SUBLINGUAL IMMUNOTHERAPY REVIEW AND UPDATE

On-Line COLA Series
February 19, 2010
Linda Cox, MD

Sublingual Immunotherapy: a review and update

Learning Objectives

- SLIT historical background
  - Advantages /disadvantages
  - Status in Europe and US
- Review of meta-analysis & recent studies: non-US and US studies
- SLIT safety
- SLIT immunological changes
- SLIT in the US: practical considerations

What is Sublingual Immunotherapy

Sublingual immunotherapy

From Wikipedia, the free encyclopedia

Sublingual Immunotherapy is method of allergy treatment that uses an allergen solution given under the tongue, which over the course of treatment, reduces sensitivity to allergens. Sublingual immunotherapy, or SLIT, has a very good safety profile and is given at home in adults and children. As more patients are treated with SLIT, additional side effects are being studied. A serious anaphylactic reaction occurred in a patient being treated with multiple allergens prepared from commercially available US extracts.

Speaking the Same Language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

- International Joint Task Force composed of members of academic, clinical & research allergy community
- Existing grading programs formed the template for grading system.
- Drafts circulated at WAO meeting Paris, January, 2009: attended by representatives from regional, national international allergy societies & healthcare organizations & NIAID

Evolution of Specific Allergen Immunotherapy

Linda Cox, MD Disclosure

Allergist: solo private practice
Associate Clinical Professor of Medicine
Nova Southeastern University
Medical advisory board/consultant:
Hollister-Stier, Stallergenes, Schering-Plough,
IDTA, Genentech/Movartis
Speakers bureau: Genentech/Novartis,
Aventis-Sano,lISTA
Organizational interests:
Member of Allergenic Products Advisory Committee of FDA
AAAAI: Board of Directors
Joint Task Force on Practice Parameters
Subcutaneous Immunotherapy: Rationale for Exploring Alternative Approaches

“In 1909, Noon and I began inoculating hay-fever patients with a grass pollen extract...”

Noting the inconvenience of the weekly build-up, Freeman began experimenting with more rapid schedules “Rush desensitization”:

7 year-old girl with horse-asthma desensitized over 4 days but developed urticaria, fluttering heat and felt “funny” and dose was decreased. Able to ride her pony without discomfort.

Probably the 1st reported SCIT systemic.

Recommendations for appropriate sublingual immunotherapy clinical trials

CHAPTER 1: INTRODUCTION AND HISTORICAL BACKGROUND TO SUBLINGUAL IMMUNOTHERAPY

• SCIT currently represents the standard immunotherapy modality, with well ascertained clinical efficacy.
• The rationale proposed for SLIT was to improve the safety and to make the treatment more convenient.
• Adequately powered, well-designed DBPC-RCTs involving hundreds of patients, published in the last 3 years have clearly confirmed the efficacy and the dose dependent effect of SLIT for grass allergens in both adults and children.

Sublingual Immunotherapy: Advantages/disadvantages


Link to the paper: http://journals.lww.com/waojournal/toc/2009/11000


SLIT appears to be associated with fewer and less severe AEs than SCIT

**Side Effects**

The section does not cite any references or sources.

Because sublingual drops are used several times per week, it is necessary to take them at home. This is in contrast to injection therapy, which should always be taken in a medically supervised setting due to the known risks of anaphylaxis (about 1 in 2,000) and death (about 10 in 100,000).

In the early years of SLIT, local reactions were reported in many patients (i.e., itching, nasal symptoms) but these could usually be managed by slow adjustments. Although as of July 2006, no deaths had been reported from SLIT (and many millions of doses have been taken), numerous cases of anaphylaxis have now been reported. In one study, for example, six patients who received a single dose from 8 to 50 years were treated over a 30-day period with a progressive dose of dust mite antigens via SLIT. In this small study, four patients had serious systemic reactions (including a reaction that occurred through the whole body), and just where the allergen is applied. All reactions were associated with swelling or worsening nasal symptoms, and one patient had angioedema and urticaria. sublingual immunotherapy - Wikipedia, the free encyclopedia

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**SLIT Disadvantages**

- In US
  - no FDA-approved formulation = no billing code (CPT) = Medicare/Medicaid and most insurers will not reimburse
  - Need to know optimal dose and dosing schedule for products available in the US
- In general: a number of “unmet needs” (ala unanswered questions): dose, schedule, safety

Canonica et al. Sub-Lingual Immunotherapy World Allergy Organization Position Paper. WAO Journal • November 2009

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**Immunotherapy Practice Patterns Across the Atlantic**

Comparison of allergen immunotherapy practice patterns in the United States and Europe


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**Percentage Of Immunotherapy Sales By Country**

