2011 Update

SLIT immunotherapy treatment in allergic subjects

Professor Paul C. Potter
Allergy Diagnostic & Clinical Research Unit
University of Cape Town Lung Institute
South Africa
Types of Allergen Immunotherapy

1. Subcutaneous (SIT)
2. Sublingual (SLIT)
3. Intranasal
4. Peptide
5. SIT plus anti-IgE
6. Oligonucleotide
Aims of immunotherapy

1. Change the natural history of the disease
2. Reduce symptoms of allergy
3. Reduce medication for allergies
4. Prevent new sensitizations
5. Cure the patient
An explosion of new SLIT studies published: >1000 patients

- Adult - Perennial Conjunctivitis (Mites)
  - Mortemousque et al
- Prevention of asthma
  - Marogna et al
- Paediatric HDM Asthma & Rhinitis
  - Ippoliti et al
- Latex allergy
  - Patriarca et al
- Ragweed SAR
  - Andre et al
- Bisensitised Individuals (Birch & Grass)
  - Cirla et al
- Paediatric HDM Rhinitis
  - Marcucci et al
- Kiwi Fruit Anaphylaxis
  - Mempel et al
- Wilson et al

Cochrane Review for rhinitis
Efficacy for SIT

- Venoms: Bee
  - Wasp
  - Yellow Jacket
- Cat
- Dog
- Horse

Efficacy for SIT and SLIT

- Grasses
- Certain weeds
- Certain trees
- House dust mites:
  - Der-f-1
  - Der-p-1
  - Alternaria
  - Cat

SLIT: Experimental

- Food allergy
- Latex allergy
Early protocols for mode of administration

- Drops held under the tongue for 2 minutes
- Daily Administration
- 4-5 vials – incrementally – 1 month
- Maintenance alternate days: 2-3 years
New SLIT protocols

Single Dose
“No updosing”

Method:
- Recent DBPC study of 135 patients (mite/grass allergic) (SLIT one)
- Age 7-55 years with rhinitis with/without asthma
- 69 with SLIT one updosing
- 66 with updosing followed by 2 months maintenance

Results:
- All adverse events:
  - with updosing = 1.79%
  - without updosing = 1.33%
    (p=0.37) (NS)
- Oral itching per dose:
  - with updosing = 0.45%
  - without updosing = 0.64%
    (p=0.53) (NS)
Compliance: - 98%

Advantages: - Effective
- Easy to transport
- No “drop counting”
Mechanisms of action I reported

- No buccal “absorption”
- Oral dendritic cells
- Specific T-cell “suppression”
- Specific IgG\textsubscript{4} increase or decrease
- Fall in Specific IgE
- Fall in ICAM-1 expression in target organ
- Fall in ECP, IL-13
- Reduction in Tryptase release
- Increased oral TGF\textbeta
- ? Increase in IL-10
Clinical patterns of action II

- **Rapid Effect (weeks)**
  - e.g. Pre-Seasonal pollen SLIT
    - ? Cytokine induced

- **Slow Effect (years)**
  - e.g. House Dust Mite Asthma
    - ? Cellular or Immunoglobulin
The first convincing clinical support (Cochrane review of SLIT in rhinitis)

**Analysis:**
- DBPC trials up to September 2002
- Search words: Rhinitis, Sublingual Immunotherapy
- 31 Full papers
- 22 Suitable for analysis, 979 patients
- Allergens: HDM (6), Grass (5), Parietaria (5), Olive (2), Ragweed (1), Cat (1), Cypress (1)

**Results:**
- SLIT is effective in rhinitis (p=<0.002)
- Overall symptoms reduced
- Significant reduction in medication (p=<0.001)
- SLIT is safe
- Insufficient data for duration, seasonal vs perennial and dose

Wilson, Torres Lima, Durham. Cochrane Database Syst Rev 2003; (2) CD002893
Safety

- Systemic reactions rare
- No fatalities reported
Grading side effects of sublingual immunotherapy: Speaking the same language

