Allergen-specific Immunotherapy (SIT) for Allergic Rhinitis (AR)

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Introduction
1. AR treatment
2. Drug formulations
Allergic Rhinitis (AR)

• AR is a global health problem

• It causes major illness and disability worldwide

• It affects approximately one quarter of the European population

• Its incidence is believed to be increasing

• Although the condition is sometimes not regarded as a severe disease, it commonly affects:
  • Quality of life
  • School performance, work productivity

In Korea

• Changes in number of patients with environmental diseases from 2002 to 2007

• Total number of patients with allergic diseases
  ◦ Number of patients with AR
  White bar: asthma, Black bar: atopic dermatitis

*2008 National Health Insurance Corporation (NHIC)*
AR treatment

Allergen avoidance (difficult for airborne allergens such as grass pollen)

Symptomatic medications
- Antihistamines
- Nasal corticosteroids
- Decongestants
- Leukotriene receptor antagonists

Specific Immunotherapy (SIT)
- Subcutaneous Immunotherapy (SCIT)
- Sublingual Immunotherapy (SLIT)
  - Drop-based formulation
  - Allergy Immunotherapy Tablets (AITs)
### How does SIT differ from symptomatic therapies?

<table>
<thead>
<tr>
<th></th>
<th>SIT</th>
<th>Symptomatic medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces symptoms</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prevents development of asthma</td>
<td>✓</td>
<td>❌</td>
</tr>
<tr>
<td>Prevents onset of new sensitizations</td>
<td>✓</td>
<td>❌</td>
</tr>
<tr>
<td>Persistent effect after end of treatment</td>
<td>✓</td>
<td>❌</td>
</tr>
<tr>
<td>Induces immunological tolerance</td>
<td>✓</td>
<td>❌</td>
</tr>
<tr>
<td>Reduces use of symptomatic medication</td>
<td>✓</td>
<td>❌</td>
</tr>
</tbody>
</table>

*Antihistamines and corticosteroids

- **SIT is the only treatment that targets the underlying cause of allergy and builds up an immunological tolerance to specific allergens.**

- **SIT prevents the development of asthma and new sensitizations, provides sustained symptom prevention, and reduces the need for symptomatic medication.**

- **Current symptomatic medications reduce symptoms but do not treat the underlying cause of allergy.**
Available SCIT products in Korea

- Allergopharma (Germany)
- Allergy Therapeutics (UK)
- Hollister Stier (USA)
3 Major companies (SLIT)

- ALK Abello: STU, specific treatment unit
- Stallergenes: IR, index of reactivity
- Allergopharma

SLITone®

Staloral300®

ALLERSLIT® forte
• Single grass allergen tablet
• Timothy grass ( 큰조아재비, *Phleum pratense*)
• Tablet formulation: more stable, more precise dosage

1. The tablet should be taken from the blister card with dry fingers
   ...placed under the tongue
   ...where it will dissolve within seconds

4. Swallowing should be avoided for 1 minute after taking the tablet.
   Food and drink should be avoided for 5 minutes after taking the tablet.
Proposed mechanism of SIT
Common cellular processes mediate the allergic response

Allergen presentation to T cells → Mast cell sensitization/leukocyte recruitment → Release of inflammatory mediators → Acute/chronic allergic airways responses → Anatomical differences in upper/lower airways lead to different symptoms

Upper airways (nasal mucosa)
- Acute inflammation
- Increased vascular permeability
- Airway obstruction

Lower airways (bronchial mucosa/smooth muscle)
- Chronic inflammation (via eosinophils)
- Increased vascular permeability
- Airway obstruction
- Acute bronchial constriction/bronchial smooth muscle hypertrophy/hyperreactivity to bronchoconstrictors
- Disruption to bronchial epithelia (remodelling)

Allergic rhinitis
- Sneezing, rhinorhoea, nasal congestion, itching

Bone marrow
- Systemic propagation of inflammation between nose and bronchi (cross-talk) via mediator-driven upregulation of basophil and eosinophil progenitor commitment

Asthma
- Wheezing, coughing, breathing difficulties

Th2
- Increased mucus production
- Histamine, leukotrienes, prostaglandins, neutral proteases, chemokines, other cytokines