Europe dominates the allergen immunotherapy market

- Germany 22%
- Italy 15%
- France 15%
- Spain 1.9%
- UK & rest of the world 15%
- Norway 14%
- Denmark 14%
- Austria 14%

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**U.S. SCIT Penetration is Minimal**

2006 US Allergic Rhinitis Sales — Total Sales = $6.72 B

Immunotherapy costs = $125 million (2%)

~2.5 million pts (~5%) of AR on immunotherapy

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Provided with permission by Stallergenes

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<table>
<thead>
<tr>
<th>Company</th>
<th>Sales ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK-Abello</td>
<td>282</td>
</tr>
<tr>
<td>Stallergenes</td>
<td>175</td>
</tr>
<tr>
<td>Allergopharma</td>
<td>92</td>
</tr>
<tr>
<td>Allergy Therapeutics</td>
<td>49</td>
</tr>
<tr>
<td>Fomif Biosciences</td>
<td>37</td>
</tr>
<tr>
<td>Others</td>
<td>260</td>
</tr>
<tr>
<td>Total</td>
<td>835</td>
</tr>
</tbody>
</table>

Source: Company Annual Reports, 2006 (ALK-Abello), (Stallergenes, Allergopharma, Allergy Therapeutics, Fomif Biosciences); Datamonitor, 2007

Datamonitor estimates that global sales of immunotherapy reached around $835m in 2006, representing about 1% of the total allergic rhinitis market when added to sales of traditional products. Most of the sales in 2006 came from SCIT with $440m and SLIT-DOSE with sales of $313m.
Minority (~16%) of rhinitis patients seen by allergist see immunotherapy.

Majority of patients seen by allergist are tested.

Less receive immunotherapy.

Inconvenience most common reason for discontinuing SCIT. Most likely reason for not starting SCIT.

Skin Tested 90%
Not Skin Tested 10%
Immunotherapy 15%
No immunotherapy 85%

1. Source: physician diary survey provided with permission Schering-Plough
2. Source: market research, provided with permission by Greer
3. More et al., Ann Allergy Asthma Immunol 2002; 88

Scandinavia: SCIT 100%, SLIT only new EMEA registered products; e.g., tablet
UK: market is relatively small for SCIT & SLIT
Germany: NP-SLIT ~25%
France: NP-SLIT 80% probably higher
Italy: NP-SLIT 80%-90% & reimbursed in 6 regions
Spain: NP-SLIT 30% in 2006 probably higher

Allergen Extract Regulation in Europe

Most SIT products on market had received national marketing authorizations (MA) prior to the new EU regulations.

Many SIT products sold as named-patient products (NPP) which do have a marketing authorization granted by a national competent authorities.

- Guidance on Allergen Products do not apply to NPP
- NPP do not have to fulfill the quality criteria of allergen products which possess an MA

Few product for have passed the new EU regulatory procedures, e.g., grass tablet

European Immunotherapy Market For Grass Allergy: Overall SLIT ~45% of SIT

Scandinavia: SCIT 100%, SLIT only new EMEA registered products; e.g., tablet
UK: market is relatively small for SCIT & SLIT
Germany: NP-SLIT ~25%
France: NP-SLIT 80% probably higher
Italy: NP-SLIT 80%-90% & reimbursed in 6 regions
Spain: NP-SLIT 30% in 2006 probably higher

Mechanisms for Allergen Extract ‘Approval’ in Europe

Centreidal Procedure (CP)

Marketing authorisation application (MAA)

National marketing authorisation (NMA) in EU

EmEA MAA

Re-Registration (conditional component authority of choice)

Bi-Registration (national competent authority of choice)

European marketing authorisation (EMA)

Single Country

Additional Countries

Increase in SCIT and SLIT

Sept-Dec 2005 vs. 2006

General IR presentation http://www.alk-abello-investor.com
2007 vs. 2006: GRAZAX launched late 2006

Revenue by product line (US$m)

Revenue by market (US$m)

2007
2006
GRAZAX
Other

North Europe
Central Europe
South Europe
Other market

Impact of SLIT in Europe

Immunotherapy Sales in 2009 compared with 2008

PHASE I & III US CLINICAL TRIALS WITH SLIT
EXTRACT SOLUTIONS & TABLETS COMPLETED:
TO DATE FDA-APPROVAL PENDING

Perception & Prescribing of SLIT Among US Practicing Allergists

Methods: On behalf of ACAAI IT/AD Committee, electronic survey sent to allergists early 2007

Results: 828 (25.7%) respondents

\*45 (5.9%) U.S. allergists reported using SLIT

\*94.1% did not prescribe SLIT:

\*Most cited reason lack of FDA approval: (61.7%)

\*Other barrier: effective dose is not known (27.5%)

\*But if approved would prescribe SLIT for:

\*Rhinitis- 65.7%

\*Moderate to severe asthmatics- 40.9%

\*Children <5 years-45.5%


SLIT Efficacy

Pitfalls of Many SLIT Studies

\* Significant heterogeneity in design & interpretation

\* Dose provided in proprietary units (e.g., ST-U, IR) and not mcg of major allergen

\* No true placebo:

\* High incidence of local AEs with active SLIT

\* Placebos used in SLIT trials do not have the same characteristics as the active extract

\* Histamine under the tongue does not elicit itching

\* Concealment of treatment allotment info not provided

\* Small number of patient studied (underpowered)

WAO Sub-lingual Immunotherapy Position Paper Efficacy Conclusions

• Up to June 2009, there were 60 DBPC-RCTs of SLIT, of which 41 conducted with grass or HDM extracts.
• 48 trials provided overall positive results and 12 were totally or almost totally negative.
• Literature suggests that overall, SLIT is effective, although differences exist among allergens.
• Available meta-analyses are in favor of SLIT (rhinitis in adults, asthma, and rhinitis in children), although the conclusions are limited by the great heterogeneity of the studies.


Cochrane Meta-analysis of Immunotherapy for Allergic Rhinitis Comparing SCIT and SLIT

<table>
<thead>
<tr>
<th></th>
<th>SCIT (SMD 95% CI)</th>
<th>SLIT (SMD 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>-0.73 (-0.97, -0.50)</td>
<td>-0.42 (-0.69, -0.15)</td>
</tr>
<tr>
<td>Medication</td>
<td>-0.57 (-0.82, -0.33)</td>
<td>-0.43 (-0.63, -0.23)</td>
</tr>
</tbody>
</table>

Size effect
- Poor > -0.20
- Medium = 0.50
- High < -0.80


Standardized Mean Difference is the difference of the means of both treatment arms divided by the pooled standard deviation.

SLIT for Allergic Rhinitis Systematic Review and Meta-analysis

- 50 DB PC studies were included (1966 - 2009)
- Patients with perennial and seasonal allergic rhinitis
- Participants: n=4,166 (2,153 active; 2,013 placebo)
- Adults (35 studies) and children (15 studies)

Radulovic S, Calderon M, Wilson D and Durham S. 2009

Provided with permission from MA Calderon 2009

SLIT for Allergic Rhinitis Cochrane Meta-analysis: Symptom Score Effect of Treatment Duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>Studies</th>
<th>SMD (random) 95% CI</th>
<th>p value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>16</td>
<td>-0.57 (-0.93, -0.20)</td>
<td>p &lt; 0.002</td>
<td>90%</td>
</tr>
<tr>
<td>6-12 months</td>
<td>16</td>
<td>-0.32 (-0.47, -0.18)</td>
<td>p &lt; 0.0001</td>
<td>38%</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>15</td>
<td>-0.63 (-0.94, -0.31)</td>
<td>P &lt; 0.0001</td>
<td>81%</td>
</tr>
</tbody>
</table>

SMD = Standardized Mean Difference

Radulovic S, Calderon M, Wilson D and Durham S. 2009

Provided with permission from MA Calderon 2009

Efficacy of SLIT for house dust mites respiratory allergy: results of a GA2LEN meta-analysis

• Methods: Searched up to March 31, 2008, for randomized DBPC trials assessing the efficacy of SLIT in AR and AA due to HDM sensitization.

Penagos M, et al., Chest 2008;133:599-609

Efficacy of SLIT for house dust mites respiratory allergy: results of a GA2LEN meta-analysis

• Methods: Searched up to March 31, 2008, for randomized DBPC trials assessing the efficacy of SLIT in AR and AA due to HDM sensitization.

Efficacy of SLIT for HDM Respiratory Allergy

Meta-analyses

Conclusions

- A relevant inter-study heterogeneity was detected.
- Promising evidence of efficacy for SLIT, using mite extract in allergic patients suffering from AR and AA, are herein shown.
- Findings suggest that more data are needed, derived from large-population-based high quality studies, and corroborated by objective outcomes, mainly for AA.


Analysis of the SLIT Meta-analyses

**Objective:** To assess the consistency, magnitude, and robustness of the results 5 meta-analyses (MAs) that seem to prove the efficacy of SLIT in allergic asthma and rhinoconjunctivitis.

**Methods:** The data reported in the MAs were checked with the data reported in the original studies. Funnel plots were performed to test for potential publication bias, and the trim-and-fill method was used to assess and correct the estimate of the effects if asymmetry was present.


Sublingual immunotherapy, meta-analysis, and knowledge in the age of information

- “All men by nature desire knowledge,” wrote Aristotle (384-322 BC). All human beings wish to understand the world around them, and to that end, some construct theories of various kinds to help make sense of it. Plato (428-348 BC),
- “For a very novel therapy, such as SLIT, initial studies might provide inconsistent results because they are assessing many fundamental variables, such as dosing, preparations, study design, and best population/disease target. As knowledge of and technology for SLIT advance, it is conceivable that both trial results and meta-analyses will become more consistent and positive. In searching for knowledge, be ready for the unexpected.”


