Allergen Immunotherapy: An Update

Susan Waserman MSc MDCM FRCPC
Professor of Medicine
Division of Clinical Allergy and Immunology
CTS
Calgary
April 26, 2014
## Presenter Disclosure

<table>
<thead>
<tr>
<th>Presenter:</th>
<th>Dr Susan Waserman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationships with commercial interests:</td>
<td></td>
</tr>
<tr>
<td>Grants/research support:</td>
<td>N/A</td>
</tr>
<tr>
<td>Speaker’s bureau/honoraria:</td>
<td>GSK, Merck, Baxter Biologics, CSL Behring, King Pharma, Pfizer Canada, Sanofi Aventis, Nycomed Canada, Shire</td>
</tr>
<tr>
<td>Consulting fees:</td>
<td>GSK, Merck, Baxter biologics, CSL Behring, King Pharma, Pfizer Canada, Sanofi Aventis, Nycomed Canada, Shire</td>
</tr>
<tr>
<td>Other:</td>
<td>Scientific Advisory Committee on Respiratory and Allergy Therapies (Health Canada) Faculty McMaster University</td>
</tr>
</tbody>
</table>
Learning Objectives

To:

• Understand the treatment of allergic rhinitis (AR)
• Discuss immunotherapy (IT) in the treatment of AR
• To introduce a new form of IT, sublingual tablets, also know as SLIT-T
Allergic Rhinitis

Seasonal Allergic Rhinitis (SAR)
• Tree, grass and ragweed pollens
• Present from spring through fall

Perennial Allergic Rhinitis (PAR)
• Dust mites, cockroaches, molds and animal dander
• Chronic condition
Treatments can be used individually or in any combination

- Allergen avoidance
- Oral antihistamines
- Intranasal corticosteroids
- Leukotriene receptor antagonists
- Allergen immunotherapy (SCIT/SLIT)
# Level of Proof for AR Treatment

## ARIA 2011

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SAR Adults</th>
<th>SAR Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral H$_1$ antihistamines</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal corticosteroids</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal chromones</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Antileukotrienes</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Anti-IgEs</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Subcutaneous immunotherapy (IT)</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Allergen avoidance</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>
Nasal steroids
# Indications For INS

<table>
<thead>
<tr>
<th></th>
<th>PAR</th>
<th>SAR</th>
<th>vasomotor</th>
<th>polyps</th>
<th>sinusitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasonex</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Flonase</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Avamys</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Rhinocort</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Omnaris</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
Nasal salines
Why do Allergists Love IT?

- Subcutaneous immunotherapy (SCIT) has been used for over 100 years
- Well documented efficacy for AR and asthma caused by pollens, HDM, and cat
- What are the benefits of SCIT?
  - Relieves symptoms
  - Has disease-modifying effects
  - May prevent new sensitization and asthma
Reality of SCIT

• Only 2% to 9% of US patients, and 4% of Canadians with AR receive SCIT, and many stop it prematurely because of frequent office visits and the 30 minute wait time after injections\textsuperscript{1,2}

• Systemic allergic reactions occur in about 5%

• Small risk of death (1/2.5 million injections) but recent 3 year survey of 25 million showed no fatalities

IT Leads to Disease Modification Seen With Grass Pollen SCIT

• RCT of grass pollen IT in patients with a history of grass pollen allergy where shots were given for 3 years, then:
  – Grass pollen IT was continued for additional 3 years
  – Grass pollen IT was discontinued for 3 years
  – Compared to controls

• Results:
  – Patients who discontinued grass-pollen IT had similar symptom scores to those who continued

Long-term Clinical Efficacy of Grass Pollen IT

Study group
- Placebo
- Immunotherapy

Immunotherapy
- None (control)
- Discontinuation
- Maintenance

IT Prevents New Sensitization

HDM IT given for 3 years to 6 year old asthmatics mono-sensitized to HDM prevented new sensitization in 3 years of follow up

<table>
<thead>
<tr>
<th>Initial sensitivity</th>
<th>Number of patients</th>
<th>New Sensitivities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Cat</td>
</tr>
<tr>
<td>SIT</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Control</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

IT May Prevent Asthma
Specific IT for Grass and/or Tree Pollen Allergy for 3 Years in Children Prevents the Development of Asthma at 10 Years


Mean age 21 years at 10-year follow-up

Odds-ratio = 2.5
~1,500,000 patients were treated with AIT in Europe in 2012

SLIT ≈ Over 1 billion doses given
Sublingual Immunotherapy Tablet (SLIT-T)

- In Canada, there are now 2 new treatments (sublingual grass tablets) available for AR from grass pollen allergy
  - Oralair™ (age ≥6 yrs)-launched Nov/2012
  - Grastek™ (age ≥5 yrs)-launched Feb/2013
- Home based therapy, effective in first season
- Given at least 8 weeks before grass pollen season and during season, 6 months duration
Grass SLIT

- **Grastek™ (ALK-Merck)**
  - contains Timothy grass pollen
  - 2800 BAU (Bioequivalent Allergy Units)
- **Oralair™ (Stallergenes-Paladin)**
  - contains 5 grass pollens (Timothy, Sweet Vernal, Orchard, Perennial Rye, and Kentucky Blue Grass)
  - 300 IR (Index of Reactivity)
Grass SLIT-T
Indications and Clinical Use

• GRASTEK™ is indicated for reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive grass specific IgE titre, and who have responded inadequately, or are intolerant to conventional pharmacotherapy
Pathway of Allergen and Mechanism of SLIT-T in Oral Mucosa and Local Lymph Nodes

A. Allergen in sublingual space

Sublingual epithelium

Lamina propria

B. Submucosa

Lymphatics

To draining lymph nodes

C. Naïve T → Treg

Interaction with naïve and/or memory T cells within local lymph nodes

Th2 memory → Anergy?/Treg?/Th1?