### Description of the local side effects related to SLIT

<table>
<thead>
<tr>
<th>LOCALLY AFFECTED AREA</th>
<th>LOCAL SIDE EFFECT</th>
<th>MeDRA PREFERRED TERM</th>
<th>MeDRA CODE</th>
<th>MeDRA Low level term (LLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOUTH/ EAR</td>
<td>Altered taste perception</td>
<td>Dysgeusia</td>
<td>10013911</td>
<td>Taste alteration</td>
</tr>
<tr>
<td></td>
<td>Itching of lips</td>
<td>Oral pruritus</td>
<td>10052894</td>
<td>Itching mouth</td>
</tr>
<tr>
<td></td>
<td>Swelling of lips</td>
<td>Lip swelling</td>
<td>10024570</td>
<td>Swelling lips</td>
</tr>
<tr>
<td></td>
<td>Itching of the oral mucosa</td>
<td>Oral pruritus</td>
<td>10052894</td>
<td>Itching mouth</td>
</tr>
<tr>
<td></td>
<td>Swelling of the oral mucosa</td>
<td>Oedema mucosal</td>
<td>10030111</td>
<td>Mucosal swelling</td>
</tr>
<tr>
<td></td>
<td>Itching of the ears</td>
<td>Ear pruritus</td>
<td>10052138</td>
<td>Ear pruritus</td>
</tr>
<tr>
<td></td>
<td>Swelling of the tongue</td>
<td>Swollen tongue</td>
<td>10042727</td>
<td>Tongue swelling non-specific</td>
</tr>
<tr>
<td></td>
<td>Glossodynia</td>
<td>Glossodynia</td>
<td>10018388</td>
<td>Glossodynia</td>
</tr>
<tr>
<td></td>
<td>Mouth ulcer</td>
<td>Mouth ulceration</td>
<td>10028034</td>
<td>Mouth ulcer</td>
</tr>
<tr>
<td></td>
<td>Tongue ulcer</td>
<td>Tongue ulceration</td>
<td>10043991</td>
<td>Tongue ulceration</td>
</tr>
<tr>
<td></td>
<td>Throat irritation</td>
<td>Throat irritation</td>
<td>10043521</td>
<td>Throat irritation</td>
</tr>
<tr>
<td></td>
<td>Uvular oedema</td>
<td>Pharyngeal oedema</td>
<td>10034829</td>
<td>Pharyngeal oedema</td>
</tr>
<tr>
<td>UPPER GASTRO INTESTINAL</td>
<td>Nausea</td>
<td>Nausea</td>
<td>10028813</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Stomach-ache</td>
<td>Abdominal pain upper</td>
<td>10000087</td>
<td>Stomach ache</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Vomiting</td>
<td>10047700</td>
<td>Vomiting</td>
</tr>
<tr>
<td>LOWER GASTRO INTESTINAL</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>10000081</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Diarrhoea</td>
<td>10012735</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>
Characteristics of the SLIT-induced anaphylaxis reported in literature

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sex (age)</th>
<th>Allergen (producer)</th>
<th>Phase</th>
<th>Onset</th>
<th>Description</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Groot, 2009</td>
<td>M (13)</td>
<td>Grass (Grazax, ALK)</td>
<td>First dose</td>
<td>15 min</td>
<td>Generalized urticaria, swelling of tongue</td>
<td>NO</td>
</tr>
<tr>
<td>De Groot, 2009</td>
<td>F (27)</td>
<td>Grass (Grazax, ALK)</td>
<td>First dose</td>
<td>5 min</td>
<td>Abdominal cramps, asthma, generalized itching</td>
<td>YES</td>
</tr>
<tr>
<td>Blazowski, 2008</td>
<td>F (16)</td>
<td>HDM (Staloral, Stallergenes)</td>
<td>Maintenance overdose (60 drops)</td>
<td>10 min</td>
<td>Collapse, flushing, urticaria</td>
<td>YES</td>
</tr>
<tr>
<td>Eifan, 2008</td>
<td>F (11)</td>
<td>dust mite + grass pollen mix (Stallergenes)</td>
<td>Maintenance</td>
<td>3 min</td>
<td>Abdominal pain, chest pain, fever, nausea</td>
<td>Not specified</td>
</tr>
<tr>
<td>Dunski, 2006</td>
<td>F (31)</td>
<td>Alternaria, cat, dog grass, ragweed, (Greer)</td>
<td>2nd day of updosing</td>
<td>5 min</td>
<td>Angioedema, dizziness, dyspnea, generalized itching</td>
<td>NO</td>
</tr>
<tr>
<td>Antico, 2006</td>
<td>F (36)</td>
<td>Latex</td>
<td>End of rush buildup</td>
<td>10 min</td>
<td>Asthma, generalized urticaria</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
## Proposed grading system for local adverse events