WAO Sub-lingual Immunotherapy Position Paper Efficacy Conclusions

- The clinical efficacy and dose dependency have been demonstrated, in adequately powered, well-designed DBPC-RCTs, for rhinoconjunctivitis because of grass pollen...*(sic particularis tablets)*
- Dose finding trials and large studies with properly defined outcomes and sample size are needed for the other relevant individual allergens.

Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis

Method: Pre and coseasonal DBPC study of 628 patients with grass-pollen AR randomized to 100 IR, 300 IR, 500 IR (ORALAIR®, Stallergenes) or placebo tablets beginning 4 months before grass season.

5 day induction
300 IR = ~25 mcg of Phl p 5

Primary outcome:
Average Rhinoconjunctivitis Total Symptom Score

Didier et al., JACI 2007;120:2007;120

Daily mean RTSS and grass pollen counts (2005)

Didier et al., J Allergy Clin Immunol 2007; 120:1338-45

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

Wahn et al., J Allergy Clin Immunol 2009; 123:160-4

Early onset of action of SLIT grass tablet evaluated in allergen challenge chamber


Progressive Effect Of SLIT Grass Tablet Ongoing Study Year 2 Extension Study

Dahl et al., J Allergy Clin Immunol 2008; 121
Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet

- **Objective:** Investigate sustained efficacy 1 year after a 3-year grass tablet Grazax (75,000 SQ-T/2,800 BAU, 15 mcg of Phl p 5).
- **Methods:** Randomized DBPC trial including adults with moderate-to-severe grass pollen ARC inadequately controlled by medications. The analysis set comprised 257 subjects at the follow-up.
- Efficacy end points: RC symptom and medication scores, QOL, % symptom and medication free days.
- **Immunologic end points:** IgG4 and IgE-blocking factor.

**Results:**
- One year after treatment SLIT-group compared with placebo had sustained reductions/improvement in:
  - mean RC symptom scores (26%, P < .001)
  - medication scores (29%, P = .022)
  - efficacy similar to that observed during the 3-year treatment period.
  - Percentages of symptom- and medication-free days
  - Quality of life.
- Sustained clinical benefit was accompanied by immunologic changes.


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**GT-08: Sustained Symptom Reduction 1 Year After Grass AIT Treatment**

<table>
<thead>
<tr>
<th>Year</th>
<th>Symptom score (median)</th>
<th>% Diff</th>
<th>Symptomatic medications alone</th>
<th>Grass AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>3.82</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>4.94</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>5.11</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>5.52</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both treatment groups had free access to symptomatic medications


**GT-08: Combined Scores 2005-2008**

<table>
<thead>
<tr>
<th>Year</th>
<th>Days from defined grass pollen season start</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
</tr>
</tbody>
</table>

Calderon M. WAO Congress - Buenos Aires 2009

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**GT-08: Grass AIT Provides Sustained and Disease-Modifying Benefit**

<table>
<thead>
<tr>
<th>Season</th>
<th>Placebo</th>
<th>Grass AIT</th>
<th>% Diff</th>
<th>Placebo</th>
<th>Grass AIT</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>3.89</td>
<td>2.42</td>
<td>37.8</td>
<td>2.49</td>
<td>1.21</td>
<td>51.4</td>
</tr>
<tr>
<td>2006</td>
<td>3.44</td>
<td>1.90</td>
<td>44.8</td>
<td>2.30</td>
<td>0.47</td>
<td>79.6</td>
</tr>
<tr>
<td>2007</td>
<td>3.28</td>
<td>1.89</td>
<td>42.4</td>
<td>2.24</td>
<td>0.79</td>
<td>64.7</td>
</tr>
<tr>
<td>2008</td>
<td>3.27</td>
<td>2.27</td>
<td>30.6</td>
<td>2.58</td>
<td>1.23</td>
<td>52.3</td>
</tr>
</tbody>
</table>

→ denotes 1st season off treatment


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**GT-08: Sustained Individual Symptom Reduction 1 Year After Grass AIT Treatment**

Individual Symptom Scores

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptomatic medications alone</th>
<th>Grass AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocked nose</td>
<td>51%</td>
<td>30%</td>
</tr>
<tr>
<td>Runny nose</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Sneezing</td>
<td>43%</td>
<td>25%</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>31%</td>
<td>12%</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>50%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Both treatment groups had free access to symptomatic mediation

Immunological changes during and 1-year after grass tablet immunotherapy

Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy (SCIT)

Sublingual immunotherapy clinical trials with grass tablets: what have we learned?

