Sublingual Immunotherapy (SLIT): Is it ready?

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- Consultant: BrainLAB, Olympus, Medtronic
- Grants: FAMRI, NeilMed, Antigen Labs

History of SLIT

1986 British Committee on Safety of Medicines report

- 26 deaths reported from SCIT anaphylaxis
- New British requirements for SCIT:
  - Injections to be given in setting with full CPR capabilities
  - 2 hr observation post injection
- Significant decrease in SCIT in Britain followed
- ↑ interest in alternative IT routes
  - Intranasal
  - Oral
  - Bronchial
  - Sublingual
Support for SLIT

• SLIT deemed a viable and safe alternative
  – 1998 – World Health Organization (WHO)
  – 1998 – European Academy of Allergology and Clinical Immunology
  – 2001 – Allergic Rhinitis and its Impact on Asthma (ARIA)
    • Adults and children
• Increasing interest in SLIT worldwide
  – SLIT citations in English
    • 21 in 1999
    • 333 in 2008

Bosquet J. Clin Exp Allergy. 2002
Malling HJ, et al. Allergy. 1998

SCIT Safety vs SLIT Safety

• **SCIT**
  – Systemic reactions (non-accelerated escalation)
    • 0.05 – 3.2% of injections
    • 0.84 – 46.7% of patients
  – Near-fatal reactions
    • 23 per year
    • 5.4 per 1 million injections
  – Fatal events
    • 3.4 per year
    • 1 per 2.5 million injections

Malling HJ, et al. Allergy. 1998

SCIT Safety vs. SLIT Safety

• AAAAI/ACAAI SLIT Task Force Report
  – 66 studies, 4378 patients, 1,181,654 doses
  – **No fatalities**
  – Systemic reaction rate: 0.056% of doses
  – **Local reactions**: 0-100% of doses (dependent on reporting)
    • Common: oral itching, rhinorrhea, nausea, abdominal pain

Saporta, Am J Rhinol. 2008

Malling HJ, et al. Allergy. 1998
Does anaphylaxis occur with SLIT?

- **2006** – first reports of SLIT anaphylaxis
  - *Dunsky, et al.* – 31 y/o woman, 3rd day of multi-Ag SLIT (not witnessed)
  - *Antico, et al.* – 36 y/o woman, rush latex SLIT
    - Subsequent treatment at reduced dose, non-rush – well tolerated
- **2007**
  - *Eifan, et al.* – 11 y/o girl, multi-pollen SLIT maintenance phase, peak pollen season (lip swelling, GI symptoms – local reaction?)
- **2008**
  - *Blazowski* – 16 y/o girl, 3 week break from HDM SLIT, then 6x overdose
- **2009**
  - *de Groot, et al.* – 2 cases of first dose Grazax®, no escalation

Anaphylaxis

- **Suggestion of increased risk for SLIT systemic reactions:**
  - Asthma
  - Inability to advance or tolerate SCIT
  - No escalation or “rush” protocols
  - Multi-Ag therapy
  - Co-seasonal administration
  - Interruption in treatment protocols
  - High dose ranges

- Despite possible indicators of severe systemic reactions in few cases, large scale studies of SLIT have included patients with many of these factors – without significant reactions.

Additional Avenues for Treatment?

- **No large scale studies evaluating special patient populations...**
  - Severe asthma
  - β-blockers

- **Will the increased safety profile of SLIT eventually allow treatment of these patient groups?**

SLIT Efficacy...
Background

- 1986 – first randomized trial of SLIT
- No large-scale SLIT efficacy trials in United States
- SLIT is not FDA approved

Definition of Efficacy

- How is efficacy defined in clinical allergy trials?

