Immunotherapy: What is the preferable route?

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Chair Immunotherapy Committee CMICA, México
Member Immunotherapy committee World Allergy Organization
Dr Larenas has received speaker’s fees from Merck-Sharp-Dôhme, Astra-Zeneca, Pfizer, Novartis, MEDA; Travel grants from Sanofi, Novartis, UCB, MSD, Astrazeneca, Pfizer, Senosiain and is member of the advisory board of Pfizer, Novartis, MEDA.
WHAT IS THE PREFERABLE ROUTE?

- Safety
- Efficacy
  - In trials: Efficacy demonstrated per allergen and per allergic disease
  - In real life:
    - Correct diagnosis
    - Adherence ~ Patient’s preference
    - Long-term efficacy
    - Mono-multi allergic patients
- Example case
SAFETY OF IMMUNOTHERAPY: CONTRAINDICATIONS
No fatalities

Several anaphylactic reactions (8 in total)

Eosinophilic esophagitis (1 report grass pollen SLIT)


US surveillance study (Bernstein et al.):

- 1 fatality 2008-2012
  1/23.3 million injection visits

- Very severe, WAO grade 4, SRs (near-fatal reactions)
  1/1,000,000 injections

No fatalities officially reported in rest of the world

AAAAI members survey on SCIT under special medical conditions: contraindications or not (N = 1085)

Survey AAAAI Membership 2012-13

- 21% response rate (1085 AAAAI members)
- Expresses their experience with immunotherapy patients
- CAVE: Recall bias

In allergic patients with certain medical conditions:

1. Do you think immunotherapy is contra-indicated?
2. What has been your experience in giving AIT to these patients?
Practicing allergists respondents that have treated, would treat or believe below conditions are a contraindication for Allergen Immunotherapy

- % who thinks AIT is contraindicated in this condition
- % that would treat, but has not had any patient with the condition yet
- % that has treated patients with the medical condition

- Pregnancy, continue
- Hypertension
- Cancer, remission
- Autoimmune disease
- Coronary art. disease
- Arrhythmias
- Cerebro-vasc disease
- HIV +, not yet AIDS
- Hx BM transplant
- Hx solid organ transpl
- Severe asthma
- Cancer, still under Rx
- AIDS
- Pregnancy, start SCT
Total number of patients* with the medical condition that has been treated with SCIT by physician respondents

- Hypertension: 5423
- Severe asthma: 4129
- Coronary art.disease: 3518
- Cancer, remission: 3075
- Autoimmune disease: 2524
- Arrhythmias: 2442
- Cerebro-vasc disease: 1975
- Cancer, stable+Rx: 1329
- HIV +, not yet AIDS: 720
- Hx solid organ transpl: 420
- AIDS: 184
- Pregnancy, start: 179
- Hx BM transplant: 174
- Other: 142
Experience of those respondents giving SCIT to patients with an underlying medical condition: outcomes (Nr. of physicians (%))

- Severe asthma: 12.5% (No problems: 66, Minor problems: 290, Mayor problems: 172)
- Pregnancy, start: 1.9% (No problems: 10, Minor problems: 445, Mayor problems: 4)
- AIDS: 1.7% (No problems: 7, Minor problems: 328, Mayor problems: 11)
- Arrhythmias: 1.9% (No problems: 73, Minor problems: 67, Mayor problems: 4)
- Cancer, stable+Rx: 0.2% (No problems: 4, Minor problems: 36, Mayor problems: 3)
- Coronary art. disease: 0.1% (No problems: 191, Minor problems: 19, Mayor problems: 201)
- Pregnancy, cont: 1.6% (No problems: 80, Minor problems: 8, Mayor problems: 192)
- HIV +, not yet AIDS: 1.6% (No problems: 468, Minor problems: 9, Mayor problems: 2)
- Child < 5Y: 0.1% (No problems: 3, Minor problems: 2, Mayor problems: 2)
- Cerebro-vasc disease: Less than 1% (No problems: 543, Minor problems: 45, Mayor problems: 5)
- Hypertension: 4.2% (No problems: 43, Minor problems: 83, Mayor problems: 10)
- Cancer, remission: 1.7% (No problems: 482, Minor problems: 93, Mayor problems: 0)
- Hx BM transplant: 1.9% (No problems: 1, Minor problems: 10, Mayor problems: 0)
- Hx solid organ transpl: 1.5% (No problems: 1, Minor problems: 10, Mayor problems: 0)
### SAFETY

