria Gastrointestinal Orbital itching</td>
<td>Abdominal pain Diarrhea</td>
<td>Adominal pain</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild to moderate</td>
<td>Mild to moderate</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Time</td>
<td>Up-dosing and maintenance</td>
<td>Up-dosing</td>
<td>Up-dosing and maintenance</td>
</tr>
</tbody>
</table>

³- Agostinis F et al. Allergy 2005; 60: 133
## Anaphylaxis to SLIT

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Patient</th>
<th>Allergens</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunsky 2006¹</td>
<td>USA</td>
<td>F 31yo</td>
<td>Multiple seasonal and perennial allergens</td>
<td>Multiple allergies (not standardised) *</td>
</tr>
<tr>
<td>Antico 2006²</td>
<td>Italy</td>
<td>F 36yo</td>
<td>Latex extract</td>
<td>Rush schedule Asthma</td>
</tr>
<tr>
<td>Eifan 2007³</td>
<td>Turkey</td>
<td>F 11 yo</td>
<td>Multiple seasonal and perennial allergens</td>
<td>Multiple allergies Asthma</td>
</tr>
<tr>
<td>Blazowski 2008⁴</td>
<td>Poland</td>
<td>F 16yo</td>
<td>HDM</td>
<td>Overdose (3rd yr maintenance) Asthma</td>
</tr>
<tr>
<td>De Groot 2009⁵</td>
<td>The Netherlands</td>
<td>M 13yo</td>
<td>Grass Pollen Tablet SCIT for Birch</td>
<td>Previous SCIT anaphylaxis. First dose taken at home</td>
</tr>
<tr>
<td>De Groot 2009⁵</td>
<td>The Netherlands</td>
<td>F 27yo</td>
<td>Grass Pollen Tablet SCIT for Birch</td>
<td>Previous SCIT anaphylaxis. First dose taken at home</td>
</tr>
</tbody>
</table>

1-Dunsky EH et al. Allergy 2006; 61: 1235  
2-Antico A et al. Allergy 2006; 61: 1236  
3-Eifan AO et al. Allergy 2007; 62: 567-8  
4-Blazowski L. Allergy 2008; 63: 374  
5- de Groot H et al. Allergy 2009
**SCIT - Fatalities**

**U.K.**
- Committee on Safety of Medicines
- 26 fatalities 1957-1986
- 16 / 17 in patients with asthma (poor control)

  BMJ 1986; 293: 948-53

**U.S.A.**
- AAAAI Survey
- 41 fatalities 1990-2001
- 1 per 2.5 million injections
- 15/17 had asthma (poor control)
- 59% occurred during maintenance

Bernstein DI et al. JACI 2004; 113: 1129-36
SLIT - Fatalities

- No fatalities have been reported with SLIT.
  Radulovic S, Calderon MA and Durham SR. AAAAI 2009

- In 1,181,654 doses administered to 4,378 patients (66 studies) no serious life-threatening reactions were reported.
Specific Immunotherapy
Children

• Clinical efficacy
• Safety
• Long-term effect
  - Prevention of new sensitisations
  - Prevention of asthma
• Practical issues
Long-term Clinical Efficacy of SCIT
12-year follow-up after discontinuation

- Non-randomized, prospective controlled open study
- n=22 children (5-16 years) severe hay fever
- 3 years SCIT with grass pollen depot allergoids

Eng PA et al. Allergy 2006; 61: 198-201
Long-term effect of SLIT: ECRIT study
Symptom and medication scores

- RCT
- 8-65 yo
- SLIT n= 99
- Placebo n= 46

Ott H et al. Allergy 2009; 64: 179-186
Grass Pollen Tablet in SAR
Immunological effect (IgG₄)

Follow up Year

MA Calderon 2009
New Sensitisations

SCIT and SLIT
SCIT Reduces New Sensitisation

Monosensitised Children under 6 years with Asthma
HDM sensitisation for 2 years
Not RCT study
3-year follow-up