- Appear to have a similar efficacy in adults and children
- Suggested dose-response in the range of 15 to 25 mcg of group 5 allergen
- May require at least 8 weeks of treatment for first season efficacy, but clinical efficacy was seen in 1st month
- No comparative dosing regimen studies but daily dosing is used in these studies—better compliance
- Updosing phase does not appear to be necessary

Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results

- Methods: Adults 18 to 50 yo with AR ± asthma 7 dose escalation in a single-session followed by 8-week open-label daily SLIT
- Results: 77/91 completed the phase 1 testing
- Maximum tolerable doses ranged from:
  - 50 to 2,090 BAU for cat hair and dust mite
  - 31 to 91 Amb a 1 Units for short ragweed
  - 50 to 21,090 BAU for timothy grass

Dose Escalation Table

<table>
<thead>
<tr>
<th>Dose</th>
<th>Concentration</th>
<th>Volume</th>
<th>Dose (BAU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1,000</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3,000</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>10,000</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>19,000</td>
<td>50</td>
<td>500</td>
</tr>
<tr>
<td>6</td>
<td>50,000</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>7</td>
<td>99,000</td>
<td>100</td>
<td>1,000</td>
</tr>
</tbody>
</table>


Sublingual Immunotherapy
Tracking the Progress To The US
Is It Ever Going To Get Here or......

US SLIT Clinical Trials

- Methods: DBPC study of 115 patients with ragweed induced RC randomly allocated to placebo, 4.8 mg Amb a or 48 mg Amb a 1/d; via a 1-day rush escalation
- Results: Both SLIT groups achieved a 15% reduction in TRCSS compared with placebo during the entire ragweed pollen season but
  - The difference was not statistically significant (P > .10)
  - Ragweed-specific IgG, IgG4, and IgA were increased after treatment in SLIT but not placebo

Skoner et al, J Allergy Clin Immunol 2010;nnn


**Results**: Analysis of covariance correcting for preseasonal symptoms in high dose group compared with placebo during entire pollen season there was a significant decrease in (P≤.05)

- mean daily symptom scores
- medication scores

**AE** similar all groups, but oral-mucosal AE in SLIT groups

**Conclusion**: Ragweed extract SLIT at doses of 4.8 to 48 mg Amb a 1/d was safe and can induce favorable clinical and immunologic changes. However, additional trials are needed to establish efficacy

Skoner et al, J Allergy Clin Immunol 2010;nnn 61

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**Ongoing & Planned Tablet Studies: Results Pending**

- **Merck/Schering-Plough/Alk-Abello**:  
  - Grass: adult and pediatric studies (with grass tablet (15mcg Phl p 5) or placebo daily.
  - completion date fall of 2009-both reportedly met primary outcome & presentations expected at AAAAI 2010 Annual Meeting
  - Phase I ragweed completed-results not released
  - Phase III planned Oct. 2009 to Nov. 2011:
    - 3 arms: placebo ,6 and 12 U Amb a 1 U,

From www.clinicaltrials.gov

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**US SLIT Trials Failing to Meet Primary Outcome**

**Extracted from press releases**

- 2007-Greer Reports Low Grass Pollen Levels Appear to Affect Outcome of Phase IIib Clinical Trial for Sublingual-Oral Immunotherapy for Timothy Grass
- **Results never presented for either study: reason for failure, patient selection? pollen counts? other?**

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**Ongoing & Planned Tablet Studies: Results Pending**

- **Greer**: Ragweed phase III: complete3d fall of 2008; results have not been releases
- **Stallergenes**: 473 adults 5 grass-pollen tablet (25 mcg group 5) or placebo daily-completion date -fall 2009: database locked; results pending
  - Pediatric study planned
  - Ragweed clinical trials planned

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**Planet Technology Phase II Cat Dose Response Studies**

**Cat**: 0.21 Units (~0.48 µg) vs. 2.1 Units (~4.8 µg): database locked; statistical efficacy reportedly not established

**Primary Endpoint**

- Average of the Total Symptom Scores during environmental chamber exposure at Week 20

**Secondary Endpoints**

- Change in the average of the Total Symptoms Scores during environmental chamber exposure at Week 20 from the average of the Total Symptom Scores at the baseline environmental chamber exposure
- Daily total, nasal, non-nasal, proportion of rescue medication-free days, rescue medication use index

From www.clinicaltrials.gov

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**Safety & Efficacy of Sublingual House Dust Mite Immunotherapy: A Randomized, DBPC U.S. Trial**

**Methods**: First PBDB trial of HDM SLIT in the US to compare high and low dose SLIT in adults with AR±asthma randomized for 12-18 months to daily

- high (4200 AU),
- low (60 AU) D. farinae SLIT
- placebo (0.038 mg histamine, N=11).

