Immunotherapy New and Emerging Issues

Linda Cox, MD

AAAAAI 2014 Annual Meeting
Linda Cox, MD Disclosure

Allergist: solo private practice
Associate Clinical Professor of Medicine Nova Southeastern University
Affiliate Associate Professor of Clinical Biomedical Science Florida Atlantic University College of Medicine
Data Safety Monitoring Committee: Circassia, Biomay (not ongoing)
Adjudication Committee: Novartis, Medimmune
Organizational interests:
• FDA Allergenic Products Advisory Committee: consultant
• AAAAI: President
• ABAI Board of Directors -member
Immunotherapy New and Emerging Issues

• At the end of the session attendees will be able to discuss and compare the efficacy and safety of different allergy immunotherapy treatments for:
  – Aeroallergens –induced disease including:
    • Accelerated SCIT
    • Sublingual immunotherapy
    • Subcutaneous with modified allergens (adjuvants & recombinants)
    • Peptide immunotherapy
    • Epicutaneous immunotherapy
    • Intralymphatic immunotherapy
SCIT is only disease modifying treatment for allergic respiratory disease
• Can provide sustained clinical benefits after discontinuation
• Prevent new allergy sensitivities
• Prevent asthma
• Is cost-effective—studies have demonstrated 30 to 80% cost-savings compared to pharmacotherapy alone

Then why look for alternative approaches??

Allergy immunotherapy: Reduced health care costs in adults and children with allergic rhinitis

Cheryl S. Hankin, PhD, a Linda Cox, MD, b Amy Bronstone, PhD, a and Zhaohui Wang, MS a  Moss Beach, Calif, and Fort Lauderdale-Davie, Fla

Study: Retrospective (1997-2009) Florida Medicaid claims analysis compared mean 18-month health care costs of patients with newly diagnosed AR who received de novo AIT more versus matched controls who did not receive AIT

• Results: Significant 18-month total health care cost reduction in AIT group compared with control
  – 42% children
  – 30% adults
• Significant savings seen beginning at 3 months

Accelerated AIT Schedules  
Date Back to early 1900’s

“In 1909, Noon and I began inoculating hay-fever patients with a grass pollen extract.... inoculations were given weekly merely because our out-patients at St. Mary’s Hospital were in the habit of coming every week.

Dr. Freeman noted the inconvenience of the weekly build-up and began experimenting with more rapid schedules. He concluded the advantages of the “rush” method were: the saving of time, convenience and patient compliance

“Rush desensitization” with associated SR

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
AIT Safety Summary

• SCIT:
  – Incidence of SRs dependent on multiple factors at a rate ~0.2% of injections and 2-5% of patients
  – Delayed & biphasic do occur and are not rare
  – Risk factors identified: symptomatic asthma, previous AIT SR
  – Fatalities rare per US survey data- ~1 in 2.5 million injections from 1945 to 2001, none confirmed from 2008 to 2012 survey

• SLIT:
  – SLIT appears to be better tolerated than SCIT
  – Majority of SLIT AE’s are local reactions - oromucosal symptoms
    • Occur during the beginning of treatment
    • Resolve within a few days or weeks without any medication or intervention
  – Systemic reactions are uncommon and SAE rare
  – Risk factors for SR not established
• **Asthma**: “If 9 patients were treated with SCIT, expect 1 to develop a SR of any severity”

• **Allergic rhinitis**: “Adrenaline was given in 0.13% (19 of 14085 injections) of those on active treatment and in 0.01% (1 of 8278 injections) of the placebo group for treatment of adverse events.”

Abramson et al., Allergen immunotherapy for asthma Cochrane Database Syst Rev. 2010;8:CD001186.

Participation—5 year study

Population: AAAAI and ACAAI member practices prescribing SCIT

<table>
<thead>
<tr>
<th>Period</th>
<th>% participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2008 - June 2009</td>
<td>49%</td>
</tr>
<tr>
<td>August 2009 – July 2010</td>
<td>37%</td>
</tr>
<tr>
<td>August 2010 – August 2011</td>
<td>27%</td>
</tr>
<tr>
<td>September 2011-September 2012</td>
<td>27%</td>
</tr>
</tbody>
</table>

Results (Years 1-4)

• Systemic reactions occurred in 82-85% of practices
  – 0.1% of injection visits
    • Similar to findings from other studies
      (Casanovas Clin Exp Allergy 2007; Nettis Clin Exp Allergy 2002)

Results (Years 1-4)

• **One confirmed fatality** with SCIT (2008-2012)
  – 43 year old male on build-up injections
  – Asthmatic, but controlled at time of reaction
  – Recently started an ACE inhibitor
  – ‘Highly sensitized’; ‘Highly allergic to weeds’
  – Reaction occurred during weed season
  – No dosing errors
  – Reaction started within 3-10 minutes after injection
    • Developed severe hypotension and cardiopulmonary arrest within 5-6 minutes
  – Immediately received Epinephrine 0.3 mg, followed by 4 more doses
  – Unsuccessful resuscitation despite IV fluids and emergency tracheostomy
WAO Severity Grading of SRs (Years 4 & 5)

• Grade I → Symptom(s)/signs of 1 organ system present: generalized urticaria with/without angioedema (NOT laryngeal, tongue, or uvular) or nausea or upper respiratory symptoms (e.g., itching of the palate and throat, sneezing) or conjunctival symptoms.

• Grade 2 → Asthma RESPONDING to an inhaled bronchodilator and/or GI symptoms including abdominal cramps, vomiting, or diarrhea, or uterine cramps.

• Grade 3 → Severe asthma NOT RESPONDING to a bronchodilator or laryngeal, uvular, or tongue edema, with or without stridor.

• Grade 4 → Respiratory failure or hypotension with or without loss of consciousness.

Modified from Cox JACI 2010
AAAAI/ACAAI Survey Years 1-4
Systemic reaction rate/ 10,000 injection visits

Bernstein AAACI 2010, Epstein AAACI 2011, 2013
## Advantages & Disadvantages of Accelerated Immunotherapy Schedules

### TABLE I. Comparison of different immunotherapy build-up schedules for aeroallergens

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Rush immunotherapy</th>
<th>Cluster immunotherapy</th>
<th>Conventional immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of visits during build-up phase</td>
<td>1-3</td>
<td>8*</td>
<td>30*</td>
</tr>
<tr>
<td>No. of injections</td>
<td>8†</td>
<td>18*</td>
<td>30*</td>
</tr>
<tr>
<td>Time to reach maintenance dose</td>
<td>1-3 d</td>
<td>5 wk*</td>
<td>15 wk at a frequency of 2 times per week or 7.5 mo if injections administered once a week</td>
</tr>
<tr>
<td>Premedication†</td>
<td>Recommended in the AIPP but no specific protocol provided. H1 antihistamine and corticosteroids were used in all protocols§ in addition to other medications (eg, H2 antihistamines, leukotriene antagonists, theophylline, and ketotifen).</td>
<td>Antihistamine recommended by AIPP with notation that 2 hours before has been shown to decrease SR and local reactions.</td>
<td>Not routinely recommended but rarely studied: one study found reduced frequency of severe SR and increased the proportion of patients who achieved the target dose with fexofenadine premedication.</td>
</tr>
</tbody>
</table>

### Range of SRs‡

| Without premedication | 15% to 100% of patients | 3% to 79% of patients (100% in 1 study classified as cluster, but protocol had 5 injections per visit; allergen: *Cladosporium* species) | 8.4% to 28.6% of patients; mean, 12.9%; SD, 10.8%§ |
| With premedication    | 14.7% to 38% of patients | 0 to 33% of patients | NA |

Experience with Accelerated Immunotherapy Schedules Utilizing Multiple and Single Allergen Extracts in a Private Practice Setting.

- 2 day modified RIT with a target dose of 0.25 ml vial 2 (aka 1:10v/v)
- 3 groups: No premedication (n=26), Premedicated 3 meds prednisone, ranitidine and loratidine (n=6) and 4 meds (previous plus zafirlukast) (n=25).

