Assessing the Relative Risks of Subcutaneous and Sublingual Allergen Immunotherapy

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AAAAAI 2013
Disclosures

• None
Objectives

• Summarize recently updated data on the risks of adverse events to subcutaneous and sublingual allergen immunotherapy (SCIT and SLIT)

• Identify risk factors for adverse events, including systemic reactions to SCIT and SLIT

• Develop informed prescribing patterns for SCIT and SLIT that incorporate relative risks
History of SCIT related adverse events

- **1916** - Systemic reactions (SR) → 3.5 percent of subcutaneous grass pollen injections
- **1932** – Case report of fatal anaphylactic shock in patient receiving ragweed injections
- **1986** - Committee on the Safety of Medicines in UK reported 26 SCIT-related anaphylactic deaths over a 10-year period
- **1987 – 2007** – Retrospective surveys in US report 1 FR per 2.5 million injections; 1 Near-fatal reaction per 1 million injections\(^1,2,3\)

\(^1\)Lockey et al, *JACI* 1987, \(^2\)Reid et al, *JACI* 1993, \(^3\)Bernstein et al, *JACI* 2004
AAAAl 39 Year History of Fatal Reactions to Immunotherapy Injections in the US

82 confirmed fatalities

No confirmed fatalities in the US 2007-2012
AAAAI/AACAI prospective surveillance study on SCIT *(initiated in 2008)*

**Project AIMS:**

1. Estimate annual incidence of fatal reactions from SCIT and skin testing in North America
2. Define relative incidence of systemic allergic reactions of varying severity
3. Generate reliable and representative safety data for SCIT that can be compared with other forms of allergen IT
4. Identify clinical practice patterns that may modify risk of fatal and non-fatal reactions

Bernstein et al AAACI 2010; Epstein et al AAACI 2011, 2013
Participation– 4 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>1,922 prescribers of SCIT</td>
<td></td>
</tr>
<tr>
<td>August 2009 – July 2010</td>
<td>37%</td>
</tr>
<tr>
<td>1,453 prescribers</td>
<td></td>
</tr>
<tr>
<td>August 2010 – August 2011</td>
<td>27%</td>
</tr>
<tr>
<td>1,072 prescribers</td>
<td></td>
</tr>
<tr>
<td>September 2011-September 2012</td>
<td>27%</td>
</tr>
<tr>
<td>1,073 prescribers</td>
<td></td>
</tr>
</tbody>
</table>

Results (Years 1-4)

- No confirmed fatalities with SCIT or skin testing reported from 2008-2012

- Systemic reactions occurred in 82-85% of practices
  - 0.1% of injection visits
    - Similar to findings from other studies

Severity Grading of SRs (Years 1-3)

- **Grade 1 → Mild systemic reactions**: generalized urticaria *and/or* upper respiratory symptoms (e.g., itching of the palate and throat, sneezing)

- **Grade 2 → Moderate systemic reactions**: asthma (e.g., PEFR falls 20-40%) *with or without* generalized urticaria, upper respiratory symptoms or abdominal symptoms (nausea, cramping)

- **Grade 3 → Severe life threatening anaphylaxis**: severe airway compromise due to severe bronchospasm (e.g., PEFR falls more than 40%), *or* upper airway obstruction with stridor and/or hypotension (with or without loss of consciousness)
AAAAI/AACAI 4 Year Survey
Systemic reaction rate/10,000 injection visits

Bernstein AAACI 2010, Epstein AAACI 2011, 2013
Factors implicated in fatal SCIT reactions
(n=34)

1. Uncontrolled asthma 62%
2. Prior systemic 53%
3. Pollen season 47%
4. Epi delay, not given 43%*
5. Dosing/Admin Errors 35%
6. None reported 17%*
7. Inadequate wait 12%
8. Reaction began after 30 min 9%
9. Home administration 9%
10. β blockers/ACE Inh 2%/2%

Reid et al JACI 1993; n=17
* Bernstein et al JACI 2004; n=17
Factors implicated in near-fatal SCIT reactions
(n=68)

1. Height of allergy season 46%
2. Dosing/Admin Errors 25% (3 IM)
3. Uncontrolled asthma 10%
4. Prior systemic 9%
5. Epi delay, not given 6%
6. Inadequate wait 3%
7. β blockers/ACE Inh 3%
8. Late onset > 30 min 4%

Amin et al JACI 2006
AAAAI/ACAAI Year 3 Survey
Pre-injection methods for screening of asthmatics?

N=270 practices

Practices with Grade 3 SRs were no more likely to screen for asthma symptoms than those with only Grade 1 or no SRs

Epstein et al AAACI 2013
Routine Dose Adjustment During Pollen Seasons for 1,201 AAAAI members

- Survey results: 40% of practices in US routinely adjust doses during peak pollen seasons
  - Practitioners with >10 years in practice were significantly more likely to adjust doses (43% versus 28%; p=0.001)
  - Non-academic practices and practices with >100 SCIT patients were significantly more likely to adjust doses (p=0.001)
ACAAI/AAAAI Year 3 Survey

Do you routinely reduce allergen doses during peak pollen seasons?

