New Directions in Immunotherapy: Accelerated Schedules and Routes for Immunotherapy

Linda Cox, MD
Disclosures for Linda Cox, MD

For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

• Grant/Research Support from: None
• Consultant for: Greer
• Speaker’s Bureau for: None
• Major Stock Shareholder for: None
• Other Financial or Material Support from: Circassia SDMC, Medimmune Adjudication Committee, Novartis Adjudication Committee

I will be discussing products that are investigational or not labeled for use under discussion.
Acceralted Schedules and Routes for Immunotherapy

• 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 build-up schedules
    • Subcutaneous with modified allergens (adjuvants & recombinants)
    • Peptide immunotherapy
    • Epicutaneous immunotherapy
    • Intralymphatic immunotherapy
**SCIT > 100 years**

**Start date 1911**

**2014**

**Paper**


**AIT Caveats**

- AIT 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

**FDA approves 3 SLIT tablets products:**
- Oralair®
- Grastek®
- Ragwitek®
Allergy immunotherapy: Reduced health care costs in adults and children with allergic rhinitis

Adults: 3,330,245
Children: 4,193,986
All AR diagnosis: 436,373 (5.8%)
New AR: 307,809

Had ≥ 2 SCIT after AR diagnosis
Adults: 2,398
Children: 5,972

No SCIT
Adults: 70,083
Children: 227,095

Newly-AR-diagnosed adults and children receiving de novo SCIT = 2.7%

Matched SCIT
Adults: 1,319
Children: 3,648

Matched to 8 variables: including Charlson Comorbidity Index

Matched Control
Adults: 4,815
Children: 14,463

38% reduction in 18-month total health care costs in AR patients treated with SCIT vs. matched controls

- **Results:** Significant 18-month total healthcare cost reduction in SCIT group compared with match control who did not receive SCIT
  - 42% children
  - 30% adults
- Significant savings seen beginning at 3 months
- Significant reductions in inpatient, outpatient and pharmacy costs

US Allergy Market: only a small percentage receive AIT

Total Estimated Sales are $4.6B for 2014 (M$)

- **Rx Market, 1,940** (40%)
- **Immunotherapy, 174** (4%)
- **OTC Market, 2,500** (56%)

The Past: 2006 US Allergic Rhinitis Sales
U.S. SCIT Penetration = Minimal

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
Perceptions of Barriers to Subcutaneous Immunotherapy By Specialty


- **Patient Concern/Lack of Commitment on the Need for Frequent Office Visits**
  - Allergists (n=46)
    - Not a barrier: 0
    - Significant barrier: 5.3
  - PCPs (n=46)
    - Not a barrier: 0
    - Significant barrier: 5

- **"Needle Phobia"**
  - Allergists (n=46)
    - Not a barrier: 2.1
    - Significant barrier: 3.4
  - PCPs (n=46)
    - Not a barrier: 2.7
    - Significant barrier: 3.4

- **Cost of Therapy**
  - Allergists (n=46)
    - Not a barrier: 2.1
    - Significant barrier: 3.4
  - PCPs (n=46)
    - Not a barrier: 2.7
    - Significant barrier: 3.4

- **Limited Efficacy**
  - Allergists (n=46)
    - Not a barrier: 2.1
    - Significant barrier: 3.4
  - PCPs (n=46)
    - Not a barrier: 2.7
    - Significant barrier: 3.4

- **Side Effects**
  - Allergists (n=46)
    - Not a barrier: 2.1
    - Significant barrier: 3.4
  - PCPs (n=46)
    - Not a barrier: 2.7
    - Significant barrier: 3.4

- **Risk of Anaphylaxis**
  - Allergists (n=46)
    - Not a barrier: 2.1
    - Significant barrier: 3.4
  - PCPs (n=46)
    - Not a barrier: 2.7
    - Significant barrier: 3.4

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**Legend**
- Purple: Allergists (n=46)
- Blue: PCPs (n=46)
SCIT treats current symptoms prevents disease progression and cost-effective

What is the downside?
Why look in ‘new directions’?