Th0
- IL-4, IL-13

IgE

Dendritic cell

B cell

Mast cell

Eosinophil

Basophil

Histamine, leukotrienes, prostaglandins, neutral proteases, chemokines, other cytokines

IL-4, IL-13

FIocchi A & Fox AT. Arch Dis Child Educ Pract Ed 2011
SIT mechanism of action
Explaining the differences with symptomatic medication

- Specific repeated administration of allergens to allergic individuals
  → activates immunomodulatory mechanisms
  → induces ‘immune tolerance’

SIT mechanism of action

In contrast to symptomatic medications, SIT has the potential to affect the underlying allergic disease processes

Adapted from Fiocchi A & Fox AT. Arch Dis Child Educ Pract Ed 2011
Immunological changes after SIT

- Increase in IgG (allergen-specific IgG4)
- Transient increase in IgE
- Increase in IgA
- Increase in IL-10 production
- Suppression of eosinophil recruitment and activation in target organs
- Decreased serum ECP levels
- Suppression of allergen-specific T-cell responses
Possible mechanism of action of SLIT

• After the presentation of appropriate amounts of allergen by the sublingual route, Th0 cells are stimulated toward the T regulatory (Treg) phenotype

• Treg cells suppress the activity of Th2 cells and promote the production of IgG and IgA antibodies rather than IgE

Adapted from Frew, NEJM, 2008
Specific antibody levels (N=31)

- Patients in group I and group II received SLIT with a standardized Dp+Df 50/50 extract (Stallergens, Antony, Paris, France) for 6 and 12 month, respectively.
- Downregulation of Der-p-1-specific IgE production
- At the end of SLIT, IgA levels did not differ between patients and controls.

*Bahceciler et al, 2005*
Mechanism of SLIT

- Reduced the expression of IL-5 and enhanced the expression of IL-10 in PBMCs stimulated with the allergen

Savolainen et al, 2006
IgG4

• **Serum allergen-specific IgG4**
  • Clear dose-response to maintenance doses of allergen

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. of subjects</th>
<th>Significant increase in IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>161</td>
<td>59 (37%)</td>
</tr>
<tr>
<td>Low</td>
<td>103</td>
<td>45 (44%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>179</td>
<td>127 (71%)</td>
</tr>
<tr>
<td>high</td>
<td>312</td>
<td>278 (89%)</td>
</tr>
</tbody>
</table>

• **Serum allergen-specific IgG4** levels increase 2- to 30- fold by 12 months and then reached a plateau

• *IgG4* is controlled by *IL-10* which downregulate T cell function and B cell switching to IgE

*Hawrylowicz et al, 2005*
T regulatory cells in SLIT

- Patients with birch pollen allergy, SPT, specific IgE (+) to birch
  - SLIT: updosing for 4 weeks, maintenance: 4.5 µg of Bet v 1
  - PBMCs were collected before, after 4 weeks and after 52 weeks of SLIT

CD25+ Anti-IL-10

Bohle et al, JACI 2007
Effect of SLIT on cellular response

- A significant reduction of T cell proliferation compared with untreated atopic patients
- SLIT normalizes cytokine profile of PBMCs
  - PBMCs from healthy subjects: a good IL-10 response to allergen
  - Cells from untreated atopic subject fail to produce IL-10
  - Cells from patients treated with SLIT respond similarly to normal subjects

_Ciprandi et al, 2005_

This preliminary study confirms reduced T-cell proliferation and provides the evidence of peripheral IL-10 production in successfully treated SLIT patients like SCIT.
Tolerogenic and proinflammatory cells in the oral immune system

- Allergens bind to epithelial cells within minutes, then cross the mucosa within the next 15–30 min.
- Being captured and processed by Langerhans cells and myeloid DCs.
- Migrate to cervical lymph nodes within 12 to 24 h, where they interact with naive CD4+ T cells, inducing Th1 and Treg cells.
Identifying suitable patients for SIT
Patient selection
For whom should we consider SIT?