SCIT Reduces New Sensitisations

Subject developing new sensitisations at 6 years

(Percent of subjects)

<table>
<thead>
<tr>
<th>New sensitisations</th>
<th>Control</th>
<th>Alutard SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietaria</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>Grass</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Olive</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Cat</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Dog</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Alternaria species</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Mugwort</td>
<td>4%</td>
<td>1%</td>
</tr>
</tbody>
</table>

SCIT Reduces New Sensitisations

<table>
<thead>
<tr>
<th>Percent of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>80</td>
</tr>
</tbody>
</table>

n=123

(5-8 yrs)

Pajno GB et al. Allergy 2001;31:1392-7
Developing Asthma

SCIT and SLIT
SCIT Reduces Risk of Developing Asthma

Children (6-14 years) with moderate/severe Allergic Rhinitis

5 & 10-year follow-up

SCIT Reduces Risk of Developing Asthma

Subject developing asthma at 3, 5, and 10 years
(percent of subjects; n=151)

- Control
- Alutard SQ

OR=2.5
OR=3.1
OR=2.5

* p<0.05

45%
SLIT Reduces Risk of Developing Asthma

Children (5-14 year) with Allergic Rhinoconjunctivitis
3-year follow-up (n=113)

- Open, randomised study
- SLIT for 3 years
- Symptomatic treatment

Odds ratio 3.80 (1.5-10.0)

SLIT Control

% of patients

0% 20% 40% 60% 80% 100%

n=8 20% 80%

n=18 40% 60%

n=37

n=26

w asthma w/o asthma

Specific Immunotherapy
Children

- Clinical efficacy
- Safety
- Long-term effect
  - Prevention of new sensitisations
  - Prevention of asthma
- Practical issues
SIT indications in children

- Symptoms induced predominantly by allergen exposure (IgE mediated)
- More than 2-3 years of perennial symptoms or with symptoms induced by succeeding pollen seasons
- Rhinitis and symptoms from the lower airways during peak allergen exposure
- No control of symptoms with antihistamines and moderate dose topical CS and aLTR
- Children/parents who do not want to be on constant or long-term pharmacotherapy
- Pharmacotherapy induces undesirable side effects
SIT contra-indications in children

- No IgE mediated disease

- Severe asthma with persistently reduced lung functions ($FEV_1$) below 70% of predicted in spite of optimal pharmacologic treatment

- Lack of compliance by child or/and parents

- Severe psychological disorders

- Serious immunological diseases

- Major cardiovascular disease

- Treatment with beta-blockers (including topical)

- Cancer

- Chronic infections

- Severe atopic eczema
SIT Patient Evaluation

- Before start SIT
  Allergist should always evaluate the clinical history
  IgE sensitisation assessed by SPT and/or sIgE antibodies

- SIT should be given by allergist specialist (no GPs)
  SCIT in hospital setting
  SLIT at home but first dose with allergist

- Every 6 months: evaluation of efficacy and safety

- Criteria for continuing or discontinuing SIT
  Inadequate treatment response
  Side effects
Conclusions

• SIT is indicated for confirmed IgE-mediated airway diseases using standardised allergen products
  Grass, birch, ragweed, olive, *Parietaria*, cypress, cat, house dust mite.

• SCIT and SLIT are both efficacious in improving, symptom and medication scores, and disease-specific quality of life.

• SCIT can cause systemic adverse reactions which in the majority of cases are readily reversible with appropriate treatment. SLIT has a very good safety profile.
Future Directions

• More confirmatory prospective, randomised, long-term studies with SCIT and SLIT

• Comparison of SCIT and SLIT for long-term efficacy

• Efficacy and safety of SCIT and SLIT in children < 5 years of age

• QoL

• Cost-effectiveness

• Optimal doses, treatment regimens and duration for SLIT

• Mechanisms of SIT in children
...Thank you!