**Safety**, Convenience and Adherence
SCIT Safety Summary

- **SCIT:**
  - Incidence of SRs dependent on multiple factors at a rate
    - ~0.1-0.2% 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
Prospective annual electronic survey AAAAI/ACAAI AIT
Overall 0.1% of injection visits

- Represents 1073-1922 providers
- Years 1 to 4: total of 23.3 million injection visits
- One confirmed fatality in 2009, 2nd fatality being investigated

“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
# Comparison of different immunotherapy build-up schedules for aeroallergens

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Rush</th>
<th>Cluster</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of visits during build-up</td>
<td>1 to 3</td>
<td>8*</td>
<td>30*</td>
</tr>
<tr>
<td>Time to reach maintenance dose</td>
<td>1 to 3 days</td>
<td>5 weeks*</td>
<td>15 weeks at a frequency of 2 times a week or 7.5 monthly if injections administered once a week</td>
</tr>
<tr>
<td>Range of systemic reactions**</td>
<td>Without premedication</td>
<td>15% to 100% of patients</td>
<td>22% to 100% of patients</td>
</tr>
<tr>
<td></td>
<td>With premedication</td>
<td>14% to 38% of patients</td>
<td>0 to 33% of patients</td>
</tr>
</tbody>
</table>

Modified from Cox L. J Allergy Clin Immunol 2008; 122:432-4. 2

*Based on examples in the Allergen immunotherapy: A practice parameter second update (AIPP) 2

** Cox et al, J Allergy Clin Immunol. 2010;125(3):569-7
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*

Cluster SCIT for Allergic Rhinitis: A Systematic Review and Meta-Analysis

- Eight trials involving 567 participants were included in this systematic review - all single allergen
- Safety: no differences existed in the incidence of either local adverse reaction or systemic adverse reaction between the cluster group and conventional or control group

Studies Comparing Cluster and Conventional Schedule utilizing single allergen- can safety data be extrapolated to multiallergen?

• RC and DBPC studies have demonstrated cluster has same AE incidence and achieves clinical efficacy sooner
  – DBPC dust mite AR ± asthma: 6-week cluster vs. 12-week:¹
    • No differences between the 2 schedules in terms of AEs
    • Improved clinical and objective parameters in the cluster 6 weeks earlier
  – RC dust mite AR comparing 6 week cluster vs. 14 week:²
    • Cluster reduced time to maintenance dose by 57%
    • Earlier symptom/medication reduction.
    • No differences in SRs compared with conventional schedule.

¹. Taber et al., J Allergy Clin Immunol 2005; 116:109-18
Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

Methods: A retrospective, observational review in a large, multicenter group
• 407 patients (92.3%) routinely premedicated 55.8% antihistamine alone, 3.4% montelukast alone, and 40.8% combination

Results: higher per patient SR rate with cluster
Cluster N= 441: SR in 48 patients (10.9%)
Clinics’ conventional AIT SR rate
N=12,963: 2.2% of patients/0.04% of AIT visits

Completed AIT: 393 with no SR: 188 completed cluster, 126 switched to conventional

Continuation, Grade, Timing and Dose Associated with Cluster SR

- SR pts completing AIT: 36/48 SR pts completed, 32 via conventional and 4 via cluster
- Based on the WAO SCIT SR Grading System: 10% grade 3
- Most SR in vial 1 or 2, none in 1:1000 v/v (vial 4)
- 55% of SR occurred >30 minutes after eliciting injection

<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>
<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>

Clinical and immunologic assessment of a cluster method during allergen immunotherapy refill dosing

- Initial dose for the cluster refill was the same as conventional refill (ie, a 50% decrease), but a second 50% dose with a second 30-minute observation period.
- Thus, study participants would reach their cumulative maintenance dose in one visit
- 53 consecutive cluster refills without systemic reaction

**TABLE 1. Characteristics of standard refill vs cluster refill**

<table>
<thead>
<tr>
<th></th>
<th>Last refill (n = 52)</th>
<th>Cluster refill (n = 52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (0)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. visits to reach maintenance dose</td>
<td>4.6 ± 1.4</td>
<td>1.0 ± 0.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. days to reach maintenance dose</td>
<td>31.0 ± 9.5</td>
<td>1.0 ± 0.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total time invested (h)</td>
<td>6.5 ± 3.6</td>
<td>1.9 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. total injections</td>
<td>7.7 ± 4.3</td>
<td>3.2 ± 1.3</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Values are mean ± SD, unless otherwise noted.
Cluster may be cost-effective

- **Prospective** randomized open study 38 DM patients treated with either-- 19 each group:
  - 3 week cluster 148 injections or
  - 13 week traditional build-up SCIT 251 injection
- **Local reactions**: 5.4% of injections in cluster and 2.4% of traditional build-up injections
- No systemic reaction was recorded.
- **Costs**: considering extract & injection costs and patient time, cluster regimen resulted in 244.95 euros per patient savings in the build-up phase.