<table>
<thead>
<tr>
<th>Age</th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+ year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+ years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5+ years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Medical conditions**
  - Pregnancy, continue prospective
  - Hx Organ transplant
  - Cancer in remission
  - Cerebrovascular disease
  - HIV sero (+)
  - Hypertension
  - AIDS
  - Ca still under Rx
  - Pregnancy start
  - Coronary artery disease, arrhythmias
  - Autoimmune disease
  - Severe asthma
Efficacy: The Trials
Evidence of Efficacy

- Dose finding studies
- Cochrane metanalysis
- Metanalysis
- Systematic reviews
  - Double-blind placebo controlled trial(s)
  - Open, randomized trial(s)
  - Open trial(s)
<table>
<thead>
<tr>
<th>Author</th>
<th>Primary Disease</th>
<th>Publ year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnstone, multi</td>
<td>Asthma</td>
<td>1961</td>
<td>SCIT</td>
</tr>
<tr>
<td>Haugaard, HDM</td>
<td>Asthma</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>Olaguibel, HDM</td>
<td>Asthma</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Franklin, ragweed</td>
<td>Rhinitis</td>
<td>1967</td>
<td></td>
</tr>
<tr>
<td>Creticos, ragweed</td>
<td>Rhinitis</td>
<td>1989</td>
<td></td>
</tr>
<tr>
<td>Frew, grass</td>
<td>Rhinitis</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ewbank, cat</td>
<td>Cat allergy</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Nanda, cat</td>
<td>Cat allergy</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Lent, dog</td>
<td>Dog allergy</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Valovirta, tree</td>
<td>Rhinitis</td>
<td>2006</td>
<td>SLIT</td>
</tr>
<tr>
<td>Durham, grass</td>
<td>Rhinitis</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Didier, grass</td>
<td>Rhinitis</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Skoner, ragweed</td>
<td>Rhinitis</td>
<td>2010</td>
<td></td>
</tr>
</tbody>
</table>

**HDM tablet: Bergmann 2013 (Stallergènes), Mosbech 2014 (ALK)**

**Ragweed Tablet: Creticos 2014 (ALK)**

**Allergic rhinitis**

**SCIT (seasonal)**

**Allergen injection immunotherapy for seasonal allergic rhinitis (Review)**


SMD symptoms: -0.73
SMD medication: -0.57

**SLIT**

**Systematic reviews of sublingual immunotherapy (SLIT)**

S. Radulovic¹, D. Wilson², M. Calderon³ & S. Durham³

¹Paediatric Allergy, King’s College, London; ²Selly Oak Hospital, University Hospitals Birmingham; ³Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

SMD symptoms: -0.49
SMD medication: -0.32

- Lin et al. JAMA 2013: Decreases rhinitis symptoms (moderate evidence)
Allergic asthma

SCIT

Injection allergen immunotherapy for asthma

Michael J Abramson¹, Robert M Puy², John M Weiner³

¹Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia. ²Department of Allergy, Immunology & Respiratory Medicine, The Alfred, Melbourne, Australia. ³AllergyNet Australia, Melbourne, Australia

NNT symptom: 3
NNT medication: 4

SLIT

Systematic reviews of sublingual immunotherapy (SLIT)

S. Radulovic¹, D. Wilson², M. Calderon³ & S. Durham³

¹Paediatric Allergy, King’s College, London; ²Selly Oak Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK; ³Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

To cite this article: Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011; DOI: 10.1111/j.1398-9995.2011.02583.x.

DBPC big trials: HDM tablets: moderate statistically significant reduction in the ICS dose required to maintain asthma control. Mosbech JACI 2014, Bergmann JACI 2013
Allergic Conjunctivitis

SCIT

DBPC

SLIT

[Intervention Review]

SLIT for allergic conjunctivitis: Cochrane systematic review and meta-analysis.


SMD symptoms: -0.41
SMD medication: -0.10 NS

Systematic review classifying evidence according to risk of bias:
Lin et al. JAMA 2013: Decreases conjunctivitis symptoms (moderate evidence)
**SCIT**

Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials.

‘SCIT has a significant positive effect on DA: NNT 3. Moderate-level evidence for the efficacy of SCIT against atopic dermatitis.’