- **Systemic reaction rate:**
  - 9/26 (35%) pts without premedication
  - 1/31 (3%) (pt was premedicated with 3 drug regimen)
  - All pts who had SR during the modified RIT had at least one allergen with **wheal of >14 mm** on prick skin testing (ALK Lancet, ALO or Greer extract)

*High degree of STR associated with greater SR risk with Modified RIT*

Cox L, ACAAI Annual Meeting 1996 & 1998 Abstract Presentations
Risk Factors for Rush Systemic Reactions FEV$_1$ & STR

**Protocol:** 125 mite-allergic asthma pts underwent a 3-day RIT.
Target dose: 3000 BU (4 μg of Der p 1) in subjects > 10 yrs and 1500 BU in < 10 yrs

**Adverse reactions:** Severe SR in 34.4%.
35 pts had asthma SR, 8 pts had anaphylaxis and 5 pts had > 1 SRs
The two significant differences between pts with severe SR and those with mild or no SR were:

- Skin prick end point titration
- FEV$_1$ (p<0.001) before RIT

73% of pts with FEV1 < 80% had asthma SR during RIT vs. 12.6 % of pts with FEV1 > 80%.

<table>
<thead>
<tr>
<th>DAY 1</th>
<th>Hour</th>
<th>BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>9:30</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>DAY 2</td>
<td>9</td>
<td>1800</td>
</tr>
<tr>
<td>11</td>
<td>2400</td>
<td></td>
</tr>
<tr>
<td>DAY 3</td>
<td>9</td>
<td>3000</td>
</tr>
</tbody>
</table>

Bousquet et al, J Allergy Clin Immunol 1989; 83 (4) 797-801
Reduced SR and Severe SR with Premedication and Preventive Measure

Table 1. Systemic Reactions According to Immunotherapy Schedule, Premedication, and Prevention Measures in Dust Mite and Pollen Allergic Patients With Allergic Rhinitis With or Without Asthma

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Allergen</th>
<th>SR per patient, %</th>
<th>SR per injection, %</th>
<th>Asthma reactions, %</th>
<th>Anaphylaxis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: 3-day RIT, 290 patients</td>
<td>Dust mite, 290 patients</td>
<td>36</td>
<td>3.8</td>
<td>30.6</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Pollen, 74 patients</td>
<td>31.3</td>
<td>3.1</td>
<td>9.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Group B: RIT plus premedication†</td>
<td>Dust mite, 160 patients</td>
<td>16.2</td>
<td>2.0</td>
<td>13.7</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Pollen, 102 patients</td>
<td>14.7</td>
<td>3.1</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Group C: RIT plus premedication and preventive measure‡</td>
<td>Dust mites, 479 patients</td>
<td>7.3</td>
<td>0.8</td>
<td>6.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Pollen 200 patients</td>
<td>7.5</td>
<td>2.3</td>
<td>2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Group D: step protocol with</td>
<td>Dust mites, 223 patients</td>
<td>5.4</td>
<td>0.6</td>
<td>5.0</td>
<td>0.4</td>
</tr>
<tr>
<td>premedication and preventive</td>
<td>Pollen, 78 patients</td>
<td>2.6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>measure§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The preventive measures were exclusion of patients with an FEV1 less than 70% of predicted and modifying the schedule for large local reactions greater than 10 cm

Rush Immunotherapy: multiple allergens with & without premedication one and two day protocols

1st study (11 pts): 2 day RIT with no premedication. SR in 55% of pts; Grades 3 to 5. All SR at dose > 0.3 ml 1:1000 w/v¹

- LR did not predict SR
- Correlation between severity of SR and number of positive ST/cumulative size

Grading of SRs:
2 = cutaneous only, rash;
3 = generalized pruritus, sneezing, mouth itchiness;
4 = wheezing, shortness of breath;
5 = anaphylaxis

Rush Immunotherapy: multiple allergens with & without premedication one and two day protocols

2nd study (22 pts) Premedication reduced SR rate: 27% of premed group vs. 73% of placebo premedication ($p=0.047$).¹

- Best predictor for SR was STR before and after premedication.
- Noted increase STR in placebo before SR

3rd study: 22 pts: one day RIT with premedication. SR in 23%.²

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 0*</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>15 mg twice a day</td>
<td>10 mg twice a day</td>
<td>5 mg</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>150 mg BID on all 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>30 mg a day on all 3 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Portnoy et al Ann Allergy 1994; 73: 409-18
2. Sharley et al Ann Allergy 1996; 76: 175-80
Fastest SCIT Rush Schedule for Inhalant Allergens

- The most accelerated schedule for inhalant allergens: 7 injections administered over day 4 hours in a one day protocol. Premedication 1 day before and morning of RIT
  - Prednisone 40 mg, cetirizine 10 mg, ranitidine 300 mg and montelukast 10 mg/zafirlukast 40mg
  - 38 % SR Rate

<table>
<thead>
<tr>
<th>Table 1. Rush Immunotherapy Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection No.</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

88% of reactions

Symptomatology of Moderate to Severe Systemic Reactions

Table 3. Moderate-to-Severe Systemic Reactions

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Reaction</th>
<th>Severity</th>
<th>Eliciting Dose</th>
<th>Treatment</th>
<th>Time to reaction, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lip swelling, nasal congestion, chest tightness, abdominal cramping, nausea, vomiting</td>
<td>Moderate</td>
<td>0.2 mL 1:10</td>
<td>Hydroxyzine, 75 mg; levocabastine, 2 gtts OU; epinephrine, 0.3 mg s.c.; loratidine, 10 mg; albuterol, 2 puffs</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Facial and trunk flushing, abdominal cramping, palmar pruritus</td>
<td>Moderate</td>
<td>0.05 mL concentrate</td>
<td>Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>Nasal congestion, sneezing, axillary pruritus and erythema, decreased FEV₁</td>
<td>Moderate</td>
<td>0.1 mL concentrate</td>
<td>Albuterol, 5 puffs; albuterol nebulizer, 0.5 mL; ipratropium, 4 puffs; prednisone, 40 mg; cetirizine, 10 mg</td>
<td>35</td>
</tr>
<tr>
<td>22</td>
<td>Severe abdominal cramping</td>
<td>Moderate</td>
<td>0.2 mL 1:10</td>
<td>Epinephrine, 0.3 mg s.c.; rofecoxib, 50 mg</td>
<td>45</td>
</tr>
<tr>
<td>31</td>
<td>Cough, wheezing, chest tightness, facial flushing, palmar pruritus</td>
<td>Moderate</td>
<td>0.05 mL concentrate</td>
<td>Epinephrine, 0.3 mg s.c.; cetirizine, 10 mg; albuterol, 2 puffs</td>
<td>40</td>
</tr>
<tr>
<td>65</td>
<td>Hypotension (systolic blood pressure 50 mm Hg), urticaria, pruritus, facial angioedema</td>
<td>Severe</td>
<td>0.1 mL 1:10</td>
<td>Epinephrine, 0.5 mg intramuscularly 2 times; intravenous fluids, 1 L; cetirizine, 10 mg; prednisone, 40 mg; ranitidine, 150 mg</td>
<td>55 (mild), 150 (severe)</td>
</tr>
</tbody>
</table>

Modified One Day Protocol: Reduced SR Rate When Target Dose Decreased to 0.1 ml of 1:10 v/v

Dose 0.1 ml of 1:10 v/v: SR 7.2% (n=111), all mild (no epinephrine)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Concentration (volume:volume)</th>
<th>Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1:10,000</td>
<td>0.3</td>
</tr>
<tr>
<td>30</td>
<td>1:1,000</td>
<td>0.3</td>
</tr>
<tr>
<td>60</td>
<td>1:100</td>
<td>0.1</td>
</tr>
<tr>
<td>90</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<tr>
<td>120</td>
<td>1:10</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Recommended UT Southwestern RIT: 2-hour Protocol
All patients observed 90 minutes after final dose

Dose ≥ 0.2 ml of 1:10 v/v: SR 18.1% (n=72)

<table>
<thead>
<tr>
<th>Injection No.</th>
<th>Time, min</th>
<th>Concentration, volume:volume</th>
<th>Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>120</td>
<td>1:10</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>1:10</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>240</td>
<td>Undiluted concentrate</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Alvares et al JACI.2012;129(2):AB194 Slide provided and modified with permission David Khan. MD
Recommended AIT build-up protocol following 2 hour RIT

Trend toward fewer 1st post-RIT day reactions when patients were pre-medicated with prednisone prior to the first post-RIT dose (6.6%) vs. (15.6%) when not pre-medicated.