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>Injection No.</th>
<th>Time, min</th>
<th>Concentration, volume:volume</th>
<th>Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1:10,000</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>1:1,000</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>1:100</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<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>

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

<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>
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</tr>
<tr>
<td>240</td>
<td>Undiluted concentrate</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Target Dose 0.1 ml of 1:10 v/v: SR 7.2% (n=111),
Previous protocol: Dose 0.05 ml of 1:1 v/v SR 18.1% (n=72)

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 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
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 TMD¹

Leukotriene receptor antagonist

– Anecdotal reports of reductions in SR rates. One DBPC study demonstrated ↓ LLR during venom RIT with moneleukast²

Omalizumab: 16 week pretreatment in asthma patients SR omalizumab 13.5%, placebo 26.2%

1. Ohashi et al, Ann Allergy Asthma Immunol 2006; 96
2. Wohrl et al., Int Arch Allergy Immunol 2007;144:137-42
Number of practices using various build-up strategies

AAAIAI/ACAAI AIT Surveillance Study (Year 4; n=270)

- Conventional build-up: 268 (93% of patients)
- Cluster build-up: 74 (4.6% of patients)
- Rush build-up: 32 (2.1% of patients)
- Other: 6 (0.5% of patients)

Provided with permission Tolly Epstein, MD
Grass and Ragweed SLIT Tablets Approved in US
WAO SLIT Position Paper Update*
Individual dose, frequency of dosing & efficacy found over a very wide range of allergen doses

A consistent relationship between allergen dose, treatment duration and clinical efficacy has not been established.

47 studies were chosen for efficacy analysis because they were either DBPC or RC studies

39 studies provided both symptom & medication scores

- **Effective**: In 14/39 (35%) of studies (included lowest dose used; 10 ng Fel d 1/3.6 mcg in 1 year)

- **No efficacy**: In 15/39 (38%) of the studies (included highest dose used; 314 mcg Amb 1-but began 4 wks before season)
SLIT superior safety: overcomes the inconvenience barrier to AIT but will it improve access??

- Majority of SLIT AEs are local reactions
  - Most oromucosal: mouth and throat itchiness, tingling
  - Some GI – considered LR if no associated systemic symptoms
  - Most occur in beginning of treatment and resolve within a few days or weeks without any intervention
  - Effect of AH premedication not known
- Few reported cases of anaphylaxis (at least 11)
  - No relationship with pattern with updosing schedule
  - No clear risk factors: a few prior SCIT SR* one after eating dry food **
- Two case reports of EoE with pollen SLIT

<table>
<thead>
<tr>
<th>Product name</th>
<th>Tablet active ingredient</th>
<th>Age years</th>
<th>Inactive ingredients</th>
<th>Dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORALAIR®</td>
<td>Sweet Vernal, Orchard, Perennial Rye, Timothy, Kentucky Blue grass pollens extract 2 strengths: 100 IR ~ 3000 BAU 300 IR ~ 9000 BAU</td>
<td>10-65</td>
<td>Mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate.</td>
<td>Pre-coseasonal: at least 4 months before</td>
</tr>
<tr>
<td>GRASTEK®</td>
<td>Timothy grass pollen extract 2800 BAU</td>
<td>5-65</td>
<td>Gelatin (fish source), mannitol, and sodium hydroxide</td>
<td>Pre-coseasonal: at least 12 weeks before. Perennial: “For sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK® may be taken daily for three consecutive years.”</td>
</tr>
<tr>
<td>RAGWITEK®</td>
<td>Short ragweed pollen extract 12 Amb a 1-U</td>
<td>18-65</td>
<td>Gelatin f(source), mannitol, and sodium hydroxide</td>
<td>Pre-coseasonal: at least 12 weeks before</td>
</tr>
</tbody>
</table>

From Sublingual Immunotherapy: a AAAAI/EAACI Practall; manuscript in preparation
SLIT Efficacy and Dose

- Wide range of doses ineffective and effective SLIT dose
- Effective dosing range between 5 and 375 times SCIT Equivalent monthly dose
- SCIT 5-25 mcg of major allergen per injection effective for many allergens
- SLIT effective dose may vary by extract and formulation
- Robust data tablet studies- possibly due to better and more consistent delivery of allergen

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Tablet</th>
<th>Extract Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass</td>
<td>15-25 mcg Phl p 5</td>
<td>?? 10- 40 mcg</td>
</tr>
<tr>
<td>Dust mite</td>
<td>Mixed Der p 1/Der f 1 148 mcg</td>
<td>*D farinae 2800 AU ( 20 mcg) or 4200 AU (70 mcg )</td>
</tr>
<tr>
<td>Ragweed</td>
<td>12 mcg</td>
<td>~50 mcg Amb a</td>
</tr>
</tbody>
</table>
## FULL PRESCRIBING INFORMATION