**Safety results: 21 completed (high N = 9, low= 7, placebo N=5)**

- Withdrawals and possible treatment-related AE similar in the 3 groups

**Efficacy**: significant difference in high dose vs. placebo:

- ↑D farinae-sIgG4 ( 9 SLIT, 5 placebo, p=0.02)
- Increased bronchial threshold to DF challenge (7 SLIT, 3 placebo, p=.04)

Bush R. et al., Journal of Allergy and Clinical Immunology 2009; 123:674.
Questions To Consider When Applying Current SLIT Literature to The Average US Allergic Patient

- The average US allergic patient is polysensitized
- All of the studies reviewed have been with single allergens:
  - Is SLIT effective in polysensitized patients?
  - Is multiallergen SLIT effective?

US is a Polysensitized Population

- NHANES 3: 10,508 subjects in general population tested to 10 allergens from 1988-1994* number of +SPT:
  - Mean 3.5, median 3: HDM (27.5%), Perennial rye (26.9%), German cockroach (26.1)
- ACRN trials: 1338 subjects to SPT to 12+ allergens/mixes: 81% had positive reactions to ≥3 allergens
- Based on 1151 extract mixtures formulated in 2002 at Greer, mean number of component extracts was 8
- CPT code 95165 is based on average cost of using 6 allergens.

Efficacy of SLIT with a Single Extract or as part of a Multi-Allergen-Extract Mixture in Patients with Grass SAR

- Objectives: DBPC study to assess efficacy of timothy SLIT alone vs. Timothy + 9 additional allergen extracts.
- Efficacy parameter: symptoms during the grass-pollen season compared with baseline observational year.
- Objective parameters: titrated PST nasal challenges, timothy-specific serum IgA and IgG before and following one year of SLIT

Formulation/Dosing of the Three Treatment Arms

<table>
<thead>
<tr>
<th>MAT Group, Allergen Extract</th>
<th>Amount</th>
<th>TM Group, Allergen Extract</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy</td>
<td>1.0 mL</td>
<td>Timothy</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Maple, Box-Elder</td>
<td>1.0 mL</td>
<td>Diluent</td>
<td>9.0 mL</td>
</tr>
<tr>
<td>Ash, White</td>
<td>1.0 mL</td>
<td>Ash, White</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Juniper, Western</td>
<td>1.0 mL</td>
<td>Juniper, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Tim, American</td>
<td>1.0 mL</td>
<td>Tim, American</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Cottonwood, Common</td>
<td>1.0 mL</td>
<td>Cottonwood, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Firebush (Kochia)</td>
<td>1.0 mL</td>
<td>Firebush (Kochia)</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Ragweed, Western</td>
<td>1.0 mL</td>
<td>Ragweed, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Sagebrush, Common</td>
<td>1.0 mL</td>
<td>Sagebrush, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Russian Thistle</td>
<td>1.0 mL</td>
<td>Russian Thistle</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Placebo Group</td>
<td>Amount</td>
<td>Diluent</td>
<td>10 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caramelized Sugar</td>
<td></td>
</tr>
</tbody>
</table>

- Amount added to 10 mL vial for 1 month of treatment
- CMD: Timothy ~ 30x SCIT dose (19 mcg Phl p 5 qday), others 15-20x
- SCIT dose: 0.25-0.28 ml q am, held under tongue for 2 minutes, then swallowed

Denver Grass Counts

The normal precipitation for the first 6 months in Denver is 8.09 inches. The precipitation for this period in 2007 was 6.44 inches and in 2008 only 3.04 inches. Due to this record low rainfall the grass pollen counts in Denver 2008 were much lower than in the observational season of 2007.

Mean Δ(2008-2007) Symptom and Medication Scores

Due to low pollen counts in 2008 all 3 groups had improved symptoms and medication scores compared with 2007.

Mean \( \Delta(2008-2007) \) Log\(_{10}\) tSPT Score, Nasal Challenge Score, & IgG\(_4\) Level

Only Timothy alone had significant difference from placebo in all 3 parameters

General Summary of SLIT Efficacy

• Appears to have similar efficacy in adults and children
• Single allergen SLIT appears to be effective in polysensitized patients
• SLIT with 2 allergens appears effective administered separately but
• Multi-allergen SLIT mixture efficacy not established
• Grass tablet efficacy at 15-25 mcg major allergen well established but
• Effective dose for SLIT solutions not well established

SLIT Safety: How Safe is Safe? Frequency and Severity of SLIT Adverse Events

• Difficulty in evaluating SLIT safety because:
  – Treatment administered at home
  – Thus adverse reactions primarily occur at home, i.e., unwitnessed and/or not evaluated by someone with medical training
  – Variability in accuracy and interpretation of patient’s reported AEs

SLIT Safety in Clinical Trials: Important Issues to Consider

• Histamine under the tongue does not elicit itching
• Concealment of allotment not provided in most studies
• Why is there such a disparity about local SE in SLIT studies?
• Could local SE associated with SLIT influence outcomes?
• Most studies, even those with a high % of local SE with allergen vs. placebo, do not factor this into their conclusions.
• If there is a high prevalence of local side effects in a study, will this lead to a greater reporting bias?