<table>
<thead>
<tr>
<th>Week</th>
<th>Concentration</th>
<th>Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Day of RIT)</td>
<td>1:10 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>1:10 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>1:10 v:v</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>1:1 v:v (concentrate)</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>1:1 v:v</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>1:1 v:v</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>1:1 v:v</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>1:1 v:v</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
<tr>
<td>13</td>
<td>1:1 v:v</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Pre-med of prednisone 40 mg for 1st post RIT dose

Generally recommend all pts take AH during build-up

Maintenance dose at 8 weeks with weekly post-RIT build-up (4 weeks with twice weekly build-up)

Slide provided and modified with permission David Khan. MD
Safety of multiple aeroallergen rush immunotherapy using a modified schedule

• Retrospective chart review was performed of 138 pts who underwent modified RIT
• Premedication: prednisone & H1 and H2-blocker - 2 hours before
• Systemic reactions: 38 (28%) pts
• Adherence: 61% of RIT vs 46% conventional still on n AIT in 2011 (started 2008)

Table 2  RIT protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose (mL)</th>
<th>Dilution (v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:15 A.M.</td>
<td>0.05</td>
<td>1:10,000</td>
</tr>
<tr>
<td>9:30 A.M.</td>
<td>0.3</td>
<td>1:10,000</td>
</tr>
<tr>
<td>10:00 A.M.</td>
<td>0.1</td>
<td>1:1000</td>
</tr>
<tr>
<td>10:30 A.M.</td>
<td>0.3</td>
<td>1:1000</td>
</tr>
<tr>
<td>11:00 A.M.</td>
<td>0.1</td>
<td>1:100</td>
</tr>
<tr>
<td>12:00 P.M.</td>
<td>0.3</td>
<td>1:100</td>
</tr>
<tr>
<td>1:00 P.M.</td>
<td>0.1</td>
<td>1:10</td>
</tr>
<tr>
<td>2:00 P.M.</td>
<td>0.2</td>
<td>1:10</td>
</tr>
</tbody>
</table>

RIT = rush immunotherapy.

Table 3  Build-up schedule to the target dose after successful completion of the RIT protocol

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (mL)</th>
<th>Dilution (v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>1:10</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>1:10</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>1:10</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>1:10</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>1:10</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>1:1</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>1:1</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>1:1</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>1:1</td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>1:1</td>
</tr>
<tr>
<td>11</td>
<td>0.5</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Subcutaneous Cluster Schedule

- Cluster entails administering several injections at increasing doses (generally 2-3 per visit) sequentially in a single day of treatment on nonconsecutive days.
- Cluster schedule associated with the same or a slightly increased frequency of SRs compared with conventional schedules.
- Few studies compare safety and most used single allergen: *can safety be extrapolated to multiallergen?*

Example of a 8 visit 18 injection schedule in 3rd ITPP updates*

---

Studies Comparing Cluster and Conventional Immunotherapy Schedule

- DBPC study of 239 pts with dust mite AR ± asthma comparing 6-week cluster with a 12-week conventional schedule found:¹
  - No differences between the 2 schedules in terms of AEs
  - Improved clinical and objective parameters in the cluster 6 weeks before conventional group

Randomized study of 96 patients with dust mite AR comparing 6-week cluster with 14 week conventional found:²
  - Cluster reduced time to maintenance dose by 57%
  - Earlier symptom/medication reduction.
  - No differences in SRs compared with conventional schedule.

Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

Methods: A retrospective, observational review in a large, multicenter group regarding cluster IT safety

Maintenance dose based on AIPP guidelines, most premedicated

Results: Data from 441 cluster patients. 48 patients (10.9%) experienced SRs

Based on the WAO SCIT SR Grading System,

- 18 grade 1 reactions (38.3%),
- 23 grade 2 reactions (48.9%),
- 5 grade 3 reactions (10.6%),

Compared with clinics conventional IT during 2-yr period with 12,963 receiving SIT:

SR rate 0.043% of IT visits and 2.2% of patients

Higher systemic reaction rate with aeroallergen cluster immunotherapy in a clinical practice

- **Risk factors** for a systemic reaction included: female sex, asthma, age 21 to 40 years, and inclusion of certain allergens in the immunotherapy vaccine (grass, weed, cat, & dog)

- **Conclusions** Cluster buildup may lead to a higher rate of systemic reactions. Identifying risk factors for systemic reactions will help improve the safety of cluster immunotherapy.

Table 7. Concentration of Immunotherapy Extract Leading to Systemic Reactions

<table>
<thead>
<tr>
<th>Concentration of extract (vol:vol)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1,000</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1:100</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>1:10</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>1:1</td>
<td>17 (35.4)</td>
</tr>
</tbody>
</table>

Table 8. Time from Eliciting Injection until Onset of Reaction

<table>
<thead>
<tr>
<th>Time until onset of reaction (minutes)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>15-30</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>31-60</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>13 (28.8)</td>
</tr>
</tbody>
</table>

Study: Controlled retrospective analysis of SR rate in a sample of cluster versus conventional schedule SCIT pts. Patients had high degree of STR: had to have at least ≥ 5mm wheal on PST to dust mites, cat, dog, or ragweed, plus at least one additional inhalant allergen.

AR ± controlled asthma: PEFR and pre-injection questionnaire before AIT administration

Cluster schedule 8 visits and 18 step protocol from ITPP 2nd Update

Both groups premedicated with an antihistamine and montelukast at least 2 hours prior to AIT injection with exception of one conventional pt pretreated with monteleukast alone.

Systemic Reactions in a Sample of Multiallergen Cluster vs. Conventional Schedule Patients

- Total of 2,157 injections between the two groups, 634 in the cluster group and 1,523 in the conventional group.
- **No statistically significant difference** in the proportion of SR per patient (p=0.414) between the cluster and conventional group.
  - Cluster (21): 4 SR in 3 patients.
    - 14.3% of patients and 0.6% of injections
  - Conventional (20): 6 SR in 6 patients.
    - 30% of patients and 0.3% of injections
- Office historical SR rate (2008): 9 SR in ~4,160 injections- 0.2% per injection.

Premedication with accelerated immunotherapy schedules.
Summary Statement 57:
Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy build-up protocols. A Cox et al, J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55

Premedication
Rush Immunotherapy (RIT)
Patients receiving 1 or 2-day RIT should receive premedication starting 2 days prior to the procedure to reduce the likelihood of a systemic reaction.