**SLIT**

**DBPC**
Venom immunotherapy

SCIT

[Intervention Review]

Venom immunotherapy for preventing allergic reactions to insect stings
Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, Oude Elberink JN.

SLIT

DBPC: large local reactions
<table>
<thead>
<tr>
<th>Efficacy</th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sx</td>
<td>Med</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AConjunctivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic derm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hymenoptera</td>
<td>Only for large local reactions</td>
<td></td>
</tr>
</tbody>
</table>
SCIT vs SLIT indirect comparison

• Both treatments are effective
• Trend in favor of SCIT, but NS

Efficacy: Real Life

- Adherence
- Long term
- Mono-multi
- SLIT is not SLIT
Real life: Adherence

• Dutch study: Adherence in real life (pharmacy data): 18% finishes 3 years. Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively (P < .001).

• Miami: low adherence for SCIT

• Anolik in US
Real life: Long term efficacy

• SCIT: 7 years
  o Randomized, controlled
    Jacobsen 2007

• SCIT 12 years
  o Open controlled
    Eng 2008

• SLIT: 2 years
  o DBPC
    Durham 2012, Didier 2013

• SLIT: 6 years (metacholine), 7-8y symptoms:
  o Retrospective: Depends on duration of SLIT: 7-8 years only after 4 years SLIT
    Marogna Int Arch Allergy Immunol 2007
Real life: SLIT: Mono-Multi issues

1. Does mono-allergen SLIT work in multi-sensitized patients?
2. Is mono-allergen SLIT safe in multi-sensitized patients? (pollen)
3. Does duo-allergen SLIT work in duo-allergic patients?
4. Does multi-allergen SLIT work in allergic patients?
Number of allergens mixed in one vial: Latin American countries

<table>
<thead>
<tr>
<th>Number of allergens mixed in one vial</th>
<th>% of countries*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mixing</td>
<td>11</td>
</tr>
<tr>
<td>Only 2 allergens</td>
<td>56</td>
</tr>
<tr>
<td>3-5 allergens</td>
<td>67</td>
</tr>
<tr>
<td>6-10 allergens</td>
<td>22</td>
</tr>
</tbody>
</table>

* In some countries several answers were given by respondents, we scored them all

Efficacy Grazax® in Mono vs. sensitized: Difference in sympt-medication scores (mean)

Mean combined difference grass SLIT vs. placebo

- **Sólo césped**: 1.62 (n=161)
- **Césped + 1 alergeno**: 1.70 (n=170)
- **Césped + 2+alergenos**: 2.15 (n=237)

*75,000 SQ-T/2,800 BAU Phleum pratense, ALK-Abelló

* Percentage reduction rounded to 1 d.p

2005 pollen season

- Weighted average daily pollen counts (grains/m³)
- Days since start of the season

**Courtesy: M. Calderón**
<table>
<thead>
<tr>
<th>Pollen sensitization type</th>
<th>One grass</th>
<th>Grass + 1 allergen</th>
<th>Grass + 2 or more allergens</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Grass SLIT</td>
<td>Grass SLIT</td>
<td>Grass SLIT</td>
<td></td>
</tr>
<tr>
<td>TEAE: Sí</td>
<td>74</td>
<td>79</td>
<td>112</td>
<td>0.7159</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>11</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Relación c/ Tx: Sí</td>
<td>63</td>
<td>71</td>
<td>103</td>
<td>0.2720</td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>19</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Prurito oral: Sí</td>
<td>41</td>
<td>43</td>
<td>61</td>
<td>0.3191</td>
</tr>
<tr>
<td>No</td>
<td>50</td>
<td>47</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Nasofaringitis No</td>
<td>14</td>
<td>16</td>
<td>17</td>
<td>0.9985</td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>74</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Edema boca: Sí</td>
<td>13</td>
<td>17</td>
<td>28</td>
<td>0.5030</td>
</tr>
<tr>
<td>No</td>
<td>78</td>
<td>73</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Influenza: Sí</td>
<td>7</td>
<td>3</td>
<td>13</td>
<td>0.4260</td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>87</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Prurito oído: Sí</td>
<td>16</td>
<td>12</td>
<td>10</td>
<td>0.2303</td>
</tr>
<tr>
<td>No</td>
<td>75</td>
<td>78</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Irritación garganta: Sí</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>0.3413</td>
</tr>
<tr>
<td>No</td>
<td>82</td>
<td>81</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Cefalea: Sí</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0.4304</td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>89</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>

Subjects with SLIT presenting treatment related adverse events: no differences between the mono- vs polysensitized

* Safety population; N=634; ** p value obtained using CMH test (general association) controlled for pollen sensitization type  
Cortesía: M. Calderón
Dual SLIT in dual-allergics

SLIT Birch only / grass only / Birch + grass

Dual grass-HDM SLIT drops reduces symptoms, medication and improves SPT and nasal challenge.