  - **Subjective:**
    - Symptom reduction
    - Medication use
    - Quality of life assessment

  - **Objective:**
    - Immunologic changes
    - Provocation tests
    - Skin test reactivity
    - Lung function parameters

Definition of Efficacy

- Assessing the current data... comparisons are difficult!
  - Studies vary widely in:
    - Defining outcome measures of efficacy
      - Symptoms
      - Medication use
    - Treatment parameters
      - Duration
      - Schedule (preseasonal, coseasonal, perennial)
      - Dosing
  - Low patient numbers... recently improving

SLIT Efficacy – Allergic Rhinitis

<table>
<thead>
<tr>
<th>Study</th>
<th># studies</th>
<th>Inclusion criteria</th>
<th>mono/poly therapy</th>
<th>seasonal/perennial</th>
<th>SLIT vs. AR</th>
<th>Conclusion – SLIT efficacy in AR?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leatherman (2007)</td>
<td>36 (33 AR)</td>
<td>SLIT v. placebo or control</td>
<td>36 M 0 P 24 S 12 P</td>
<td>23 (+) 10 (-)</td>
<td>SLIT effective for AR</td>
<td></td>
</tr>
<tr>
<td>Cox (2006)</td>
<td>47</td>
<td>DBPC or RCT</td>
<td>_____ ~79% S _____</td>
<td>_____</td>
<td>65% efficacy in symptom, meds, or both</td>
<td></td>
</tr>
<tr>
<td>Malling (2006)</td>
<td>39</td>
<td>DBPC</td>
<td>_____</td>
<td>_____</td>
<td>28% effective 33% possibly effective</td>
<td></td>
</tr>
<tr>
<td>Canonica (2004)</td>
<td>27 (24 AR)</td>
<td>DBPC</td>
<td>27 M 0 P 18 S 9 P</td>
<td>17 (+) 3 (-)</td>
<td>SLIT effective for AR</td>
<td></td>
</tr>
<tr>
<td>Canonica (2003)</td>
<td>22 (20 AR)</td>
<td>DBPC</td>
<td>22 M 0 P 15 S 7 P</td>
<td>13 (+) 3 (-)</td>
<td>SLIT effective for AR</td>
<td></td>
</tr>
<tr>
<td>Malling (2002)</td>
<td>23 (21 AR)</td>
<td>DBPC</td>
<td>23 M 0 P 15 S 8 P</td>
<td>13 (+) 8 (-)</td>
<td>Most studies inadequate design</td>
<td></td>
</tr>
</tbody>
</table>
## SLIT Efficacy – Allergic Rhinitis
### Meta-analyses

- Update of Wilson meta-analysis 2002-2006
- 39 DBPC trials, 2746 pts
  - Standard mean difference
  - Symptom reduction ($p < 0.00001$)
  - Medication use ($p < 0.00001$)
  - Effect increases as treatment duration increases

→ **Conclusion – SLIT effective for AR**

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## SLIT Efficacy – Asthma
### DBPC Pediatric Studies

<table>
<thead>
<tr>
<th>Study</th>
<th># pts (age)</th>
<th>Allergen</th>
<th>↓ sympt vs. BL</th>
<th>↓ sympt vs. placebo</th>
<th>↓ meds vs. BL</th>
<th>↓ meds vs. placebo</th>
<th>Lung Fxn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahcelier</td>
<td>15 (7-18)</td>
<td>HDM</td>
<td>$p = 0.05$</td>
<td>$p = NS$</td>
<td>$p = 0.03$</td>
<td>$p = NS$</td>
<td>↑ PEFR</td>
</tr>
<tr>
<td>Rolinck-W.</td>
<td>97 (3-14)</td>
<td>Grass</td>
<td></td>
<td>$p = NS$</td>
<td></td>
<td></td>
<td>$p = 0.003$</td>
</tr>
<tr>
<td>Lux</td>
<td>20 (6-12)</td>
<td>HDM</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.047$</td>
<td>$p = 0.034$</td>
<td>$p = NS$</td>
<td>↑ PEFR 1 FEV1</td>
</tr>
<tr>
<td>Vavlovia</td>
<td>88 (5-15)</td>
<td>Tree</td>
<td></td>
<td>$p = 0.03$</td>
<td></td>
<td></td>
<td>$p = 0.04$</td>
</tr>
<tr>
<td>Stelmael</td>
<td>50 (6-17)</td>
<td>Grass</td>
<td>$p = 0.016$</td>
<td>$p = 0.02$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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## SLIT Efficacy – Asthma
### Preventative Effects