- **H-1 antagonist**
  - Cetirizine
  - Fexofenadine
  - Diphenhydramine

- **H-2 antagonist**
  - Ranitidine

- **Corticosteroid**
  - Prednisone
  - Monteleukast

- **Leukotriene receptor antagonist**
Measures to Improve Safety Premedication

Antihistamines

– Studies with RIT & cluster suggest decreased incidence of local and SRs with inhalant and VIT

– Conventional IT:
  • One DBPC study found premedication with fexofenadine reduced # of severe SRs, ↑ number of pts who reached TMD & ↓ time to TMD\(^1\)

Leukotriene receptor antagonist

– Anecdotal reports of reductions in SR rates. One DBPC study demonstrated ↓ LLR during venom RIT with moneleukast\(^2\)

1. Ohashi et al, Ann Allergy Asthma Immunol 2006; 96
2. Wohrl et al., Int Arch Allergy Immunol 2007;144:137-42
Effect of 16 week pretreatment with omalizumab on the tolerability of AIT in moderate persistent allergic asthma inadequately controlled with ICS

Severity of First Systemic Allergic Reaction
Patients who experienced SR: omalizumab 13.5%, placebo 26.2%

P = 0.017

Accelerated Immunotherapy Schedules

Onset of Efficacy

"Time course of improvement. Summary Statement 22: Clinical and physiological improvement can be demonstrated very shortly after the patient reaches a maintenance dose. A"

Effect of RIT on airway inflammation and AHR after bronchoprovocation with allergen in asthma.

- **Protocol**: 8 dust mite-allergic asthma pts treated with RIT vs. 6 untreated controls. Protocol included premedication with antihistamine and dose increment modified for LR> 8 cm.

- **Efficacy parameters studied**: Laboratory studies performed at baseline and 6 months after RIT: total & EG2 eosinophils, sputum ECP

- **Results**: All of the parameters studied after 6 months of RIT were significantly changed in the RIT group.

- **Symptoms scores** improved significantly after one month from baseline and showed progressive improvement through 6 months. Similar pattern seen in PEF measurements.

Kohno et al, J Allergy Clin Immunol 1998; 102 (6) 927-9349
Cluster Immunotherapy: Immunological changes at 5 weeks predictive of 52 weeks

- 3 studies (28 pts each) that investigated dose response of cat or dog extract compared placebo, 0.5, 3 and 15 mcg of Fel d 1\(^{1,2}\) or Can f 1\(^3\)
- Found 15 mcg had the greatest/most consistent efficacy in terms of objective parameters
- Immunological changes at 5 weeks reflective of 52 weeks
- Loaratadine, r loratadine +zarfirluscast 2 hrs before: 1 SR in 3 studies-urticaria 1\(^{\text{st}}\) dose in vial 1 (loratadine +zafirlucast) \(^2\)

1. Ewbank JACI 2003; 111: 155-161
2. Nanda et al, JACI; 2005 114: 1339-1344
3. Lent et al, JACI 2006 118: 1249-125
Cat Immunotherapy Objective Parameters: Dose and Timing

**Titrated Nasal Challenge**

![Graph showing titrated nasal challenge results.](image)

**End Point Dose of Cat Extract of Titrated Prick Skin Tests**

![Graph showing end point dose results.](image)

**Cat-Specific IgG4**

![Graph showing cat-specific IgG4 levels.](image)

Dose Response
- 5 weeks $p = 0.014$
- 1 year $p = <0.0001$

Maintenance dose of Fel d 1
Summary: Alternative Schedules & Premedication

• **Aeroallergen RIT** - greater risk, **cluster** - data conflicting

• **Venom RIT** appears as safe as conventional with no predmedication - but verdict out on fire ant

• **Risk Factors For Systemic Reaction With Accelerated AIT**
  • Degree of skin test reactivity
    • Portnoy et al found that the most important predictor of a systemic reaction was the initial wheal size.
    • Bousquet et al found a correlation with STR & SR
  • FEV₁ < 80% predicted
  • Dose: increased SR with > vial 2 (1:10 v/v) 0.1 ml

• Premedication reduced SR rate in RIT & Cluster aeroallergen studies

• Premedication does not increase severity or frequency of SR by masking early warnings.

• Clinical efficacy can be seen early with accelerated AIT
WAO Sublingual Immunotherapy Position Paper: SLIT Efficacy

• Up to June 2013: 78 RCT-DBPC trials of SLIT with aeroallergen.
  – 62 conducted with grass (39) or HDM(23) extracts.
  – 5 with parietaria, 4 ragweed, 7 with other allergens (Alternaria, Ambrosia, cypress, cat, olive).
  – 5 were totally negative, 8 inconclusive.
• Dosing range between 5 and 375 times that used in equivalent SCIT course, but largely variable from trial to trial.
• Several large (N>100) grass tablet studies dosing -15-25 mcg Phl p 5
  – Symptoms and medication scores: 20 to 35% over placebo
  – Literature suggests that overall, SLIT is effective, although differences exist among allergens and formulation.

SLIT Efficacy: Effective dose may vary by extract and formulation

- Grass
- Dust mite
- Cat
- Ragweed
- Cockroach
- *Alternaria*
- Trees
First Successful Phase III North American Grass Tablet Study

**Methods:** DBPC study of 345 children (ages 5-17 years), 89% of the multisensitized. Treated ~ 16 weeks before and during 2009 grass pollen season with 2,800 BAU, ~ 15 mg of Phl p 5 or placebo

**Results:**

- **Efficacy:** SLIT compared with placebo had improved
  - Combined score (26%, P=0.001)
  - Daily medication score (25%, P= 0.002)

- **Safety:** Majority of AE were local reactions.
  - Epinephrine (3): 2 SLIT, 1 placebo
    - SLIT: cough, lip angioedema 1st dose
    - SLIT: ER visit – dx with viral pharyngitis
    - Placebo: 12 hours after 137 dose-wheezing but thought to be related exposure to grassy field

* Blaiss et al., J Allergy Clin Immunol. 2011;127(1):64-71
Clinical Efficacy of Grass Table SLIT by Baseline Timothy-specific Serum IgE

- Significant improvement in CS in patients with sIgE >0.1 kUa/L
- No improvement or increased symptoms in patients with sIgE <0.1 kUa/L
- No treatment-related reports of anaphylaxis, asthma or epinephrine use

Efficacy and Tolerability of a Ragweed Allergen Tablet During Peak Season in North American Patients

- **Study:** 565 adults with ragweed-pollen induced AR/ARC randomized to daily 6, or 12 Amb a 1-U tablets or placebo; 4 months pre and, coseasonal, followed for total 52 weeks
- **Efficacy:** Compared with placebo a dose dependent response
  - 12 Amb a 1-U: 27% and 6 Amb a 1-U: 21 % (p<.05 both)
  - AIT 12 Amb a 1-U similar improvement in subgroups with/without Local Reactions
- **Safety:** Most AE local reactions with no SR reported,
  - 6 Amb a 1-U : pharyngeal edema, ER visit, epinephrine administered DDX allergic reaction vs anxiety

RC-DBPC, Parallel Trial of Standardized Short Ragweed SLIT Liquid Extract in Adult Subjects with Ragweed-Induced ARC

- **Study**: DBPC study of 429 (18-55 years) subjects with minimum ≥2 year history of moderate to severe ragweed AR/ARC randomized to SLIT with ragweed extract or placebo for minimum of 8 week pre-seasonal and co-seasonal
  - 3 step build-up: placebo, 18, 50 Amb1-U
- **Results**: Dose 94% achieved MTD - 50 Amb a 1 Units (1 Unit = 1 mcg Amb a 1); 3% Dose 2 - 18 Amb a 1 Units; 3% stepped-down from 50 to 18 Amb a 1 Units.
- RW pollen counts; Entire season: 44 pollen grains/m3; peak RW season: 86 pollen grains/m3

Creticos et al, JACI. 2013;131(2):AB146.
**Efficacy: Sublingual Ragweed Liquid**

**Efficacy:** Change in baseline - 43% reduction in the CSM score across the entire ragweed season relative to placebo.

**Safety:** No reported cases of anaphylaxis, no epinephrine use, and none of the TR-SAEs

Creticos et al, JACI. 2013;131(2):AB146.
Efficacy of SLIT with a Single Extract or as part of a Multi-Allergen-Extract Mixture in Patients with Grass SAR

<table>
<thead>
<tr>
<th>MAT Group, Allergen Extract</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Maple, Box-Elder</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Ash, White</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Juniper, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Elm, American</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Cottonwood, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Firebrush (Kochia)</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Ragweed, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Sagebrush, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Russian Thistle</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TM Group, Allergen Extract</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Diluent</td>
<td>9.0 mL</td>
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<tr>
<td>Caramelized Sugar</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>10 mL</td>
</tr>
<tr>
<td>Caramelized Sugar</td>
<td></td>
</tr>
</tbody>
</table>

• 54 randomized patients treated for 10 months
• CMD : Timothy ~ 30 x SCIT dose (19 mcg Phl p 5 q day or 2794 BAU)
• SCIT dose: 0.25-0.28 ml q am, held under tongue for 2 minutes, then swallowed

Clinical Efficacy of SLIT may be reduced with 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, sIgG₄, and decreased IFN-g levels compared to placebo
- **Multiallergen**: significant improvement in titrated SPT compared to placebo, but less than with TM
- Timothy alone arm demonstrated efficacy with 19 mcg Phl p 5 daily

**Clinical implications**: The clinical efficacy of SLIT may be reduced with the addition of multiple allergens, potentially limiting its use in polysensitized individuals.