- **Current guidelines**
  ARIA treatment guidelines, 2008
  - SIT is indicated in patients insufficiently controlled on symptomatic therapies

- **Possible future guidelines**
  - Future treatment strategies may involve *SIT being considered a first-line treatment* – further evidence should be obtained to support this approach
Efficacy
SIT is highly effective in existing AR

❖ Short-term efficacy
  • SIT is efficacious against the symptoms of AR
    • Meta-analyses of randomized, controlled trials (RCTs) of SIT showed significant reductions in symptoms and symptomatic medication requirement in adults and children
    • Additional subsequent studies support these findings, and show improved quality of life

❖ Long-term efficacy
  • The clinical effects of SIT are sustained for several years after treatment completion
    • Symptom scores/medication use significantly reduced vs. control groups for up to 12 years after the completion of SIT in children with AR and/or asthma
    • Similar effects seen in adults
SCIT efficacy

• Dose dependent
• Appears to be dependent on duration of treatment

• The overall efficacy of SCIT for AR was confirmed in a Cochrane meta-analysis
  • A significant overall reduction in the *symptoms scores* (Standardized Mean Difference [SMD] -0.73; 95% CI -0.97 to -0.50; p<0.00001) and *medication scores* (SMD -0.57; 95% CI -0.82 to -0.33; p<0.00001) was seen in the SCIT-treated groups compared with placebo
The Preventive Allergy Treatment (PAT) study
SIT reduces symptoms of rhinitis and conjunctivitis

- Symptoms of rhinitis and conjunctivitis measured by visual analogue score (VAS) were significantly reduced in the SIT group compared with the control group (p<0.05)

![Graph showing change from baseline in mean VAS score (±SEM) for rhinitis and conjunctivitis over years 3, 5, and 10, with p-values for comparison between SIT and control groups.](image)

Jacobsen L et al, Allergy 2007
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age Range, yr</th>
<th>Active/Placebo</th>
<th>Dropout Active/Placebo</th>
<th>Allergen</th>
<th>Duration</th>
<th>Dose</th>
<th>Symptom ↓, %</th>
<th>Medication ↓, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balda et al</td>
<td>1998</td>
<td>18–58</td>
<td>51/60</td>
<td>1/5</td>
<td>Mixed trees (3)</td>
<td>7 wk preseason</td>
<td>1–3 µg</td>
<td>28</td>
<td>62</td>
</tr>
<tr>
<td>Jutel et al</td>
<td>2005</td>
<td>25 (median)</td>
<td>29/28</td>
<td>0</td>
<td>Mixed grass (5)</td>
<td>21 mo</td>
<td>Cumulative: 490 µg total</td>
<td>36.5</td>
<td>36.5</td>
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<tr>
<td>Corrigan et al</td>
<td>2005</td>
<td>18–60</td>
<td>77/77</td>
<td>11/15</td>
<td>Mixed grass (6)</td>
<td>2 consecutive pre-seasons</td>
<td>30 µg (median max.)</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergoid absorbed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frew et al</td>
<td>2006</td>
<td>18–60</td>
<td>203/104</td>
<td>16/15</td>
<td>Single grass</td>
<td>10 wk</td>
<td>2 µg 20 µg depot (8 injections)</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Colas et al</td>
<td>2006</td>
<td>18–50</td>
<td>41/19</td>
<td>2/1</td>
<td>Russian thistle</td>
<td>4 wk preseason</td>
<td>Cluster 45 µg/ml 450 µg/ml Polymerized Cumulative: 597.65 µg</td>
<td>33</td>
<td>11 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pauli et al</td>
<td>2008</td>
<td>18–50</td>
<td>98/36</td>
<td>15/6</td>
<td>Birch</td>
<td>2 yr</td>
<td>Recombinant Licensed Natural Maintenance 15 µg</td>
<td>52</td>
<td>65</td>
</tr>
</tbody>
</table>

Cox et al, 2011
SLIT efficacy

• Many DBPC randomized trials on SLIT have been published

• Several trials have confirmed the clinical efficacy of SLIT in AR caused by grasses, trees, ragweed, Parietaria and mites

• A meta-analysis of SLIT for AR (22 trials and 979 patients) → a significant reduction in both symptoms (SMD -0.42; 95% CI -0.69 to -0.15; p=0.002) and medication use (SMD -0.43; 95% CI -0.63 to -0.23; p=0.00003)