(n=272 practices)

57%

44%

35%

65%

0%

10%

20%

30%

40%

50%

60%

70%

Percent of Practices

Only Grade 1 or No SRs

Any Grade 2 or 3 SRs

p<0.05

Epstein et al. AAACI 2013

Practices always reducing doses during peak pollen seasons were significantly less likely to report Grade 2 and 3 reactions than those reducing often, sometimes or never.
Does adjusting doses during Peak Pollen seasons in Build-up or Maintenance vials impact SR rates (Year 4; n=235)?

Practices never reducing doses during peak pollen seasons in build-up or maintenance vials were significantly more likely to report Grade 3 or 4 SRs.
Adverse reactions to Sublingual Allergen Immunotherapy (SLIT)

- Double-blind placebo controlled (DBPC) trials, outside US:
  - Adverse events reported in 17%- 60% of patients on SLIT and 8 - 14% on placebo

- Post-marketing studies on children and adults, outside US:
  - Side effects in 3 - 18% of patients, and less than 0.1% of doses

Most reactions are local (application site reactions), very mild, and resolve quickly

### Safety data from published trials in US

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>N/duration</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al, <em>JACI</em> 1993 Cat liquid</td>
<td>DBPC</td>
<td>41 subjects/ 105 days</td>
<td>Primarily oropharyngeal pruritus</td>
</tr>
<tr>
<td>Esch et al, <em>AAACI</em>, 2008 Timothy grass, Ragweed, Dust mite, Cat liquid</td>
<td>Phase 1, Open label</td>
<td>91 subjects / single-session escalation then 8 week open label</td>
<td>7.5 SAEs per 1,000 doses (91% local)</td>
</tr>
<tr>
<td>Amar et al, <em>JACI</em> 2009 Timothy grass liquid/ 9 pollens</td>
<td>Single center, DBPC</td>
<td>54 subjects/10 months</td>
<td>No difference in AEs between treatment groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No systemic reactions</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Study</td>
<td>N/Duration</td>
<td>Adverse events</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Skoner et al, JACI 2010</td>
<td>Multi-center DBPC</td>
<td>115 subjects/ 1-day dose-escalation then maximum tolerated dose through season</td>
<td>No sig difference between groups</td>
</tr>
<tr>
<td><strong>Ragweed liquid</strong></td>
<td></td>
<td></td>
<td><strong>None asthma-related, None required EPI</strong></td>
</tr>
<tr>
<td>Nelson et al, JACI 2011</td>
<td>Multicenter Phase 3 DBPC</td>
<td>439 with &amp; with/out asthma/ 16 weeks prior to season</td>
<td>73.8% treated, 27.6% placebo</td>
</tr>
<tr>
<td><strong>Timothy grass tablet</strong></td>
<td></td>
<td></td>
<td>One Grade 1 systemic reaction, treated with EPI</td>
</tr>
<tr>
<td>Cox et al, JACI 2012</td>
<td>Multicenter DBPC</td>
<td>473 adults/ 4 months before and through season</td>
<td>No Treatment-related SAEs</td>
</tr>
<tr>
<td><strong>300 IR 5-grass pollen tablet</strong></td>
<td></td>
<td></td>
<td>No Anaphylaxis or EPI</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Study</td>
<td>N/Duration</td>
<td>Adverse events</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>-----------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Creticos et al, 2013</td>
<td>Phase 3 DBPC</td>
<td>429 adults/ 8-16 weeks prior then through season</td>
<td>No Treatment-related SAEs, No Anaphylaxis or EPI</td>
</tr>
<tr>
<td>Ragweed liquid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nolte et al, 2013</td>
<td>Four DBPC trials</td>
<td>2,268 subjects/ Two 28-day and Two 52-week trials</td>
<td>No SAEs</td>
</tr>
<tr>
<td>Ragweed tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
List of Adverse Events experienced by 5% or more of SLIT-treated subjects

(Nelson et al. *JACI* 2011)

<table>
<thead>
<tr>
<th>AEs, no. (%)</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grass AIT group (n = 213)</td>
</tr>
<tr>
<td>Oral pruritus</td>
<td>75 (35.2)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>62 (29.1)</td>
</tr>
<tr>
<td>Ear pruritus</td>
<td>42 (19.7)</td>
</tr>
<tr>
<td>Oral paresthesia</td>
<td>29 (13.6)</td>
</tr>
<tr>
<td>Mouth edema</td>
<td>17 (8.0)</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>16 (7.5)</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
<td>14 (6.6)</td>
</tr>
<tr>
<td>URTI</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>9 (4.2)</td>
</tr>
<tr>
<td>Swollen tongue</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>4 (1.9)</td>
</tr>
</tbody>
</table>
Application site (local) reactions are common with SLIT