“The superiority of one route of administration over the other is not known.”
Lin et al Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2013.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ALLERGEN</th>
<th>DESIGN</th>
<th>DURATION</th>
<th>N</th>
<th>OUTCOME</th>
</tr>
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<tbody>
<tr>
<td>Yukselen, 2011</td>
<td>HDM</td>
<td>Ran, DB, PC, DD</td>
<td>1 year</td>
<td>30</td>
<td>SCIT = SLIT (except for asthma scores when SCIT &gt; SLIT)</td>
</tr>
<tr>
<td>Keles, 2011</td>
<td>HDM</td>
<td>Ran, open, PG, Con</td>
<td>1.5 years</td>
<td>50</td>
<td>SCIT &gt; SLIT (rhinitis and total symptom and medication scores)</td>
</tr>
<tr>
<td>Eifan, 2010</td>
<td>HDM</td>
<td>Ran, DB, PG, Con</td>
<td>1 year</td>
<td>43</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Ventura, 2009</td>
<td>Cypress</td>
<td>Ran, DB, PC</td>
<td>1 year</td>
<td>40</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Tahamiler, 2008</td>
<td>HDM</td>
<td>Ran, open, PG</td>
<td>3 years</td>
<td>193</td>
<td>SCIT &gt; SLIT (symptom score)</td>
</tr>
<tr>
<td>Mauro, 2007</td>
<td>Trees</td>
<td>Ran, open, PG</td>
<td>1 year</td>
<td>34</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Khinchi, 2004</td>
<td>Birch</td>
<td>Ran, DB, DD</td>
<td>2 years</td>
<td>71</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Mungan, 1999</td>
<td>HDM</td>
<td>Ran, SB, PG, PC</td>
<td>1 year</td>
<td>36</td>
<td>No comparisons of SLIT/SCIT vs placebo or SLIT vs SCIT were made</td>
</tr>
<tr>
<td>Quirino, 1996</td>
<td>Grass</td>
<td>Non-Ran, DB, DD</td>
<td>2 years</td>
<td>20</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Piazza, 1993</td>
<td>HDM</td>
<td>Ran, open, PG, Con</td>
<td>2 years</td>
<td>43</td>
<td>SCIT &gt; control (combined symptom medication)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SLIT = control (combined symptom medication)</td>
</tr>
</tbody>
</table>
Efficacy of SCIT and SLIT with grass allergens for SAR: A meta-analysis-based comparison

• An indirect meta-analysis-based comparison between SCIT and SLIT tablets and solution. 36 RC-DBPC trials (3014 patients; 2768 controls) were analyzed

• The overall effect size of SCIT for symptom score was significantly higher than SLIT
  – SCIT (SMD, -0.92; 95%CI, -1.26 to -0.58)
  – SLIT drops (SMD, -0.25; 95% CI, -0.45 to -0.05)
  – SLIT tablets (SMD, -0.40; 95%CI, -0.54 to -0.27).

• Similar results were reported for medication score

• Conclusion: “Our results provide indirect but solid evidence that SCIT is more effective than SLIT” in controlling symptoms and medications in SAR

SLIT Compared With SCIT: 5 studies some combination of SCIT

- **Birch: Cirla 2003**: SLIT (birch) as add-on to SCIT (grass) cough better in combined vs SCIT alone
- **Mold: Bernardis 1996**: SCIT vs. SLIT: *Alternaria*: SLIT > rhinitis improvement (p= .013)
- **Grass: Quirino 1996**: DBDD SLIT vs. SCIT in grass SAR: symptom (both p=0.002) + meds (SLIT p=.002 and SCIT p=.0039) equally effective but significant change in SPT & sIgG in SCIT only
- **Dust mite: Mungnan 1999**: SLIT vs. SCIT vs. placebo in HDM rhinitis; improved med + symptom both, but improve asthma SCIT only
- **Birch: Kinchi 2004**: DBDD PC SLIT vs. SCIT Birch SAR: both groups improved, but > degree in SCIT
Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, PCDB, double-dummy study.

- Method: 3-year randomized, PCDB, double-dummy study in 71 adult (ages 20-58 yrs) rhinitis patients treated for 2 consecutive years after baseline year. SLIT +P, SCIT +P
- Cumulative median dose:
  - First year: 4.7 mg Bet v 1 in SLIT and 27 µg in the SCIT group
  - Second year: 11.2 mg in SLIT vs. 51 µg in SCIT.
- This corresponds to a difference of 175-219 times.


Figure 1. Flow-chart describing study including the number of patients at different time-points and withdrawals.
SLIT vs. SLIT
Greater magnitude of Improvement but not statistically significant

Relative Change in Symptom Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT</td>
<td>0.78</td>
<td>0.60, 1.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCIT</td>
<td>0.48</td>
<td>0.28, 1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>+1.45</td>
<td>0.87, 2.09</td>
<td>-</td>
</tr>
</tbody>
</table>

Relative Change in Medication Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT</td>
<td>1.03</td>
<td>0.77, 1.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SCIT</td>
<td>0.78</td>
<td>0.30, 2.00</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.01</td>
<td>1.02, 3.56</td>
<td>-</td>
</tr>
</tbody>
</table>

Effectiveness of Subcutaneous SLIT vs. SCIT for the Treatment of ARC and Asthma: A Systematic Review

• MEDLINE, Embase, and the Cochrane databases were searched through December 21, 2012

• 8 RCT compared the 2 forms of AIT in managing allergic asthma and ARC were reported in 4 and 6 clinical trials, respectively.

• **Low-grade evidence** supports greater effectiveness of SCIT than SLIT:
  – asthma symptom reduction
  – reducing a combined measure of rhinitis symptoms and medication use.

• **Moderate-grade evidence** supports greater effectiveness of SCIT than SLIT for nasal and/or eye symptom reduction.

• **Safety**: All 8 trials reported on adverse events with an episode of anaphylaxis reported in a child treated with SCIT.

A novel approach in SIT: combination of SLIT and SCIT

- Study 51 dust-mite asthmatic children randomized to SCIT, SLIT, SCIT plus SLIT, or pharmacotherapy for 18 months (ALK Alutard SQ & glycerinated extract)
- Build-up and maintenance phases was
  - 1.5 and 52.8 mcg of Der p 1 in SLIT group,
  - 16.2 and 44.1 mcg of Der p 1 in the SCIT group
  - 16.2 and 43.2 mcg of Der p 1 in the SCIT plus SLIT group

<table>
<thead>
<tr>
<th>TABLE E1. Immunotherapy schedule of the groups for 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLIT group</strong></td>
</tr>
<tr>
<td>Build-up phase</td>
</tr>
<tr>
<td>Vial 0: 1-5 drops</td>
</tr>
<tr>
<td>Vial 1: 1-5 drops</td>
</tr>
<tr>
<td>Vial 2: 1-5 drops</td>
</tr>
<tr>
<td>Vial 3: 1-5 drops</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Cumulative dose (Der p 1)</td>
</tr>
<tr>
<td>Cumulative dose (Der f 1)</td>
</tr>
<tr>
<td>750.7 STU</td>
</tr>
<tr>
<td>Maintenance phase</td>
</tr>
<tr>
<td>5 drops of vial 4 three times a week</td>
</tr>
<tr>
<td>Cumulative dose (Der p 1)</td>
</tr>
<tr>
<td>Cumulative dose (Der f 1)</td>
</tr>
<tr>
<td>26,400 STU</td>
</tr>
</tbody>
</table>

SQ-U, Standard quality unit; STU, skin test unit.