  Wilson et al, 2005

• Results were similar in magnitude to those observed in a comparable study of SCIT

  Durham et al, 2008
## SLIT efficacy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age Range, yr</th>
<th>Active/Placebo</th>
<th>Dropout Active/Placebo</th>
<th>Allergen</th>
<th>Duration</th>
<th>Single Dose (If Mix Total is Given), µg</th>
<th>Cumulative Monthly Dose</th>
<th>Symptom, ↓ %</th>
<th>Medication, ↓ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durham et al(^1)</td>
<td>2006</td>
<td>18–66</td>
<td>569/286</td>
<td>39/26</td>
<td>Grass Phy p5 3 doses Tablets</td>
<td>6 mo</td>
<td>0.5</td>
<td>15 µg</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dahl et al(^2)</td>
<td>2006</td>
<td>18–65</td>
<td>316/318</td>
<td>42/46</td>
<td>Grass Phy p5 Tablets</td>
<td>6 mo</td>
<td>15</td>
<td>450 µg Cumulative 6-mo dose: 4.5 mg</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Dahl et al(^2)</td>
<td>2006</td>
<td>18–64</td>
<td>74/40</td>
<td>13/8</td>
<td>Grass Phy p5 Tablets</td>
<td>5 mo</td>
<td>15</td>
<td>450 µg</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>Roder et al(^2)</td>
<td>2007</td>
<td>6–18</td>
<td>108/96</td>
<td>26/24</td>
<td>5 Grass (G5) Mix Solution</td>
<td>2 yr</td>
<td>21</td>
<td>168 µg</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Didier et al(^4)</td>
<td>2007</td>
<td>25–47</td>
<td>472/156</td>
<td>59/10</td>
<td>5 Grass (G5) Mix Tablet</td>
<td>6 mo</td>
<td>8</td>
<td>240 µg</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>De Blay et al(^5)</td>
<td>2007</td>
<td>12–41</td>
<td>61/57</td>
<td>8/8</td>
<td>3 Grass Mix (G3) Solution</td>
<td>10 mo</td>
<td>21</td>
<td>250 µg Cumulative 10-mo dose: 2.5 mg</td>
<td>None</td>
<td>22 (P = .02)</td>
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<tr>
<td>Pfaar and Klimek(^6)</td>
<td>2008</td>
<td>17–59</td>
<td>94/91</td>
<td>17/9</td>
<td>6 Grass (G6) Mix Solution</td>
<td>2 yr</td>
<td>40</td>
<td>1.2 mg</td>
<td>Combined symptom-medication score benefit for AUC (&lt;.01) and VAS</td>
<td></td>
</tr>
</tbody>
</table>
### Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Range</th>
<th>N Gender</th>
<th>Route</th>
<th>Duration</th>
<th>Dose</th>
<th>Peak</th>
<th>N Reactors</th>
<th>N Control</th>
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</thead>
<tbody>
<tr>
<td>Wahn et al</td>
<td>2009</td>
<td>5-17</td>
<td>139/139</td>
<td>4/8</td>
<td>5 Grass (G5) Mix Tablets</td>
<td>8 mo</td>
<td>20</td>
<td>600 μg</td>
<td>28</td>
</tr>
<tr>
<td>Ott et al</td>
<td>2009</td>
<td>20-50</td>
<td>142/67</td>
<td>3/1</td>
<td>5 Grass (G5) Mix Solution</td>
<td>5 yr, 4 seasons</td>
<td>21</td>
<td>630 μg Cumulative dose: 1.5 mg major allergen/season</td>
<td>47</td>
</tr>
<tr>
<td>Bufe et al</td>
<td>2009</td>
<td>5-16</td>
<td>126/127</td>
<td>12/7</td>
<td>Grass Phl p5 Tablets</td>
<td>6 mo</td>
<td>15</td>
<td>450 μg</td>
<td>24</td>
</tr>
<tr>
<td>Horak et al</td>
<td>2009</td>
<td>18-50</td>
<td>45/44</td>
<td>3/4</td>
<td>5 Grass (G5) Mix Tablets</td>
<td>4 mo</td>
<td>20</td>
<td>600 μg</td>
<td>29</td>
</tr>
<tr>
<td>Durham et al</td>
<td>2006</td>
<td>18-65</td>
<td>170/138</td>
<td>—</td>
<td>Grass Phl p5 Tablets</td>
<td>3 yr</td>
<td>15</td>
<td>450 μg</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>—</td>
<td>157/126</td>
<td>13/12</td>
<td>—</td>
<td>No Tx</td>
<td>Off Tx</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>Skoner et al</td>
<td>2010</td>
<td>18-50</td>
<td>75/40</td>
<td>12/6</td>
<td>Ragweed Amb a 1 Solution</td>
<td>23 wk</td>
<td>4.8</td>
<td>83 μg low</td>
<td>15 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>823 μg high</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