<table>
<thead>
<tr>
<th>Symptom/sign (see Table 1)</th>
<th>Grade 1 – Mild</th>
<th>Grade 2 – Moderate</th>
<th>Grade 3 - Severe</th>
<th>Unknown severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, Diarrhea</td>
<td>● Not troublesome AND</td>
<td>● Troublesome OR</td>
<td>Grade 2 AND SLIT discontinued because of local side effects</td>
<td>The treatment is discontinued but there is no subjective and/or objective description of the severity from the patient/physician</td>
</tr>
<tr>
<td>Ear itching</td>
<td>● No symptomatic treatment required AND</td>
<td>● Requires symptomatic treatment AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/swelling of mouth, tongue or lip</td>
<td>● No discontinuation of SLIT because of local side effects</td>
<td>● No discontinuation of SLIT because of local side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Uvular oedema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each local adverse event can be early (<30 minutes) or delayed
Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in paediatric patients 3-18 years. Meta analysis of randomised placebo controlled trials

M Penagos, W Canonica et al
Ann Allergy Asthma and Immunology, 2006; 97: 141-148
• 75 articles (1966-206)
• 10 fulfilled selection criteria
• 484 subjects (245 SLIT, 239 Placebo)
• Significant symptom improvement (p=0.02)
• 18 months better for pollen rhinitis
• Polysensitised do not do well
• Pollen better than mites

**NB:** Small studies UNDERESTIMATE TREATMENT EFFICACY (Type II Error)
Special considerations in children

1. Age
2. Allergen profile
3. Caregiver
4. Social circumstances
5. Possible prevention of asthma
6. Good long lasting effect
7. Safety
8. Convenience (at home)
9. Cost effectiveness
Multiple daily administration of low dose sublingual immunotherapy in allergic rhinoconjunctivitis

V Bordignon, S Burastero
Ann Allergy Asthma and Immunology, 2006; 97: 158-163
continued …

- Lower dose (1/5)
- More frequent administration (2-3x/day)
- 64 patients
- ↓ skin reactivity <0.001
- ↓ Drug use <0.001
Available in Europe

SLIT in tablet form
GRAZAX®: Highly significant efficacy over 2 years of continuous treatment.

GRAZAX® reduces median symptom and medication scores compared with placebo in the first and second treatment years.\(^{21,22}\)

GRAZAX® patients feel better and use less symptomatic medication over 2 years of continuous treatment.\(^{21,22}\)

In the long-term efficacy study all patients had access to standard symptomatic medication.\(^{22}\)

*\(p<0.0001\) for difference between GRAZAX® and placebo mean scores, tested with a parametric mixed model.

\(^{1}\) 1st year placebo group: \(n=286\); 2nd year placebo group: \(n=144\)
Psychological stress affects response to sublingual immunotherapy in asthmatic children allergic to house dust mite

Ippoliti F, De Santis W et al
Pediatr Allergy Immunol, 2006; 17: 337-345
Long lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: A 10-year prospective study

V Di Rienzo, F Marcucci, P Puccinilli, S Parmiani, F Frati, L Sensi, G Canonica, G Passalacqua
Clin Exp Allergy 2003; 33: 206-210
Mean PEFR (L/min) SEM in the two groups of patients at the three time points. Inter-group P-values are indicated upon the bars.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End SLIT</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients taking anti-asthma medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLIT</td>
<td>31/35</td>
<td>4/35</td>
<td>3/35</td>
</tr>
<tr>
<td>Controls</td>
<td>23/25</td>
<td>24/25</td>
<td>24/25</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Number of patients with multiple sensitizations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLIT</td>
<td>19/35</td>
<td>21/35</td>
<td>22/35</td>
</tr>
<tr>
<td>Controls</td>
<td>9/25</td>
<td>11/25</td>
<td>11/25</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Indications for Immunotherapy in Allergic Rhinitis

1. Monosensitive allergies
2. Incomplete control with antihistamines on topical medications
3. Patients who do not wish to be on pharmacotherapy
4. Patients who develop side effects from pharmacotherapy
5. Patients who desire a cure
6. Where avoidance measures are impossible or ineffective
7. To prevent the development of asthma in young children
Which asthmatics may receive SLIT?

- Mild intermittent
- Where rhinitis is a dominant symptom
- Mild persistent
Asthma

• Young patients with asthma and monosensitive allergies respond better than adults to immunotherapy.

• SIT or SLIT can be used to supplement drug therapy for asthma in children over 5 years.

• Give to asthmatics with pollen, dust mite or cat allergy
Immunotherapy is invariably a form of combination therapy.
Assessing the outcome of immunotherapy using Quality of Life and a Global Score
How do we assess efficacy of immunotherapy?

- Symptom score?
- Medication requirements?
- Quality of life?
- Cost effectiveness?
Difficulties in interpreting studies of efficacy in rhinitis?