Keles et al, Journal of Allergy and Clinical Immunology. 2011;128(4):808-15 e7
A novel approach in SLIT: combination of SLIT and SCIT

- Asthma attacks and ICS decreased compared with baseline values at the months 4, 12, and 18 in the SCIT and SCIT plus SLIT groups but only at month 12 in SLIT group.
- Rhinitis VAS was significant only in the SCIT plus SLIT group.
- Increases in the levels of regulatory and TH1 cytokines were observed both in the SCIT and SLIT groups, with some differences in dynamics.
- Antigen-specific IgG4 levels increased in the SCIT and SCIT plus SLIT groups but not in the SLIT group.

Keles et al, Journal of Allergy and Clinical Immunology. 2011;128(4):808-15 e7
WARNING

Dangerous To Place Hands and/or Feet Near Eels.
They Do Bite!

SLIT Safety
SLIT Safety in Published Literature

- SLIT appears to be better tolerated than SCIT.
- No reports of SLIT-related fatalities to date in an estimated one billion doses.
- Majority of SLIT AEs are local reactions in the mouth and throat are common at the beginning of treatment, but resolve within a few days or weeks without any medication intervention.
- Dose-response relationship with AEs in some studies.
- No apparent relationship with updosing schedule and AEs.
- Several large (N>300 patients) grass-pollen tablet studies demonstrate good safety profile with no updosing.
- Few reported cases of anaphylaxis (at least 11).*

Sublingual Immunotherapy Safety Summary

- SLIT should only be prescribed by physicians with appropriate allergy training and expertise.
- Specific instructions should be provided to patients regarding the management of adverse reactions, unplanned interruptions in treatment and situations when SLIT should be withheld.
- Risk factors for the occurrence of SLIT severe adverse events have not yet been established. Although there is some suggestion that there may be increased risk in patients who have had prior SCIT systemic reactions.
- A uniform classification system for grading for AIT systemic reactions\(^2\) and SLIT LR has been developed by WAO\(^3\)

3. Passalacqua. Grading local side effects of sublingual immunotherapy: speaking the same language. Submitted for publication
SLIT in US Practical Considerations

- No FDA-approved formulation for SLIT
  - But FDA Allergenic Advisory Committee voted favorable on two SLIT grass-tablet in Nov 2013, considering a ragweed tablet end of Jan 2014
- To date no CPT code for SLIT
- Effective dose for many SLIT US licensed extracts not known
- Efficacy of monoallergen SLIT in polysensitized pts established but
- Efficacy of multi-allergen SLIT mixtures has not been established & most US patients are polysensitized
- Questions remain concerning appropriate patient instructions for management of this ‘at-home’ treatment e.g., gaps in treatment, when not to take
Perception of SLIT Among US Practicing Allergists

Two ACAAI Surveys
• 2007:¹ 828 (25.7%) respondents
  • 5.9% US allergists reported using SLIT
  • 94.1% did not prescribe SLIT:
    • Most cited reason lack of FDA-approved product approval: (61.7%)
    • Other barrier: effective dose is not known (27.5%)
• 2011:² 523 (16.7%) respondents
  • 59 (11.4%) answered they have used SLIT in their practice (compared with 2007, p<0.007)
  • Lack of FDA-approved product still # 1 reason
    • 90.2% cited this reason compared with 61.7% in 2007

1. Tucker MH, Tankersley MS. Annals of Allergy, Asthma and Immunology 2008; 101:419-25
Allergy Immunotherapy
Safety, Costs, Patient Preference and Adherence

Some Bad Outcomes
AIT Adherence with SCIT and SLIT= problematic

- Studies have reported widely varying rates of premature discontinuation for both SCIT and SLIT.
  - SCIT: rates of SCIT premature discontinuation: ranged from 6% to 84% (15 studies)
  - RCTs: Rates of adherence to SLIT have been generally good (70-90%);
  - The highest rate of SLIT premature discontinuation was reported in a retrospective analysis of pharmacy claims; among 3690 Dutch adults who initiated SLIT, only 7% completed 3 years of treatment.
  - A study that examined sales data from 2 large SLIT manufacturers found that less than 20% of SLIT prescriptions were continued after 3 years.
Poor Adherence Likely = Treatment Failure = Poor Outcomes

SCIT Duration in the Florida Medicaid Database Studies

**Adults (N=1,265)**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only once</td>
<td>30.0%</td>
</tr>
<tr>
<td>&lt;6 mos</td>
<td>18.2%</td>
</tr>
<tr>
<td>6-12 mos</td>
<td>10.0%</td>
</tr>
<tr>
<td>1-2 yrs</td>
<td>13.4%</td>
</tr>
<tr>
<td>2-3 yrs</td>
<td>9.6%</td>
</tr>
<tr>
<td>3-4 yrs</td>
<td>5.3%</td>
</tr>
<tr>
<td>&gt;4 yrs</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

Only 18.8% of adults completed a 3-year course of SIT

**Children (N=2,886)**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Only once</td>
<td>29.6%</td>
</tr>
<tr>
<td>&lt;6 mos</td>
<td>11.6%</td>
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<tr>
<td>6-12 mos</td>
<td>13.6%</td>
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<tr>
<td>1-2 yrs</td>
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<td>2-3 yrs</td>
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<tr>
<td>3-4 yrs</td>
<td>6.3%</td>
</tr>
<tr>
<td>&gt;4 yrs</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

Only 17.5% of children completed a 3-year course of SIT

Provided with permission Cheryl Hankin, PhD
How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' view

Italian sales figures from 2 large manufacturers representing 60% of AIT market

- SLIT treatments sold in 2006
- How many of the same SLIT prescriptions were renewed in subsequent 3 years,

Senna, et al. JACI 2010;126:668-9
## Comparison of Reason for Discontinuation Of Immunotherapy Between Different Administration Routes

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>SCIT</th>
<th>SLIT</th>
<th>LNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineffective</td>
<td>13.0%</td>
<td>24.9%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Expensive</td>
<td>39.6%</td>
<td>36.4%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>8.7%</td>
<td>5.8%</td>
<td>56.6%</td>
</tr>
<tr>
<td>Time consuming</td>
<td>24.2%</td>
<td>17.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Family problems</td>
<td>14.5%</td>
<td>15.0%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Panjo et al JACI 2005;116:1380-81
Improved SLIT Compliance with More Frequent Scheduled Visits

- **Study**: 300 children 6-16 yrs prescribed SLIT and randomized to 3 follow-up groups (100 each). Non-compliance if stopped before 2 years.

- Found significant difference between groups based on visit frequency
  - 4 visits a year; 18.5%
  - 2 visits a year; 32.3%
  - 1 visit a year; 70.4%

Figure 1: Percentage of patients who withdrew from treatment (SLIT) during the first, and the second year among those who had four clinical visits per year (Group A), two clinical visits per year (Group B) and one clinical visit per year (Group C).