*Cox et al, 2011*
SLIT vs. SCIT

• The magnitude of effect on clinical parameters in 3 large clinical grass-tablet trials\(^1-3\) is similar to that of SCIT\(^4\)
  
  • Symptom score reduction: SLIT 21%–37% versus SCIT 32%
  • Medication score reduction: SLIT 29%–46% versus SCIT 41%

Comparison of effective dose range

- Effective SLIT cumulative monthly dose (CMD) may be as high as 10-100 times the usual monthly SCIT maintenance dose.

### Effective dose range for SCIT and SLIT

<table>
<thead>
<tr>
<th>Allergen Extract</th>
<th>Major Allergen</th>
<th>SCIT</th>
<th>SLIT</th>
<th>Monthly Dose at Maintenance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dust Mite F</td>
<td>Der f 1</td>
<td>10 μg</td>
<td>No studies using only Der F1</td>
<td>10 μg&lt;sup&gt;132&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dust Mite P</td>
<td>Der p 1</td>
<td>7–11.9 μg&lt;sup&gt;51,132,133&lt;/sup&gt;</td>
<td>0.86–3.75 μg&lt;sup&gt;134–136&lt;/sup&gt;</td>
<td>7–11.9 μg&lt;sup&gt;51,132,133&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dust mite P + F or unlisted</td>
<td>Der P 1 and Der F 1</td>
<td>7–21 μg&lt;sup&gt;51&lt;/sup&gt;</td>
<td>7.6–84 μg&lt;sup&gt;137–140&lt;/sup&gt;</td>
<td>7–21 μg&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ragweed, short</td>
<td>Amb a 1</td>
<td>6–12 μg&lt;sup&gt;21,141,142&lt;/sup&gt; (6–12 μg 1000–4000 AU)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>314 μg tablets,&lt;sup&gt;39,143&lt;/sup&gt; 314 μg solution 314 μg&lt;sup&gt;143&lt;/sup&gt;</td>
<td>6–12 μg&lt;sup&gt;21,141,142&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grass, timothy</td>
<td>Phl p 5</td>
<td>4–50 μg&lt;sup&gt;23,144&lt;/sup&gt; (1000–4000 BAU)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>15 μg&lt;sup&gt;41,44,82,125&lt;/sup&gt;</td>
<td>4–50 μg&lt;sup&gt;23,144&lt;/sup&gt; every 2–6 wk</td>
</tr>
<tr>
<td>Grass, Bermuda</td>
<td>Cyn d 1</td>
<td>4.6–63.3 μg (300–1500 BAU)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>None</td>
<td>4.6–63.3 μg</td>
</tr>
<tr>
<td>3, 5, 6, Grass mix</td>
<td>G3, G5, G6</td>
<td>4–44 μg&lt;sup&gt;121,122,145–147&lt;/sup&gt; (1000–4000 BAU)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>20–25 μg&lt;sup&gt;42,45,127,129,148&lt;/sup&gt;</td>
<td>4–44 μg&lt;sup&gt;121,122,145–147&lt;/sup&gt;</td>
</tr>
<tr>
<td>Birch</td>
<td>Bet v 1</td>
<td>3.28 μg&lt;sup&gt;150&lt;/sup&gt;, 12 μg&lt;sup&gt;151&lt;/sup&gt;; 15 μg&lt;sup&gt;124&lt;/sup&gt; (No US standardized product)</td>
<td>49.2 μg&lt;sup&gt;150&lt;/sup&gt; Not provided&lt;sup&gt;152,153&lt;/sup&gt;</td>
<td>3.28 μg&lt;sup&gt;150&lt;/sup&gt;, 12 μg&lt;sup&gt;151&lt;/sup&gt;; 15 μg&lt;sup&gt;124&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mixed Trees</td>
<td>Group 1 major allergen&lt;sup&gt;120&lt;/sup&gt; T3 = Bet v 1, Cor a 1, Aln g 1&lt;sup&gt;154&lt;/sup&gt;</td>
<td>1–12 μg&lt;sup&gt;120&lt;/sup&gt; (No US standardized product)</td>
<td>1.8–15 μg&lt;sup&gt;154&lt;/sup&gt;</td>
<td>1–12 μg&lt;sup&gt;120&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dog</td>
<td>Can f 1</td>
<td>15 μg&lt;sup&gt;24,27&lt;/sup&gt; (No standardized US product)</td>
<td>None</td>
<td>15 μg&lt;sup&gt;24,27&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
The preliminary results of a 13-year follow-up study demonstrated that the optimal duration of a SLIT course could be at least 4 years.
Optimal dose of 5-grass pollen tablets