- **Marogna et al. (2008)**
  - Open RCT, 216 pts (ages 5-17), AR with/without asthma
  - SLIT (144 pts) vs. pharmacotherapy (72 pts)
  - Completion of therapy (3-years)
    - ↓ mild persistent asthma dx in SLIT group vs. control ($p < 0.001$)
    - Methacholine challenge positivity in SLIT group vs. baseline ($p < 0.001$)
    - New sensitizations in SLIT group vs. control ($p < 0.001$)

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## SCIT vs. SLIT

- **Double-Blind Double Dummy**
- **Quirino et al. (1996)** – grass pollen allergy
  - SCIT ($n = 10$) vs. SLIT ($n = 10$)
  - No placebo group
  - Equal efficacy for SCIT and SLIT in ↓ symptoms and ↓ medication
  - ↓ skin reactivity for SCIT only
  - ↑ total IgG and IgG4 for SCIT only

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*Radulovic et al. Allergy. 2007*


*Quirino et al. Clin Exp Allergy. 1996*
SCIT vs. SLIT

- Placebo Controlled Double-Blind Double Dummy
  - Kinchi et al. (2004) – birch pollen allergy
    - 71 pts randomized: SCIT vs. SLIT vs. placebo
    - All groups received drops and injections
    - Significant ↓ in symptom scores and medication use
      - SCIT vs. placebo
      - SLIT vs. placebo
    - No difference: SCIT vs. SLIT
- Cox review (2008) – Comparison of SCIT and SCIT
  Cochrane analyses: magnitude of improvement with SCIT may be greater

Monotherapy vs. polytherapy...

Monotherapy vs. polytherapy

- SCIT in U.S. - typically multiple antigens
- Vast majority of SLIT studies – monotherapy
  - Belief that IT is more effective in monosensitized or paucisensitized patients
  - Possibility of increased adverse reactions with polytherapy?
- Marogna et al. (2007)
  - 58 pts with seasonal reactivity to grass & birch
    - 48 completed
  - Randomized to SLIT-grass, SLIT-birch, SLIT-grass/birch, or pharmacotherapy
  - Symptom scores, medication use, nasal eosinophils
  - Improvement: polytherapy > monotherapy > control

Polytherapy – U.S. preliminary studies

- Saporta et al. (2007)
  - Observational survey design
  - Multiple antigen immunotherapy – SCIT & SLIT
  - 66 pts
    - Group I: SCIT → SLIT
      - 75% SLIT as effective as SCIT
      - 17% SLIT more effective
      - 8% SLIT less effective
      - 64% complete or near complete relief of symptoms
    - Group II: SLIT only
      - 70% complete or near complete relief of symptoms

Saporta et al. Ear Nose Throat J. 2007
SLIT Dosing...

SLIT Dosing

- Optimal SLIT dose and frequency of maintenance therapy has not been established
  - Effective allergen dose ranges 3-500x SCIT dose
  - Frequency – Up to TID
  - Treatment duration: months to years
    - Pre-seasonal
    - Co-seasonal
    - Pre- and co-seasonal
    - Perennial
- Despite wide ranges in dosing, SLIT efficacy & safety are preserved in most studies.

SLIT Dosing

- AAOA Sublingual Immunotherapy (SLIT) Update, Winter 2009
  - No universally accepted SLIT dosing schedule
    - Optimal SLIT dose ranges not yet determined
    - Effective allergen dose → 3-500x standard SCIT dose
  - No Ag products with U.S. FDA approval for SLIT
  - Majority of SLIT studies – single Ag
    - Dose extrapolation to multi-Ag vials?