Sublingual Immunotherapy in the US circa 2013

• SLIT Efficacy has been established i.e. proof of concept but
  • Effective dose and dosing regimen known for US licensed allergen extracts?
  • Because a consistent relationship between dose and efficacy has not been established each formulation must demonstrate its effective dosing regimen

• SLIT appears to be safer than SCIT and home administration is the standard of SLIT care in Europe
  • But adverse reactions may occur
  • Prescribing physicians should prescribe appropriate instructions: treatment of AEs, when not to administer, etc.
  • Should obtain informed consent including off-label status until FDA-approved product available
  • Adherence may be as problematic as SCIT-need strategies to improve
Novel AIT may increase the AIT

SCIT

Cons

Pros/benefits

Reduced symptom & medication scores, long term remission, prevention from disease progression

Inconvenience/patient time, cost, safety

55 Million
Allergy Sufferers

2 - 3 Million
Subcutaneous

10 - 15 Million
Undiagnosed/Expanding Immunotherapy
SCIT & SLIT Practical Consideration
Treatment initiation & adherence, barriers to care, and unmet needs

• Globally SCIT and SLIT prescribed at near equal frequency but only to a minority of allergic patients
  – ~2-9% of US AR population receives SCIT\(^1\)
  – Equally low usage in Europe ~5%

• Many factors likely account for low treatment initiation
  – Provider related: PCP A/I knowledge, willingness to refer/recommend and access to A/I specialist
  – Patient: costs; SLIT extract > SCIT, convenience; SCIT = requires more patient time

• Both require multiple year treatment courses and are associated with *very poor* adherence

U.S. SCIT Penetration is Minimal

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

- Rx: $5,497 (82%)
- OTC: $1,100 (16%)
- Immunotherapy: $125 (2%)

Sources: Rx figures from IMS; OTC figures from Chain Drug Review; Immunotherapy based on average of several sources
Immunotherapy Adjuvants

Toll-Like Receptor Ligands

- Mycobacteria
- DS RNA
- Endotoxins/Lipid A
- Flagellin
- Mycoplasma
- ssRNA
- CpG DNA

Protein Kinases → Transcription Factors → Gene Transcription

Provided with permission Tom Casale
Immune Stimulatory Sequence (ISS) CpG B type

• ISS of DNA containing a CpG motif covalently linked to the major ragweed allergen Amb a 1 (Tolamba)
• TLR9 agonist: shift immune response toward TH1
• Masks binding sites of Amb a 1 to IgE
• Stimulates Th2 to Th1 shift
• Improves safety margin
• Protocol: 6 injections in phase II and III trials with highest dose from 12 to 30 mcg Amb a 11

Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis

Method: 25 adults who with ragweed SAR six weekly injections of the CPG-Amb a 1 or placebo

0.06 to 12 mcg Amb a 1

Results: no change in primary end point NPC.

Significant improvement in 1st and 2nd year:

Peak-season rhinitis VAS
Peak-season daily nasal symptom diary scores
Midseason overall quality-of-life scores

Future of CPG?

*Dynavax Reports Interim TOLAMBA TM Ragweed Allergy Results from DARTT Trial press release. In; 2007.*
A-type CpG ODN is a strong inducer of IFN but has an unstable phosphodiester. Packaging A-type CpG ODN into virus-like particles (VLP) protects it against digestion by DNase I. A particle size of around 30 nm enhances transport into draining lymph nodes, and enhances phagocytosis, thus delivering the CpG directly to TLR9 in the endolysosome.
Use of A-type CpG oligodeoxynucleotides as an adjuvant in AIT in humans: a phase I/IIa clinical trial

Study: QbG10 as an adjuvant to HDM SCIT (10 weeks) in 20 patients

Results:

• **Clinical:** Within 10 weeks of therapy, “patients were nearly symptom-free and this amelioration lasted for at least 38 weeks post-treatment.” QbG10 was well tolerated.

• **Objective:** CPT almost complete tolerance, increase in allergen-specific IgG increased, and reduced STR. Skin reactivity to HDM was reduced.

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>34 weeks</th>
<th>48 weeks</th>
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<tbody>
<tr>
<td>RcSDL</td>
<td>10.5 (5.17)</td>
<td>1.5 (0.7)</td>
<td>3 (0.12)</td>
<td>2 (0.8)</td>
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<tr>
<td>AsSDL</td>
<td>2 (0.6)</td>
<td>0 (0.3)</td>
<td>0 (0.3)</td>
<td>0 (0.3)</td>
</tr>
<tr>
<td>CoR</td>
<td>3 (1.4)</td>
<td>0 (0.3)</td>
<td>1 (0.2)</td>
<td>0 (0.2)</td>
</tr>
<tr>
<td>CoA</td>
<td>3 (0.4)</td>
<td>0 (0.4)</td>
<td>0 (0.4)</td>
<td>0 (0.3)</td>
</tr>
</tbody>
</table>

Sent et al, Clinical & Experimental Allergy, 2009: 562,
Monophosphoryl Lipid A (MPL)

- MPL is TR-4 agonist derived from *Salmonella minnesota* cell wall
- MPL is adjuvant in licensed vaccines for many years: Melacine® & HPV vaccine, Ceravarix®
- Was added in the 90’s to an ultra short-course vaccine used since 70’s for SAR from grass, tree or ragweed:
  - Glutaraldehyde-modified allergen(aka allergoid) adsorbed onto L-tyrosine depot (delayed absorption)
- 4 pre-seasonal injections: highest dose 24 mcg of group 1 grass-pollen allergen
- US trials with positive results for grass and ragweed
A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, MPL reduces allergic symptoms after only 4 preseasonal injections

- DBPC study of 121 grass-pollen allergic who received 4 preseasonal injection: highest dose 24 mcg of group 1 grass-pollen allergen
- Statistical significant change vs placebo
  - nasal (P=0.016) and ocular (P=0.003) symptoms and combined symptom and medication scores (P=0.013) and titrated STR

Drachenberg KJ et al., Allergy 2001; 56: 498-5
Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

Method: DBPC 1027 patient randomized to 4 injection of modified grass vaccine (MATA MPL)

- Primary efficacy outcome – combined symptom medication score

Result: 13.4% benefit over placebo in the 4 peak pollen weeks (p = 0.0038).

• Post hoc analysis

  - Significant benefits over placebo were observed in subjects with severe symptoms (17.1%; p = 0.0023)
  - history of ARC for up to 35 years (up to 37.2%; p = 0.0059)
  - sites with a higher burden of disease (38.3%; p < 0.0001)

Ultra-short course grass AIT Efficacy in subgroup analysis

Mucoadhesive and MPL may Improve SLIT Efficacy

• **Mice**: BALB/c mice were OVA formulated with maltodextrin -- polysaccharidic formulated core (PSC-OVA)-enhance SLIT efficacy. ¹

• **Humans**: 80 grass pollen-sensitive subjects were randomized grass pollen extract with 4 different MPL content.
  - The 2 highest amount of MPL-SLIT groups had the highest proportion of negative NCTs after 10 weeks (47 and 44%, vs. 20% with placebo).
  - These patients also showed earlier median increases in specific IgG and smaller increases in IgE levels

1. Razafindratsita J Allergy Clin Immunol 2007;120
Recombinant Vaccines

**Advantages**
- Ultrapure defined molecules
- Consistent pharmaceutical quality
- Dosage in mass units: absolute standardization
- Dose optimization and formulation
- Precise monitoring of clinical and laboratory outcomes

**Disadvantages**
- Stringent production requirements
- Selection of isoforms
- High development costs, limited market potential
Allergen-specific immunotherapy with recombinant grass pollen allergens

- Method: DBPC study of mixture of 5 recombinant grass pollen allergens of 57 AR SAR, with or without asthma treated from 2002- fall 2003 (2 grass pollen seasons)
- 10 dose build-up subcutaneous injections at 7-day intervals then maintenance increased stepwise to 14, 28, and finally 42 day.
- Efficacy assessment: diary for 3 months during grass pollen season

Allergen-specific immunotherapy with recombinant grass pollen allergens

Results: Clinical significant improvements in favor of recombinant SCIT

– Combined Symptom + Medication score:
  • 38.9% reduction, p=0.04
– Rhinitis QAL in overall assessment and in 5 of 7 separate domains.
– Conjunctival provocation showed a “clear trend in favor of active treatment” although it was not statistically significant (P = .081).