- Both the 300IR and 500IR groups had highly significant improvements in Rhinoconjunctivitis Total Symptom Score.
- Rhinoconjunctivitis Quality of Life Questionnaire score confirmed the optimal dosage 300IR at peak and at the end of the pollen season (Horak et al, 2009).
No induction phase

• In a study of 855 patients that compared 3 doses of grass allergen tablets administered with no induction phase, it was reported that the tablet was well tolerated and showed “no safety concerns”

• These studies also suggest that there is no need for a buildup phase with SLIT

Durham et al, 2006
AR and asthma
The impact of AR in childhood

• AR is not a trivial disease in childhood
• It reduces quality of life and may be a precursor to asthma

- Reduction in quality of life
  - Symptomatic discomfort
  - Associated issues:
    - Impaired learning
    - Sleep deprivation
    - Isolation from peers
    - Emotional problems
    - Tiredness
    - Limitations in daily activities & family life

- A precursor to asthma
  - ARIA guidelines, 2008: “Allergic and non-allergic rhinitis are risk factors for asthma”
  - Numerous studies show AR is associated with subsequent development of asthma
Increased incidence of asthma in AR patients
A retrospective analysis

- **AR, being female, having pets at home, and being sensitized to Parietaria judaica** all significantly increase the risk of developing asthma

Odds ratios (95% confidence interval) for factors predicting the development of new onset asthma

Model – Multivariate (significant factors only)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of AR</td>
<td>7.81</td>
<td>3.05–20.04</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.83</td>
<td>1.79–4.49</td>
</tr>
<tr>
<td>Presence of pets in the home</td>
<td>2.02</td>
<td>1.27–3.21</td>
</tr>
<tr>
<td>Sensitization to <em>Parietaria judaica</em></td>
<td>2.01</td>
<td>1.16–3.47</td>
</tr>
<tr>
<td>Treatment with allergen Specific Immunotherapy**</td>
<td>0.53</td>
<td>0.32–0.86</td>
</tr>
</tbody>
</table>

Polosa R, et al. 2005
Childhood AR increases the risk of developing asthma

Childhood AR-associated risk of asthma by period of asthma onset

Hazard ratio: increased asthma risk

- Adult life (20–44 years): 2.19*
- Adolescence (12–20 years): 4.34*
- Preadolescence (7–12 years): 7.12*

Period of asthma onset

Childhood AR has been associated with a significant 2- to 7-fold increase in the incidence of asthma in later life

Burgess JA et al. JACI 2007
Clinical implication

“Asthma burden in later life might be reduced by more aggressive treatment of AR in early life”

Burgess JA et al. JACI 2007
Prevention of asthma development
End of study treatment period

Retrospective trial, subgroup analysis, adults with AR, ≥3 years SIT treatment, N=332

Development of asthma in AR patients

The incidence of new asthma in patients with AR was significantly lower in those treated with SIT

Prevention of asthma development
End of study treatment period

Open-label, 3-year, randomized, controlled trial, children with AR, N=113

Patients with AR – 3-year follow-up

The likelihood of developing asthma after 3 years was 3.8 times greater in patients NOT receiving SLIT