- Symptoms are variable
- Some are more troubled by symptoms than others
- Medications to control symptoms vary
- Placebo gives up to 30% improvement
- 50% above placebo effect?
- Is it worth the effort?
Pilot study

- 20 patients on SLIT in clinic situation
- 7-49 years
- Monosensitive to house dust mites
- 2-3 years Der-p-1 – Der-f-1 SLIT
- Baseline medication
- Baseline QOL score (Juniper)
- 6-monthly assessment up to 3 years
- Calculation of Global Score
### Global Score

#### A. Juniper Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>18</td>
</tr>
<tr>
<td>Nasal</td>
<td>48</td>
</tr>
<tr>
<td>Non-Nasal</td>
<td>60</td>
</tr>
<tr>
<td>Sleep, Emotional, Practical</td>
<td>72</td>
</tr>
</tbody>
</table>

#### B. Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine</td>
<td>20</td>
</tr>
<tr>
<td>Intranasal steroid</td>
<td>30</td>
</tr>
</tbody>
</table>

**Total** 248
Results

- 20 Patients: 12 Females, 8 Males
- Mean change in Juniper Score = 1.81
- Mean score of worst nasal baseline symptom = 5
- Mean score of worst nasal 18-36 month symptom = 1.75
- % improvement in QOL = 52%
- 15 patients: 2 years
  9 patients: 3 years
Mean Total Nasal Score
(Max 48, 63% reduction)

Baseline: 27.4
Last Visit: 10.3

63% reduction from baseline.
Combined Sleep, Emotional & Practical Problem Score (Max 72, 49% reduction)

Baseline: 38.1
Last Visit: 19.4
Mean Total Medication Score
(Max 50, 75% reduction)
Global Score
(Max 248, 62% reduction)
Conclusions

1. Rhinitis patients are heterogeneous and should be carefully selected for SLIT.

2. Assessing nasal, non-nasal symptoms (QoL), severity of disease expression and requirements for medication serially is clinically useful to assess efficacy.

3. Patients vary in their scoring in the 5 different domains assessed.

4. All patients in the study improved between 49% and 75% in all of the domains (of 30% known placebo effect).
5. Improvement in Global Score was 62% confirming that SLIT was highly effective in **ALL** the patients properly selected in this study.

6. Improvement in the QOL was 52% overall.

7. SLIT is highly cost effective.

8. Comparative improvements in a control group treated with conventional rhinitis treatment should be compared.
Will wider usage by non-specialists in unselected patients lead to misuse or abuse?
Assessing the clinical response to sublingual allergen immunotherapy

- Not all “respond”
- How can we assess “response”?
- Can we predict a responder phenotype?
Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy: a statement of the World Allergy Organization (WAO) task force

Canonica GW, Baena-Cagnani C, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, Passalacqua G, Potter PC, Valovirta E.
Allergy 2007; 62: 317-324
Addressing the problems with clinical trials with SLIT

1. Mostly small studies
2. Baseline symptom scores and medication requirements need long observation times, especially for perennial allergens
3. Patients have variable degrees of severity, intensity, duration of symptoms and exposure to allergens
4. Patients enter trials at variable times on the natural history of the disease
5. Some may be going into spontaneous remission when entering a trial
6. Prolonged (>2yrs) immunotherapy trials with perennial allergens are needed
Assessment of Outcome

1. Symptom score
2. Medication requirements
3. Quality of life
4. Objective measurements, e.g.:
   - Lung function
   - Specific IgE
   - Cytokine profiles in the nose
   - Eosinophils in target tissues
   - ENO
   - Organ challenge
   - Post challenge tryptase
   - Eosinophilia and ECP
   - Effects on in vitro allergen stimulated cytokine release (e.g. from lymphocytes or basophil mediator release)
Possible influences on outcome in SLIT

- Specific IgE level
- Exposure to allergen
- Other allergens in the vaccine
- Total dose of SLIT
- Frequency of SLIT
- Dominant allergen
- Polysensitive
- Duration of SLIT
Quality of life and symptom assessment in sublingual immunotherapy (SLIT) for patients with house dust mite perennial rhinitis: definition of a responder profile.