### WARNING: SEVERE ALLERGIC REACTIONS

- **GRASTEK** can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer **GRASTEK** to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- **GRASTEK** may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- **GRASTEK** may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)


No established patient guidelines for for EAI use in response to SLIT AE because this is not a routine or recommended practice outside of US
Limitations of Extrapolating SLIT Effective Dose From Published Studies

• Uncertainty regarding exact extract potency
  • Globally: lack of standardized allergen extract potency assays
    • Making comparisons and extrapolation very difficult
  • Europe: most allergen extracts reported in proprietary units,
  • US: only standardized assay for Amb a 1 and Fel d 1
• Some allergens not studied
  • Thus difficult to extrapolate effective dose if not studied
Costs of Epinephrine Not Insignificant

CVS Pharmacy

• Epipen estimated cash price $391 w/coupon $329.15
• Auvi-Q estimated cash price $431 w/ coupon $360.91

Source: National pharmacies
http://www.goodrx.com accessed 1/25/14

Source: Local Broward County Pharmacies- April 2014
SLIT and “required” Epinephrine Autoinjector Prescribing

- No safety signal to justify across the board AIE prescribing
  - Safety data very reassuring:
    - SCIT- One fatality in >23 million injections which occurred in office setting.
    - Severe SCIT SR outside of 30 minute wait rare and EAI did not seem to change outcome
    - SLIT: >one billion doses and nearly 3 decades=NO fatalities with standard practice being NO routine EAI
  - NO evidence that routine EAI prescribing for AIT saves lives OR evidence of improved healthcare outcome
“She’s going to need a prescription for light-headedness. She fainted when I told her how much her meds cost.”
ALLERGY IMMUNOTHERAPY ADHERENCE

SIMILAR TO OTHER THERAPIES FOR CHRONIC ILLNESS - POOR
Florida Medicaid Retrospective Claims
12 years; 7.5 million enrollees; 4151 received SCIT

SCIT Duration

Adults (N=1,265)

Children (N=2,886)

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

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

Real-world adherence to sublingual immunotherapy per pharmaceutical sales data

Question? How many new start SLIT prescriptions in 2006 were renewed until 2009

Answer: Not many and did not vary with seasonal vs. perennial

Senna, et al. JACI 2010;126:668-9
### Most Commonly Cited Reasons for AIT Discontinuation

**Among top 2 reasons listed for AIT discontinuation/nonadherence**

<table>
<thead>
<tr>
<th>SCIT (9 studies)</th>
<th>SLIT (7 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inconvenience (8)</td>
<td>Cost (4)</td>
</tr>
<tr>
<td>Concurrent illness (3)</td>
<td>Inability to take medication according to schedule/time consuming (3)</td>
</tr>
<tr>
<td>Cost (3)</td>
<td>Ineffectiveness (3)</td>
</tr>
<tr>
<td>Ineffectiveness (3)</td>
<td>Adverse reactions (3)</td>
</tr>
</tbody>
</table>

SCIT/SLIT effective but many barriers and unmet needs

- Globally SCIT and SLIT prescribed at near equal low frequency to allergic patients
  - ~2-9% of US AR population receives SCIT
- 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
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: successful phase II but failed phase III possibly due poor pollen season/patient selection

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.

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
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
Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

**Method**: DBPC 1027 patient randomized to 4 injections of Grass MATA MPL

- MATA: tyrosine-adsorbed, glutaraldehyde treated

**Result**: 13.4% improvement in CSM scores over placebo in peak pollen weeks (p = 0.0038).

- Post hoc analysis significant benefits over placebo were observed in subjects
  - with severe symptoms (17.1%)  
  - history of AR for up to 35 years (up to 37.2%)  
  - sites with a higher burden of disease (38.3%)

MPL-Ragweed Ultra-short SCIT

Study: RC-DBPC study of 288 ragweed AR comparing MATA-MPL, - MATA versus placebo in an environmental exposure chamber (EEC)
• 4 injections increasing dose one week apart
• EEC 3 weeks after treatment.

Results:
• MATA-MPL 48% greater mean improvement in symptoms scores with vs placebo, $p < .05$; (median improvement, 82%).
• No severe systemic AEs or serious AEs occurred during the study.