Novembre E et al. JACI 2004
International guidelines

• SIT is the only treatment that:
  • May effect the natural course of allergic disease
  • May prevent the development of asthma in AR patients
  • Influences IgE-mediated inflammation as a whole

  **WHO position paper, 1998**

• SLIT may alter the natural history of respiratory allergy by preventing the onset of new skin sensitizations and/or reducing the risk of asthma onset
  • Two randomized, open, controlled studies suggest that SLIT reduces the risk of asthma onset in children with rhinitis
  • Two randomized, open studies show that SLIT reduces the onset of new allergen sensitizations
  • One randomized, DBPC trial and one non-randomized, prospective study suggest the persistence of the clinical effects of SLIT for 3–5 years after treatment completion

  **WAO position paper, 2009**
Safety and adverse events of SIT
Safety

SCIT
• Associated with both local and systemic adverse events (AEs)
• But, risk is minimized when administered in a controlled, clinical setting

SLIT
• Studies demonstrating favorable tolerability profile in both children and adults:
  • Meta-analysis of adult and pediatric studies (Cochrane review 2003)

SCIT vs. SLIT
• SLIT has a more favorable tolerability profile than SCIT
  • Study comparing grass SCIT with a grass AIT
    → Both were safe treatments for AR
    → More systemic side effects with SCIT than AIT

Practical Allergy (PRACTALL) consensus report:
“Effective SLIT may be an attractive alternative to SCIT for children, parents and physicians”
Safety and AEs of SLIT

• In all reported DBPC trials, SLIT was well tolerated

• The most frequent AEs being local (oral itching or swelling) or gastrointestinal (nausea, vomiting, diarrhea, and stomachache)

• Overall rate of AEs ranged between 3% and 18% of patients and was less than 1 reaction per 1,000 doses

• Either mild and self-limiting or manageable by a temporary dose reduction
SLIT-related severe AEs

• According to an extensive review of the literature, 14 serious adverse events (mainly asthma) were reported

  Cox et al, 2006

• There were no mortality cases

• Eleven cases with anaphylaxis
  • 3 cases: mixture of multiple allergens
  • 1 case: taking a dose 6-times greater than prescribed
  • 3 cases: natural rubber latex
  • 2 cases: HDM (standardized)
  • 2 cases: previously stopped SCIT d/t severe systemic AEs

  Calderon, 2012
Potential factors associated with anaphylaxis

- No clear predictors for SIT AE have been identified
- *Previous systemic AEs* to SLIT and SCIT and *a history of asthma* appear to be risk factors

**SCIT- and SLIT-related factors**
- Allergen mixtures
- Rush protocol
- Overdose
- Nonstandardized allergens
- Interruption in dose regimen

**Patient-related factors**
- *Previous systemic AE, including anaphylaxis*
- Previous severe local AE
- Acute infection (URI)
- Fever
- Oral infections of lesions to SLIT
- Asthma, especially if severe or uncontrolled
- Emotional stress
- High pollen counts

*Calderon, Allergy, 2012*
Latest developments in SIT
Latest developments in SIT
New formulations

❖ Allergy Immunotherapy Tablets (AITs)
- Sublingual tablets for home administration, available as:
  - Grass AIT (GRAZAX, SQ-standardised Phleum pratense, ALK)
  - 5-grass mix pollen allergen extract tablets (Oralair, Stallergenes)

Adults with AR
- Both formulations shown efficacy and favorable tolerability profiles in the first pollen season of treatment
- Sustained effects after the completion of treatment

Children with AR
- Both formulations shown significant efficacy and favorable tolerability in the first pollen season of treatment
Future of SIT
Prophylaxis immunotherapy

• SLIT containing HDM, Timothy grass, and cat allergens
  • Young children between the ages of 18 and 30 months
  • History of atopic dermatitis or food allergy
  • Without sensitization to inhalant allergens
  • Parent or one sibling has a well documented history of atopy

• Development of allergen sensitization and asthma will be monitored for 3 years after 1-year daily treatment with SLIT or placebo

• If the trial is successful, *the dream of prophylaxis immunotherapy for allergic disease may be finally realized*

*Holt et al, 2007*
SNUH experiences
Clinical and immunologic effects of early sublingual immunotherapy in house-dust mite-allergic rhinitis

Seung-Tae Kim, M.D., Yang-Gi Min, M.D., a

ABSTRACT
Background: There have been reports on sublingual immunotherapy (SLIT) for house-dust mite (HDMs). This study aimed to investigate the efficacy of SLIT in treating mite-allergic rhinitis.