Reasons for variability among trials unclear, but in part may be due to lack of standardized criteria to describe reactions

TABLE I. Summary of percentage of patients with local symptoms from SLIT allergen versus placebo

<table>
<thead>
<tr>
<th></th>
<th>Grass</th>
<th>Mite</th>
<th>Tree</th>
<th>Parietaria</th>
<th>Ragweed</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen</td>
<td>0-65</td>
<td>0-52</td>
<td>0-65</td>
<td>0-5</td>
<td>~70</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Placebo</td>
<td>0-29</td>
<td>0 to &lt;5</td>
<td>0-25</td>
<td>0-5</td>
<td>13-40</td>
<td>0 to &lt;5</td>
</tr>
</tbody>
</table>

Casale, JACI 2009
Most application site reactions occur and resolve early in treatment course.

<table>
<thead>
<tr>
<th>AE</th>
<th>Grass AIT group (n = 213)</th>
<th>Grass AIT group (n = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Median</td>
</tr>
<tr>
<td>Oral pruritus</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>Mouth edema</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>63</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
<td>14</td>
<td>2.5</td>
</tr>
<tr>
<td>Stomatitis*</td>
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</tr>
<tr>
<td>Ear pruritus</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Oral paresthesia</td>
<td>29</td>
<td>1</td>
</tr>
</tbody>
</table>

*Indicates mild erythema and not ulcerations or infection.

Nelson et al, JACI 2011
Application site reactions rarely impact adherence

- Study of 316 subjects receiving grass tablets
  - 46% developed oral pruritus and 18% mouth edema
  - Less than 4% of subjects discontinued SLIT

Dahl et al JACI 2006; Cox Immunol Clin North Am 2011; Calderon Allergy 2012
Systemic Reactions (SRs) to SLIT

• **NO FATALITIES** have been reported with SLIT

• Review of 66 SLIT studies (4378 patients) that provided information on safety
  – Various dosing regimens, study designs, and reporting protocols
  – SRs occurred with 0.056% of doses administered
  – 14 probable treatment-related SAEs
    • 7 asthma exacerbations, 5 considered severe
    • Abdominal pain/vomiting, uvula edema, and urticaria

Cox  *JACI* 2006
Anaphylaxis is rare, but can occur with SLIT

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Scenario</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blazowskiet al, Allergy 2008</td>
<td>Missed doses for 3 weeks then self-administered 6X dose</td>
<td>Hypotension, asthma, ICU</td>
</tr>
<tr>
<td>Eifan et al, Allergy 2007</td>
<td>New start multi-allergen SLIT</td>
<td>Severe lip swelling, fever, chest pain, GI symptoms</td>
</tr>
<tr>
<td>Dunsky et al, Allergy 2006</td>
<td>New start multi-allergen SLIT</td>
<td>Generalized pruritus, severe hand/foot swelling, dizziness, wheezing</td>
</tr>
<tr>
<td>de Groot et al, Allergy 2009</td>
<td>2 cases with Grass tablet, <strong>both patients had previous SRs to SCIT</strong>, 1 patient with mild asthma</td>
<td>Case #1: Angioedema (tongue, eyes), urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case #2: Hypotension, asthma</td>
</tr>
<tr>
<td>Cochard et al, JACI 2009</td>
<td>Two cases with multiallergen liquid SLIT, Case #1: <strong>previous large local reactions to SCIT</strong>, Case #2: <strong>asthma exacerbations with SCIT</strong></td>
<td>Case #1: Repeated asthma attacks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case #2: Heavy nasal congestion, asthma</td>
</tr>
</tbody>
</table>
Summary and Conclusions

- The safety profile of SCIT may be improving since implementation of evidence-based guidelines in the US
  - No confirmed fatalities since 2007
  - SR rates of all severity grades have been stable
  - Risk factors are well defined
  - Asthma screening is almost universal
  - Strategies to further reduce risk, such as dose adjustment in peak pollen seasons warrant further study
Summary and conclusions

• Local reactions to SLIT are very common, but risk of SRs/anaphylaxis with SLIT is much lower
  – Caveats:
    • Potentially higher risk for reactions to SLIT among patients experiencing previous reactions to SCIT

• Consider risks of home administration with SLIT
  – More difficult to monitor for uncontrolled asthma and poor compliance
Summary and Conclusions

• Many unanswered questions about SLIT safety:
  – ‘True’ rate of local and systemic reactions to approved and unapproved products
    • Lack of standardized grading system for reactions
    • Many reactions not directly observed by physicians
    • Long term surveillance data in US needed in order to directly compare to SCIT
  – ?Risk of SRs to SLIT among patients with controlled and uncontrolled asthma
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