Conclusion: Study demonstrated that an ultra-short course of Ragweed MATA MPL is effective in a EEC and well tolerated

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
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
• **Intralymphatic (ILIT):** open study 165 grass-pollen AR 3 ILIT vs 3 year SCIT found faster onset efficacy per nasal challenged which persisted through 3 years

• Increased tolerance to nasal provocation within 4

ILIT: DBPC demonstrates clinical efficacy in nasal challenge response

- DBPC placebo (8) or active (7) grass ILIT received 3 injections of birch or grass ILIT 4 week intervals
- **Outcome:** patient assessment of symptoms - clear improvement over baseline seen in ILIT but not placebo
- **Nasal challenge:** ILIT associated improvement in nasal allergic symptoms and lowered levels of inflammatory cells and IL-8.

DBPB ILIT ‘natural exposure’ outcome study questions ILIT efficacy.

Study: DBPC study of 43 pts ARC randomized to 3 groups: 3 or 6 ILIT injections or placebo given “at least 2 weeks” apart

Results: No significant change

- Primary outcome SMS
- Global assessment or RQLQ scores
- The 3 injection group displayed a slightly negative result with a 12% higher total SMS

• Objective parameters:

- No difference skin test (ID) – no difference, sIgE
- Significant increase in IgG4 with ILIT (~2.9 fold)

Cat ILIT allergy induces tolerance after only 3 injections of modified vaccine

- Modular antigen transporter (MAT) vaccine (MAT–Fel d 1): rFel d 1 fused to the HIV-derived translocation peptide TAT
- Study: 3 intralymphatic injections with MAT-Fel d 1 compared with placebo statistical difference:
  - 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

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 of 2 dosing regimens vs. placebo: **same cumulative dose**
  - 8 doses x 2 weeks apart
  - 4 doses x 4 weeks apart
- Assessed in a environmental exposure chamber
  - Change in symptoms during cat allergen challenge
    - 2 year after treatment: efficacy with 4 dose regimen TRSS -5.87 vs. -2.02 placebo
- Phase III in progress: still recruiting—note inclusion must have 8 hrs/day cat exposure

**Protocol for a double-blind RC trial of low dose intradermal grass pollen AIT vs. control in SAR (PollenLITE)**

- **Rationale for ID AIT**: ID injection in animal models results in 100-fold higher rates of drainage to regional lymph nodes than SQ
  - more efficient pulsing of lymph node dendritic cells.
  - Dermis: rich LC, dermal DC, and lymphatics vs
  - SQ: mostly adipose and CT
- **Study**: Effect of 7-8 ID injections of 7 ng Phl p 5 on combined SMS in 90 subjects during grass-pollen season

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

- Proof of concept: 30 adults sensitized to tree pollens were randomized to receive
  - 6 repeated intradermal injections at 2-week intervals of grass pollen extract (estimated 7 nanogram of Phl p 5 per injection)
  - 2 intradermal injections separated by 10 weeks,
  - 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 produced significant reduction in LPR

Epicutaneous Immunotherapy for Aeroallergen AR

- 132 patients with grass pollen-induced ARC randomized to placebo or 3 different doses of EPIT
  - Before and during the pollen season 2008, patients received 6 weekly patches.
  - Application was prepared by tape stripping the site on the upper arm 6 times with scotch tape.
- Hay fever symptoms reduced by more than 30% in 2008 and by 24% in 2009 in the high-dose group as compared with placebo group.

Grading system per WAO Grading System for SR

Eleven patients (8.3%) stopped treatment because of a systemic allergic reaction.

Heat-denatured milk & egg — safe & effective for 75% - 80% of milk & egg allergic patients who tolerate heat-denatured protein; caveat - # developing EoE unknown

OIT — high rate of adverse reactions (~10% - 25% of doses mild and 5% moderate – severe of doses), ~75% - 80% will become desensitized initially (? long-term sustainability); caveat – up to 10% - 20% may develop EoE
- combined with anti-IgE may markedly improve safety

SLIT — safe but marginal desensitization, i.e. at least 10 to 20-fold less than OIT; no reports of EoE

EPIT — safe but low level desensitization to date, i.e. at least 10-fold less than OIT; awaiting results of longer-term, higher dose clinical trials; no reports of EoE

Provided with permission Hugh Sampson, MD
Allergen Immunotherapy
Current Practice and New Directions

• SCIT and SLIT most widely prescribed and both have:
  • Established efficacy and safety under recommended conditions
  • Appear to be cost-effective, disease-modifying
  • However, both require multi-year treatment
  • Have significant adherence issues
  • SLIT tablets he first new allergen product approved in US
• Accelerated schedules may make SCIT more convenient
• CRD may help make AIT more specific
• Novel approaches seem promising but in relatively early stages in terms of ‘approval in the US’
  • Intralymphatic/epicutaneous for aeroallergens
  • Recombinants –? If > efficacy over native
  • Peptide cat via intradermal promising sustained effects