• Immunological parameter: rSCIT-strong allergen-specific IgG1 and IgG4 antibody responses.
• Some patients were not sensitized to Phl p 5 but nevertheless developed strong IgG antibody responses to that allergen.
Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis

• **Method**: DBPC trial to compare the following 3 vaccines in 134 adults with birch pollen allergy: rBet v 1a, licensed birch pollen extract, natural purified birch pollen allergen (nBet v 1), and placebo.

  – 2 weekly injections followed by monthly injections of the maintenance dose containing 15 mcg Bet v 1 for 2 years.

• **Results**: New IgE specificities were induced in 3 of 29 patients treated with birch pollen extract, but in none of the 32 rBet v 1-treated or 29 nBet v 1-treated patients.

Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis

- All 3 treatment groups had significant reductions (about 50%) in RCSS, rescue medication and STR compared with placebo during 2 consecutive pollen seasons.
- Improvement associated with marked increase in Bet v 1-s IgG levels, which were higher in the rBet v 1-treated group.

Recombinant Vaccine Summary

• AIT with recombinant native pollen allergens appears to have a similar safety profile to commercially available SCIT preparations
  – >30% decrease in symptom-medication scores have been reported
• Hypoallergenic recombinant vaccines may provide safer treatments, but clinical efficacy has not been clearly established.
• Recombinant products include: - Dust mite - Cat - Grass - Ragweed - Tree
Peptide Immunotherapy

- Identifies and uses T-cell epitopes
  - Binds to MHC class II on APCs to induce TRegs to blunt allergic response
  - Less safety issues
- Lack of B cell epitopes in peptides avoids cross linking of mast cells avoiding need to dose escalate
- Too Small to Activate Mast Cells But Not T Cell
- Short course of immunotherapy
Cat Peptide Immunotherapy
Two Year Persistent Treatment Effect of Cat-Peptide Antigen

• Study: DBPC of 202 subjects who received one 2 dosing regimens vs. placebo
  8 doses x 3nmol 2 weeks apart
  – 4 doses x 6nmol 4 weeks apart
• Assessed in an environmental exposure chamber
  – Change TRCSS to cat allergen before and after treatment with 2 different regimens of Cat-PAD over a 3-month period.

Final product is a room temperature stable, lyophilised vial containing a mix of 7 peptides for injection.

Response to Cat Peptides in Chamber After 50-54 Weeks After Starting Treatment

Clear separation from placebo on all days

Repeated low-dose intradermal allergen injection suppresses allergen-induced cutaneous late responses

- Thirty adults sensitized to tree pollens were randomized to receive
  - 6 repeat intradermal injections at 2-week intervals of grass pollen extract (estimated 7 ng of Phl p 5 per injection,
  - 2 intradermal injections separated by 10 weeks, or)
  - A single intradermal injection at 10 weeks.
Repeated low-dose intradermal allergen injection suppresses allergen-induced cutaneous late responses

Visit 6

**Group A:** 6 repeat intradermal injections at 2-week intervals

History of EPIT

1911
- Immunological rationale for epicutaneous antigen administration: induction of specific AB (Besredka)

1917
- First case report on successful EPIT: cutiréaction répétées (Vallery-Radot)

1921
- Intradermal allergen-specific immunotherapy (Phillips)

1926
- Successful 'cuti-vaccination' against pollen allergy (Ramirez)

1936
- Use of the adjuvant alum to enhance safety and efficacy of SCIT

1000 BC
- India: first delivery of epicutaneous vaccination 'variolation' against smallpox
History of EPIT

- **1957**: Successful ‘quadrillage cutanée’ against pollen allergy (Patrizel and Blamoutier)
- **1970**: Concept of SALT Skin as an immunological organ (Streilein)
- **1983**: First RCTs proving clinical efficacy of EPIT against pollen allergy with the method of ‘adhesive tape-stripping’ (Senti and Kündig)
- **1998**: SLIT accepted by the WHO: first needle-free administration route of SIT
- **2009**: First RCTs of EPIT with the Viaskin system against food allergy (Dupont and Benhamou)

Senti et al. Allergy 2011
Epicutaneous Immunotherapy

- Epicutaneous (EPIT): Epicutaneous patch with grass pollen extract applied once weekly for 12 weeks and left in place for 48 hours each time beginning 4 weeks prior to and continued through the 2006 grass pollen season.

- Subjects receiving EPIT reported fewer symptoms than the placebo treated subjects for both the 2006 and 2007 grass pollen seasons.

- The major adverse effect was an eczematous reaction at the application sites.

Senti et al, JACI 2009;124:997-1002.
Epicutaneous Immunotherapy for Aeroallergen

• 132 patients with grass pollen-induced rhinoconjunctivitis redomized to placebo or 3 different doses of allergen
  – Before and during the pollen season 2008, patients received 6 weekly patches.
• Efficacy was assessed 4 to 5 months later (n = 110) and during the pollen season of the treatment-free follow-up year in 2009 (n = 93) via VAS.
• Hay fever symptoms during the pollen season were reduced by more than 30% in 2008 and by 24% in 2009 in the high-dose group as compared with that in the placebo group.

• Application was prepared by tape stripping the site on the upper arm 6 times with scotch tape
• Then, the patch was applied and the patient was observed
• for 30 minutes

EPIT Symptoms Improvement

Symptoms reduced by more than 30% in 2008 and by 24% in 2009 in the high-dose group as compared with that in the placebo group.

Adverse Reactions to EPIT

- Grading system per WAO Grading System for SR
- Eleven patients (8.3%) stopped treatment because of a systemic allergic reaction.

Intralymphatic Immunotherapy

<table>
<thead>
<tr>
<th>SLIT</th>
<th>SCIT</th>
<th>ILIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>

Allergen dose administered

Drainage to immune system

"Immunogenicity"

Allergen delivered to immune system

Clinical efficacy
Intralymphatic Immunotherapy

- **Intralymphatic (ILIT)**: non-controlled study was conducted with 165 grass-pollen allergic subjects comparing 3 injections of grass allergen extract into the inguinal lymph nodes at 4 week intervals to 3 years SCIT 3
- The total extract dose was more than 1000-fold less with ILIT.

ILIT shorter time to clinical efficacy and less systemic reactions

- Increased tolerance to nasal provocation within 4 months
- Systemic reactions were less frequent
- After three years, there were no clinical differences in outcomes between the two treatments.

Pain Associated with Intralymphatic Immunotherapy

Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections

- rFel d 1 fused to the HIV-derived translocation peptide TAT, mediating cytoplasmic uptake
- To enhance presentation through the MHC class II pathway
- Results in a modular antigen transporter (MAT) vaccine (MAT–Fel d 1)
- MAT–Fel d 1 in alum compared to ILIT with placebo (saline in alum) in cat allergic patients

Cat ILIT allergy induces tolerance after only 3 injections

- 3 intralymphatic injections with MAT-Fel d 1 compared with placebo statistical differences:
  - increased nasal tolerance 74-fold.
  - ILIT with MAT-Fel d 1 stimulated Treg responses
  - increased cat dander-specific IgG(4) levels by 5.66-fold.
  - IgG(4) response positively correlated with IL-10 production.

- Suspected drug-related adverse events was higher in the placebo group than in the MAT–Fel d 1 group but not statistically significant.

Allergen Immunotherapy In the Future in the US

General Take Home Points

• SLIT has established efficacy and safety but also has adherence issues as SCIT
• SLIT tablets most likely to be the first new allergen product approved in US
• Novel approaches seem promising but in relatively early stages in terms of ‘approval in the US’
  • Intralyphamatic/epicutneous for food and aeroallergens
  • Recombinants –? > efficacy over native
• Peptide cat via intradermal promising sustained effects
• OIT, SLIT and EPIT for food allergy: studies in progress