D. Treg

B cell

IgG4

IgA

IgE

(-) B cell class switch

? Migration to effector mucosa

Th2

Inhibition of Th2 cells

Disease Modification Has Been Shown After 3 Years of Treatment in a Randomized Trial of Grass SLIT-T

Stephen R. Durham, MD, Waltraud Emminger, MD, Alexander Kapp, MD, PhD, Jan G. R. de Monchy, MD, Sabina Rak, MD, Glenis K. Scadding, MD, FRCP, Peter A. Wurtzen, PhD, Jens S. Andersen, PhD, Bente Tholstrup, MSc, Bente Riis, PhD, and Ronald Dahl, MD

*J Allergy Clin Immunol 2012;129:717-25*
Primary Endpoint

Total Combined Score = Daily Symptom Score + Daily Medication Score

TCS = DSS + DMS

- This is currently the agreed primary endpoint of many regulatory agencies (World Allergy Organization, the European Medicines Agency, and the Food and Drug Administration).

3 R. Raben. 2011; PEI seminar.
Combined Symptom and Medication Score For The Five Grass Pollen Seasons

Durham et al., J Allergy Clin Immunol 2012; 129: 217-25
Adverse Reactions Product Monograph ADR Adults /Pediatrics

- oral pruritus (26.7% vs. 3.5% placebo)
- throat irritation (22.6% vs. 2.8%)
- ear pruritus (12.5% vs. 1.1%)
- mouth edema (11.1% vs. 0.8%)
- most local allergic events were mild and transient with no progression to anaphylaxis
- more common in the first month of treatment
- symptoms generally resolved over time
Prevention of Asthma with SLIT

• 216 sensitized children without asthma randomized to treatment with:
  – medication alone or
  – medication + SLIT for 3 years
• IT with HDM (98), grass (41), birch (4), parietaria (1)
• Outcomes after 3 years:
  – clinical symptoms
  – methacholine reactivity
  – skin prick testing

Clinical Outcomes After 3 Years of SLIT

<table>
<thead>
<tr>
<th></th>
<th>Drugs + SLIT</th>
<th>Drugs Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Asthma</td>
<td>1.5%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Methacholine Positive</td>
<td>17.7%</td>
<td>47.0%</td>
</tr>
<tr>
<td>Polysensitized</td>
<td>44.6%</td>
<td>71.2%</td>
</tr>
</tbody>
</table>

p<0.001 for all parameters
# Metanalysis SLIT and SCIT Studies

Seasonal Allergic Rhinitis Symptoms and Medication Score improvement

<table>
<thead>
<tr>
<th></th>
<th>Studies Published</th>
<th>No. Studies Included</th>
<th>Participants Active/Placebo</th>
<th>Reduction in Symptoms/Reduction in medication usage</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT</td>
<td>1966-2009</td>
<td>49</td>
<td>2333/2256</td>
<td></td>
<td>&lt;.00001 for both*</td>
</tr>
<tr>
<td>SCIT</td>
<td>1984-2006</td>
<td>51</td>
<td>1645/1226</td>
<td></td>
<td>&lt;.00001 for both</td>
</tr>
</tbody>
</table>

*In SLIT metanalysis, of >2330 participants, none reported severe reactions or the need for epinephrine

## Comparison of symptomatic medications and AIT in seasonal allergic rhinitis

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Type of treatment</th>
<th>Number of symptoms scored</th>
<th>Evaluation period</th>
<th>% improvement vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analysis Benninger</strong></td>
<td>38</td>
<td>12,926</td>
<td>Anti H1</td>
<td>5</td>
<td>2 weeks</td>
<td>~9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCSs</td>
<td>4</td>
<td>2 weeks</td>
<td>~26%</td>
</tr>
<tr>
<td><strong>Meta-analysis Wilson</strong></td>
<td>11</td>
<td>3,924</td>
<td>Anti H1</td>
<td>5</td>
<td>2 weeks</td>
<td>~7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCSs</td>
<td>4</td>
<td>2 weeks</td>
<td>~17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LTRAs</td>
<td>4</td>
<td>2 weeks</td>
<td>~5%</td>
</tr>
</tbody>
</table>

**EU Clinical trials with Oralair®**  
3 patients  
1,539 patients (VO34, VO53, VO52)  
AIT  
6 (all the symptoms)  
~30 days (pollen season)  
~30%  
~40% for the highest tertile

**EU Clinical trials with Grazax®**  
3 patients  
1,742 patients (GT-02, GT-08, GT-12)  
AIT  
6 (all the symptoms)  
~30 days (pollen season)  
~30%  
~40% for the highest tertile
When to Refer AR to an Allergist

- To identify allergic triggers for proper allergen avoidance
- Patients’ AR symptoms are not controlled on medication
- Patient is having side effects to or does not want to take medication
- For consideration of IT
Dose Administration

• Tablet should be placed under the tongue, where it dissolves
• Instruct the patient not to swallow for 1 minute, and to avoid eating and drinking for 10 minutes
• Should be administered daily at approximately the same time each day
First Dose of SLIT-T

• Under MD supervision, 30 minutes of observation, appropriate equipment
  • Grastek™:
    • No build up-start at 2800 BAU
  • Oralair™:
    • Build up-100 IR Day 1
    • 200 IR Day 2
    • 300 IR daily

• Patients should be counseled that they may feel itching/swelling in the mouth/throat, itching in the ears
Conclusions

• In patients with grass pollen allergy who have not responded to or are intolerant to medication:
  • SLIT-T is a new, effective treatment option
    – demonstrated safety
    – suitable for pediatric use
    – administered at home
• Ragwiteck tablets for ragweed is coming!!