### Efficacy of SLIT with a Single Extract or as Part of a Multi-Allergen-Extract Mixture

- No significant difference in the symptom or medication scores in either treatment groups compared with placebo
  - Perhaps due to very low grass pollen season 2008
- Timothy alone: significant improvement in tSPT, NC, sIgG\(_4\), and decreased IFN-g levels compared to placebo
- Multiallergen: significant improvement in tSPT compared to placebo, but less than with TM
- Timothy alone arm demonstrated efficacy with 19 mcg Phl p daily

Mean \( \Delta(2008-2007) \) Log\(_{10}\) tSPT Score, Nasal Challenge Score, & IgG\(_4\) Level


### SLIT Safety

In 66 SLIT studies AE there were no fatalities or anaphylactic reactions accompanied by hypotension (up to October 2005) in \( \sim 1,181,000 \) doses of allergen to 4765 patients

• Majority of studies in rhinitis/rhinoconjunctivitis ± asthma
  – Oral-mucosal symptoms very common
  – 14 probable SLIT-related SAE during 5377 SLIT treatment years, 1 SAE per 384 treatment years
  – No clear relationship between AE rate and dose or induction schedule


### Summary of SLIT Adverse Events

SLIT Safety in Published Literature

- No reports of SLIT-related fatalities to date (October 2009) in an estimated ___ billion doses
- Most AEs occur in the beginning of treatment
- Dose-response relationship with AEs in some studies
- No apparent relationship with updosing schedule and AEs
- Several large (>300 patients) grass-pollen tablet studies in adults & children demonstrate good safety profile with no updosing
- Few cases of anaphylaxis (at least 8) reported

Case Reports of SLIT-Anaphylaxis

- 31 year old woman with AR & A on 3rd day of build-up with a multiallergen SLIT extract
- 11 year old girl with AR & A after mixed pollen SLIT at the height of pollen season one month after beginning maintenance
- 16-year-old girl with AR & A after a 3 week gap in treatment & a dose 6 times higher. History of 2 prior SLIT SR (wheezing).
- Four cases of anaphylaxis in pts who d/c SCIT due to SR: 2 occurred with first grass tablet dose

Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy

We report 2 adolescents on SLIT after significant side effects with SCIT. In both patients, SLIT had to be stopped after systemic side effects.

- 14 yo girl with asthma & AR reported a "severe asthma attack" 1 week on maintenance (8 drops) together with mouth itches immediately after SLIT, lasting for several hours. She was instructed to stop SLIT for 2 days and then to restart with progressive doses up to 4 drops. However, she had to discontinue SLIT because of repeated asthma attacks time-related to the treatment.

SLIT Anaphylaxis with First Grass Table Dose

- 24 yo female with AR & asthma also d/c grass SCIT due SRs
  - After 1st grass tablet taken at home, she immediately experienced asthma sx, generalized itching, faintness and abdominal cramps; she recognized this from the SCIT side effect, but felt much worse!
  - She took a lot of antihistamines, ICS & sympathicomimetics, and rushed to the GP office;
  - In distress on arrival: wheezing, pale, nearly fainting, BP 90/50 mmHg. Given adrenaline.
  - She recovered in the next few hours.

SLIT-Anaphylaxis: are there identifiable risk factors?

- Risk factors in these cases? dose, gap in treatment, history of previous SR, updosing phase, multi-allergen treatment, delay in epinephrine, height of season, asthma???
- Multiallergen SLIT Safety: Two postmarketing surveys (1 adult, 1 pediatrics) found no difference in safety of between single allergen & multiple allergen SLIT.
- Previous SR: prospective study of 43 pts receiving SLIT: 3/5 pts with SLIT had previous SCIT SRs


1. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy 2009; 64:963-4.

Sublingual Immunotherapy Safety Summary

- SLIT appears to be better tolerated than SCIT
- Majority of SLIT AE’s appear to occur during the beginning of treatment
- A few cases of SLIT-related anaphylaxis have been reported but no fatalities
- Risk factors for the occurrence of SLIT SAE have not yet been established
- There is a need for a generally accepted system of reporting adverse reactions/anaphylaxis


Sublingual Immunotherapy Safety Summary

- Specific instructions should be provided regarding the management of AE, unplanned interruptions in treatment and situations when SLIT should be withheld.
- SLIT should only be prescribed by allergy-trained physicians


Allergy Dosage Instructions

- It is not necessary to refrigerate slits.
- To administer, open the sachet, take the slit (drops from the sachet) and hold it under your tongue and let it there for 30 seconds to allow it to absorb without touching before swallowing.
- Please note that the administered dose size may vary. It is recommended that you hold the tablet vertically.
- If you spill a single slit when you administer your dose, a spacer can also be used to administer the dose. This helps to keep it more absorbable.
- Please call us several times a day to answer any questions.