Methods: Fifty-eight patients with mite-allergic rhinitis were included in this study. Symptom scores, blood eosinophil counts, and specific IgE levels were measured at baseline and after 6 and 12 months of treatment.

Results: All of the symptoms and blood eosinophil counts and total IgE did not change significantly after 6 months of SLIT. At 12 months, significant reductions in symptom scores and blood eosinophil counts were observed, and specific IgE levels for mites were reduced.

Conclusion: SLIT improved symptoms and specific IgE levels, and specific IgE levels for mites were reduced. SLIT was effective in treating mite-allergic rhinitis.

Key words: Allergic rhinitis, mites, patient selection, sublingual immunotherapy

INTRODUCTION
The incidence of allergic rhinitis (AR) in the general population is currently around 10%-20%. Medical costs for AR treatment are increasing, and considering comorbid diseases including asthma, the treatment of AR has become more than just treating the rhinitis itself. AR treatment can be classified into four categories: (1) avoidance and environmental control, (2) pharmacotherapy, (3) surgical treatment, and (4) immunotherapy. Avoidance and environmental control is the safest way, but these are not always feasible. Intranasal corticosteroids and oral antihistamines have been accepted to be effective with fewer adverse effects. However, medical therapy only reduces allergic symptoms rather than reversing basic immunologic profiles of the AR patients. Surgical treatment is usually performed to correct structural problems which can aggravate nasal allergic symptoms and reduce the effective delivery of intranasal corticosteroids.

Allergen-specific immunotherapy (ST) has been studied and used for 1 century since Noon’s first report in 1911. ST is the only treatment option that modified fundamental allergic mechanisms by inducing desensitization. At first, ST was used for allergic diseases caused by pollen allergens, such as hay fever or
Clinical efficacy of 1-year HDM SLIT in children and adults (N=76)

- Changes in TNSS

- Changes in AMS

△TNSS: 5.1

△TNSS: 5.3

△score: 57.2

△score: 35.7

Youngsters (n=54)  Adults (n=22)

Youngsters (n=49)  Adults (n=20)

(in Press)
Efficacy and safety of once-daily SLIT without updosing in AR patients (N=153)

Changes in TNSS

• Group 1, Pangramin (N=75)
  Initial: 6.3
  6 month: 3.4

• Group 2, SLITone (N=78)
  Initial: 8.7
  6 month: 3.7

P = 0.028
Changes in AMS

- **Group 1 (N=75)**
  - Initial: 116.2
  - 6 month: 74.1

- **Group 2 (N=78)**
  - Initial: 123.3
  - 6 month: 53.1

- Group 1: Drop-out rate: 20/75 (27%)
- Group 2: Drop-out rate: 21/77 (27%)

$P = 0.037$
Long-term follow-up results of SLIT in SNUH (N=97)

Induction phase (1 month): 97 Patients

Maintenance phase (6 months): 68 Patients

Maintenance phase (1 year): 61 Patients

Maintenance phase (2 years): 54 Patients

Maintenance phase (3 years): 34 Patients

29 Patients drop-out

7 Patients drop-out

7 Patients drop-out

20 Patients drop-out
Changes in TNSS

- 3-year long-term compliance: 35% (34/97)

Changes in AMS

*P < 0.05, compared to baseline
Summary
Summary and conclusions

• SIT represents disease modifying effects for AR

• SIT can reduce the risk of developing asthma and new allergen sensitization

• Early intervention for AR might prevent such disease progression

• Increasing data support the safety and efficacy of SIT and its validity as a first-line treatment option for AR

SIT has been shown to be effective in AR patients and offers potential for more AR patients to receive a disease-modifying therapy that targets the cause, not just the symptoms of AR.
Thank you very much for your attention!