Recent Large Scale SLIT Dosing Studies

- Multinational randomized DBPC dosing trials
  - 628 adult pts with grass pollen rhinoconjunctivitis (559 completed)
  - 100 IR, 300 IR, and 500 IR regimens (5-grass pollen mix)
    - ↓ symptoms (300 IR & 500 IR), ↓ rescue meds (300 IR)
  - No change: 100 IR or placebo
  - ↑ side effects: 500 IR
- → 300 IR dose recommended (considered “high dose” SLIT)
- Cox review (2008) – Clear dose-response relationship in AR studies
SLIT Escalation Protocols

• High safety profile → short SLIT escalation
  – Few effector cells (mast cells, basophils, eosinophils) in oral mucosa → ? increased tolerability
• Most SLIT escalation protocols: 4-6 weeks
  – Current consensus AAOA protocol: 12 weeks**
    • ** Potential updates to AAOA SLIT escalation protocol - Fall 2009
  – Rush (days), ultra-rush (hours), no escalation
• Quantitative allergy testing not necessarily required

Leatherman. AAOA Medical Update. 2007
Rodriguez et al. Int Arch Allergy Immunol. 2006
Kleine-Tebbe et al. Allergy. 2006
Ott et al. Allergy. 2009

SLIT Escalation Protocol
Taking the drops

• Place drops under the tongue for 2 minutes, then swallow
  – Looking in mirror or someone else watching
  – Responsible adult present

• Log date & time each SLIT dose is taken

• Epinephrine emergency injector accessible
  – Check expiration date when patients come to clinic!

SLIT Escalation Protocols
Proposed AAOA SLIT Escalation Revision

• Based on Greer short ragweed data presented at AAAAI
• 10-day escalation period
• 0.2 mL delivered per day during maintenance phase
  – Needle-free TB syringe used for daily dosing
• Maintenance dose of 7 mcg Ag per day

Sublingual Immunotherapy (SLIT) Update. AAOA Today. Winter 2009
**SLIT Escalation Protocols**

Many other options...

- Low dose SLIT with BID-TID administration
  - Escalation over many months
- Rush escalation: hours - days
  - Many U.S. allergen supply companies conducting studies
- No escalation
  - Grazax® tablet (ALK Abello, Horsholm, Denmark)
    - Rapidly dissolving single grass tablet – *Phleum pratense*
    - Not available in the U.S.

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**SLIT Immunology and Quality of Life**

- No known predictors of which patients will benefit from SLIT
  - Demographic factors
  - MQT EP
  - % positive Ags
- QoL improves over 400 days with continued SLIT

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**Adding SLIT to your practice...**
Adding SLIT to your practice

Mixing

• Options for mixing treatment vials
  – In-office
  – Send-out to third-party pharmacy

• In-office mixing safety measures
  – Keep SCIT and SLIT vials separate and distinctly marked!
  – Consider using different bottle types for SLIT and SCIT (e.g. glass dropper bottle vs. standard injection vial)

Adding SLIT to your practice

SLIT Safety Precautions

• Other considerations...
• Patient education
  – SLIT side effects
  – Signs of anaphylaxis
• Prescription for epinephrine self-injector for all IT patients
• Responsible adult present when drops dosed
• Dose & count drops while looking in mirror
• Consider giving first dose in clinic

Conclusions...

Conclusions

• SLIT traditionally has a higher safety profile vs. SCIT
• Many studies and meta-analyses support the efficacy of SLIT
  – Allergic rhinitis and asthma
  – Adults and children
• SLIT dosing & escalation protocols vary widely
  – Higher doses generally more efficacious
  – Maintenance typically reached in ≤12 weeks
• Immunologic changes are similar to those seen with SCIT
• Exact mechanism of action of SLIT is unclear
• Relationship between immunologic changes, QoL and SLIT outcomes remain to be defined
Unanswered Questions

- Statistical vs. clinical significance
- Magnitude of SLIT efficacy
  - Are we willing to accept slightly decreased efficacy for increased convenience & safety?
- Monotherapy vs. polytherapy
- Dosing regimens & escalation protocols
  - Safest & most efficacious
  - Dependent upon treatment Ag’s?
  - Seasonal vs. perennial?
  - Pre-seasonal, co-seasonal, continuous?
- SCIT vs. SLIT
- Long term efficacy of SLIT – preventative?