What sort of instructions should be provided to SLIT patients?


Sublingual Immunotherapy Safety: Unmet Needs

- The safety of SLIT in moderate to severe asthmatics
- The safety of SLIT in patients who have had SR with SCIT
- The safety of SLIT with multiple allergens
- Interruptions in treatment: how long between doses is it safe to administer usual dose?
- Is it safe to administer SLIT with no induction with all formulations?
- Are oropharyngeal infections or lesions risk factors for SLIT SRs?
- Under which clinical situation should an SLIT dose be withheld?
- The safety of SLIT in pregnant or breast-feeding women.
- The safety of SLIT in patients on beta-blockers.
- Are there any risk factors that identify which patients may experience a SR with SLIT?


SLIT: How Does It Work? Pharmokinetics and Immunological/Objective Changes

- Inhibition of eosinophils, reduction of adhesion molecules in target organ.
- Some evidence of increase in peripheral T cell IL-10.
- SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in oral mucosa and/or regional lymph nodes are likely important.


Mechanisms Of Sublingual Immunotherapy

- Sublingual immunotherapy is associated with:
  - Retention of allergen in sublingual mucosa for several hours.
  - Marked early increases in antigen-specific IgE, blunting of seasonal IgE.
  - Modest increases in antigen-specific IgG4 and IgE blocking activity.
  - Inhibition of eosinophils, reduction of adhesion molecules in target organ.
  - Evidence of increase in peripheral T cell IL-10.
  - SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in oral mucosa and/or regional lymph nodes are likely important.

It may be all about location

Distribution of Langerhans cells & mast cells in human oral mucosa: new application sites of allergens in sublingual immunotherapy?

• Rationale: oral Langerhans cells (LC) are thought to play a major role in the effectiveness of SLIT, oral mast cells (MC) most likely account for AE e.g., oral itching and sublingual edema caused by histamine release
• Biopsies from autopsies for immunohistochemistry and flow cytometry used to detect MCs, LCs & FceRI expression of LCs. Mixed lymphocyte reactions were performed to assess their stimulatory capacity.

SLIT: Does Location Matter?

Maybe

• Mast cells
  – Highest density detected in gingiva, & lowest in palatum & lingua.
  – Sublingual MCs located within lobe & duct of salivary glands—may explain swelling of sublingual caruncle
• Langerhan cells
  – Highest density of LCs within vestibular region & lowest density in sublingual region.
  – Highest expression of FceRI on LCs within the vestibulum.
• Conclusions: Different mucosal regions might represent alternative SLIT application sites

PBMC proliferation and anti-IL-10 at 4 & 52 weeks

Conclusions: Different immune mechanisms are operative during early & later phase of SLIT treatment
  • 4 weeks: Treg suppression through IL-10
  • 52 weeks: Immune deviation of allergen-specific T cells & specific non-reactivity, possibly through anergy or clonal deletion

SLIT Beyond Aeroallergen Sensitivity

• Food allergy: hazelnut challenge 2.29 g to 11.56 g (P = .02)1, milk, peanut (US clinical trials ongoing)
• Atopic dermatitis: at 9 months- significant (P = .025) difference between groups in change in SCORAD2
• Latex: several studies have shown increased tolerance
• Honeybee large local reactions: from 20.5 to 8.5 cm (P = .014), diameter ↓ by >50% in 57% of patients on 525mcg venom monthly.3

SLIT Roadblocks in the United States

1. No FDA- approved formulation for SLIT thus
2. No CPT code for SLIT
3. Effective dose for SLIT US licensed extracts not known
4. Cost-effectiveness not be assessed until effective dosing regimen known
5. Efficacy of multi-allergen SLIT mixtures has not been established & most US patients are polysensitized
6. Risk factors for SLITs have not been established
7. Questions remain concerning appropriate patient instructions for management of this ‘at-home’ treatment
Sublingual Immunotherapy

General Take Home Points

• Clinical studies with some allergens have demonstrated clinical and immunological changes similar to SCIT
• Some evidence of sustained benefits after discontinuation and possible prevention of allergic disease progression like SCIT
• Considering pharmacotherapy is only treating the 'tip of the allergy iceberg', the convenience of SLIT may increase utilization of the only disease modifying treatment for allergic disease: specific allergen immunotherapy