# Multi-mix SLIT: The Amar-Nelson Study

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Medication</th>
<th>Nasal provocation</th>
<th>Titrated SPT</th>
<th>Specific IgE</th>
<th>Specific IgG₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tim</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tim+9</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Bar chart](image)

- Symptom Score
  - Tim: $P=0.001$
  - T+9: $P=0.02$
  - Placebo: $P=NS$

**Delta Symptom Score**

- Tim: $-0.60$
- T+9: $-0.40$
- Placebo: $-0.20$

**Delta Log 10 Dose (BAU/mL)**

- Tim: $0$
- T+9: $0.20$
- Placebo: $0.40$

**P-value**

- Tim: $P=0.96$
SLIT : Mono-Multi issues

Yes
Does mono-allergen SLIT work in multi-sensitized patients?

Yes
Is mono-allergen SLIT safe in multi-sensitized patients?
(pollen)

Yes
Does duo-allergen SLIT work in duo-allergic patients?

Less
Does multi-allergen SLIT work in allergic patients?
SLIT IS NOT SLIT
# Relative monthly SLIT doses

Monthly doses of SLIT maintenance therapy given with the products of four prominent European manufacturers, relative to the US recommended SCIT monthly maintenance dose*  

<table>
<thead>
<tr>
<th>Manufacturers</th>
<th><em>D pteronyssinus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eur1</td>
<td>1</td>
</tr>
<tr>
<td>Eur2</td>
<td>1</td>
</tr>
<tr>
<td>Eur3</td>
<td>3</td>
</tr>
<tr>
<td>Eur4</td>
<td>16</td>
</tr>
</tbody>
</table>

* Monthly probably effective doses recommended in US for SCIT are given a relative value of 1. For house dust mite 1 = 1000AU, timothy grass pollen 1 = 2000BAU, cat 1 = 3.8 Fel d 1 Units and Short Ragweed pollen 1 = 9 Amb a 1 Units.(2)
Diferente composición extractos de ácaros: EEUU y Europea

Content of major allergens Der p 1 and Der p 2

Lab1 Der p 1  Lab2 Der p 1  Lab1 Der p 2  Lab2 Der p 2

<table>
<thead>
<tr>
<th>Der p 1 and 2 Concentration (µg/mL)</th>
<th>Eur1</th>
<th>Eur2</th>
<th>Eur3</th>
<th>Eur4</th>
<th>US1</th>
<th>US2</th>
<th>US3</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT maintenance solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCIT concentrates</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Relative potency (BAU) of grass Tablets

- Grazax® 2.800 BAU
- 10.000 BAU *Phleum pratense* 1.56cm² wheal surface.
- Tablets wheal surfaces correspond with 4.200 – 7.300 BAU

**Tablet A**

\[ y = 0.5198x + 0.1511 \]
\[ R^2 = 0.9856 \]

**Tablet B**

\[ y = 1.0201x + 0.143 \]
\[ R^2 = 0.9891 \]
What is the preferable route? Depends on:

- Correct diagnosis: which allergens?
- Availability of quality products
  - SCIT standardized, where possible
  - SLIT: high local concentration
  - Multi-allergic: SCIT might be preferable
- Allergic disease:
  SCIT/SLIT have different efficacy and safety profiles
- (Age of the patient)
- Logistics and Preference of the patient: ADHERENCE
EXAMPLE CASE

- France: 57yo female with allergic rhinitis symptoms all year long, exacerbating in spring, when she cleans the dusty environment and in her daughter’s home where there is a cat. She does not want to take so much medication any more.
- SPT positive for *D farinae*, cat, Alternatia and *Dactylis glomerata* and *Phleum pratense*.
- Would you give Immunotherapy?
- SCIT or SLIT?
- If SLIT: drops or tablets, mono or multi?