Methods

Design
- 60 patients DBPC Phase IV study
- 39 patients on active 300IR Der pteronyssinus vaccine
- 21 on placebo vaccine for 2 years

Patients
- Symptomatic >2 years
- Der p 1 >4mm wheal
Monitoring

- Adverse events
- Global symptom evaluation
- Total 5 symptoms score physical examination (TSS5)
- Juniper Rhinitis QOL at 6 month intervals
- Medication scores
# Definition of Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Improved QOL or TSS5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Intermediate Responders</td>
<td>30-59%</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>&lt;30%</td>
</tr>
</tbody>
</table>
No significant difference in baseline measurements

- Height
- Mass
- Age (18-60 years)
- Sex
- TSS5
- Medication
- Non-nasal symptoms
- Global evaluation of rhinitis
- Wheal diameter Der p 1
- Total number of IR taken in the first 6 weeks
## Quality of Life Assessments

<table>
<thead>
<tr>
<th>Activity</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>48</td>
</tr>
<tr>
<td>Non Nasal</td>
<td>60</td>
</tr>
<tr>
<td>Sleep emotional practical</td>
<td>72</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>198</strong></td>
</tr>
</tbody>
</table>
Bar Graph of Baseline and End Point non-Nasal Symptom Score (TNNSS)

Baseline
- Active: 7.91
- Placebo: 6.78

End point
- Active: 3.53
- Placebo: 4.25
Heterogeneity of response within active and placebo groups for nasal and QOL parameters

<table>
<thead>
<tr>
<th></th>
<th>Responder*</th>
<th>Non Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;60%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Active (32)</td>
<td>QOL 18</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>TNSS 18</td>
<td>14</td>
</tr>
<tr>
<td>Placebo (16)</td>
<td>QOL 4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>TNSS 6</td>
<td>10</td>
</tr>
</tbody>
</table>
Outcome

1. Clinical responders TSS5
   % responders in active group versus placebo group significantly higher (p=0.05)

2. QOL responders
   % responders for global symptom higher in active group (p=0.04)

3. Correlation between TSS5 + QOL overall
   Odds ratio 15 (p=<0.0001)

4. Correlation between TSS5 + QOL in active group
   Odds ratio 8.75 (p=<0.006)
Adverse events

1. Oral pruritis
   (Active 53.8%, Placebo 33%)

2. Glossitis
   (Active 15.4%, Placebo 14.3%)

Note: There have been 7 recent reports of systemic reactions to SLIT which although rare can occur if patients are not carefully selected.
Conclusions

1. Patients were heterogeneous in their response to SLIT over a 2 year period using a 60% cut off.
2. Patients may be heterogeneous in their response to different house dust mite species and antigens (microarray studies in progress).
3. “Responders” found in placebo group. May be due to “spontaneous remission”.
4. QOL correlates extremely well with symptom score. It is a good index of patient satisfaction.
5. Studies on correlation between response and cytokines were then analysed.
Changes in peripheral blood mononuclear cell IL5/IFNγ release associated with clinical improvement in sublingual immunotherapy and placebo treated patients with persistent allergic rhinitis

Nurse B, Brown N, Combebias A, Potter PC

Paper to be submitted 2011
Results

IL5/IFN\(\gamma\) ratio:
(Defined as the ratio of IL5 (pg/ml) to IFN\(\gamma\) (pg/ml) released in each culture)

A) SLIT and Placebo patients

In the Good, Med and NI groups, changes in IL5/IFN\(\gamma\) ratio over time were similar in SLIT and Placebo treated patients

For further analysis patients were divided only on their clinical response
B) All patients

At 24 months, the IL5/IFNγ ratio in the Good group was significantly decreased relative to 0 months \((p=0.0008; \text{ Wilcoxon Matched Pairs})\) and relative to the Med group at 24 months \((p=.04; \text{ Kruskal-Wallis})\)
Results

Proliferation:

**Spontaneous proliferation** was low relative to the stimulated proliferation in the majority of cultures. Median (10 & 90 percentile) values for the whole cohort were: 651 dpm (184 & 2586 dpm) at baseline and 3544 dpm (607 & 11557 dpm) at 24 months.

**HDM-stimulated proliferation**: No significant changes in proliferation were found.

(Δ Proliferation: HDM-stimulated minus spontaneous proliferation)
A significant decrease in the IL5/IFNγ ratio is associated with clinical improvement in persistent allergic rhinitis. In the patient group with ≥ 60% improvement on both TSS5 and Juniper Quality of Life scores at 24 months, HDM-stimulated IL5/IFNγ release from PBMC was significantly decreased at 24 months both relative to 0 months, and to the intermediate improvers group at 24 months. A decreased Th2/Th1 cytokine ratio could, however, be a cause, or a marker of clinical improvement.
Conclusions

1. SLIT is a highly effective treatment for carefully selected patients with allergic diseases and can be given at home.

2. In addition to mite, cat and pollen allergies, SLIT should be considered experimental for occupational (e.g. Latex) and food allergies, where it should only be done in specialised allergy centres under surveillance.