Sublingual Immunotherapy: A New Player in Allergy Management

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Grand Rounds
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Learning Objectives

- Review basic immunology of IgE-mediated allergic disease
- Understand the role of immunotherapy in immunomodulation
- Compare and contrast subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT)
- Reference the literature supporting the efficacy of SLIT
Disclosures

- I have no disclosures

- Will discuss off-label use of allergen extract in sublingual immunotherapy
OSU Otolaryngology-Head and Neck Surgery

- General Otolaryngology
- Head and Neck Oncology
- Skull Base Surgery
- Sinus and Allergy
- Laryngology/Voice Institute
- Neurotology/Otology
- Facial Plastics and Reconstructive Surgery
- Pediatric Otolaryngology
- Sleep Surgery
Why is allergy important in ENT?

- Chronic/recurrent sinusitis
- Nasal Obstruction
- Otitis Media/Effusions
- Laryngeal/Voice disorders
- Smell disorders
- Cough disorders
Allergic March
Immunology Overview
Types of Immune Responses

- Skin and Mucous Membrane Barriers
  - Location of Dendritic and Langerhans APC cells

- Innate Immunity
  - Complement, Neutrophils, Macrophages, NK cells
  - Phagocytosis

- Adaptive Immunity
  - Antibodies, B Lymphocytes, T Lymphocytes
  - Antigen driven
Immunology of Allergic Disease
Immunology of Allergic Disease: The Team

- Antigen/Allergen: usually protein epitope
  - Allergen is antigen that induces sIgE response
  - Requires prior exposure called sensitization

- Mast cells/Basophils
  - Second exposure elicits degranulation and release of histamine

- Eosinophils

- Antigen Presenting Cells (APC): MHC II
  - Monocytes/dendritic cells/Langerhans cells
Immunology of Allergic Disease: The Team

- **B cells**
  - APC, antigen specific plasma cells and memory cells
  - sIgA, sIgE and sIgG
- **T helper cells: TH2 and TH1**
- **T regulatory cells: down-regulate immune response**
- **Chemical mediators**
  - Histamine, Major basic protein
  - Cytokines IL4, IL13, IL5, IL10
  - PGE2, LTB4, LTC4
Immunology of Allergic Disease
Immunotherapy brings about balance by shifting the allergic immune response from a dominant Th2 response by increasing Th1 activity.
slgG4

- Up-regulated in immunotherapy
  - “blocking antibody”
- Defines immunomodulation
- Can class switch to slgE
- IgG1 increased as well

The allergen-induced B-cell response. Reprinted from
Journal of Allergy and Clinical Immunology, 113/5, Rob C. Aalberse,
Thomas A.E. Platts-Mills, How do we avoid developing allergy:
Modifications of the Th2 response from a B-cell perspective, 983–
986, Copyright (2004).
Allergy Management Options

- Avoidance
- Medications
  - Nasal and Inhaled Steroids, Nasal Antihistamines, Oral Antihistamines, Leukotriene Inhibitors, Cromolyn, Oral Steroids, Mucolytics, Decongestants, LABA, Beta-2 Agonists, IgE Inhibitor
- Immunotherapy
  - Subcutaneous immunotherapy (SCIT)
  - Sublingual immunotherapy (SLIT)
Forms of Specific Immunotherapy

- Oral (OIT)
- Subcutaneous (SCIT)
- Local Nasal (LNIT)
- Bronchial
- Sublingual (SLIT)
Benefits of Immunotherapy

- Studies support safety and efficacy
- Relieves allergic symptoms and medication use
- Improved overall QOL
- Infers a long-term benefit after completion of therapy through immunomodulation
- Prevention of asthma and new sensitizations

Burton MJ *OHNS* 2007;136:511-514
Sublingual Immunotherapy
SLIT drops

- Aqueous form
- Administered via dropper/pump
- Higher amount of antigen used than SCIT
- Up to 10 antigens per vial
- Perennial/seasonal
SLIT Drop Challenges: **DOSING**

- No universally accepted dosing schedule
  - AAOA effective dose 3-500x SCIT
  - No optimal SLIT dose or maintenance schedule
- Allergen content unknown and can vary widely
- Studies show the higher the dose the greater the reduction in symptom scores and medication use

Cox et al Curr Allergy Asthma Rep 2008
Larenas-Linneman Allergy Asthma Proc 2008;29:130-139
SLIT Vial Prep

- 1ml of concentrate for each allergen up to 10
- 50% glycerin used as diluent for 15ml
- Make a maintenance vial (Vial #2) and 1:5 dilution escalation vial (Vial #1)
- Lasts 3 months
AAOA Standard SLIT Escalation

<table>
<thead>
<tr>
<th>Vial #1</th>
<th>Vial #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 drop</td>
<td>1 drop</td>
</tr>
<tr>
<td>2 drops</td>
<td>2 drops</td>
</tr>
<tr>
<td>3 drops</td>
<td>3 drops</td>
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<tr>
<td>4 drops</td>
<td>4 drops</td>
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<tr>
<td>5 drops</td>
<td>5 drops</td>
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<tr>
<td>Day 1</td>
<td>Day 1</td>
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<td>Day 2</td>
<td>Day 2</td>
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<tr>
<td>Day 3</td>
<td>Day 3</td>
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<tr>
<td>Day 4</td>
<td>Day 4</td>
</tr>
<tr>
<td>Day 5</td>
<td>Day 5</td>
</tr>
</tbody>
</table>
SLIT Tablets: Greer

- Ages 10-65
- 3 day escalation ages 10-17
- 4 months pre-seasonal and continue co-seasonal
- 25% oral and 22% throat pruritis

5 grass tablet: sweet vernal, orchard, perennial rye, timothy and kentucky bluegrass
SLIT Tablets: Merck

- Grastek- Timothy grass
  - Ages 5 -65
- Ragwitek- Short Ragweed
  - Ages 18 -65
- Start 12 weeks pre-seasonal and continue co-seasonal
SLIT Candidate

- IgE mediated allergic disease
- Failed medical therapy
- Time constraints outweigh out-of-pocket costs
- Difficult to escalate on SCIT
- Needle phobia
SLIT

- Allergen uptake by oral dendritic cells (MHC) in sublingual epithelium
- Migration to regional lymph nodes
- Increase allergen specific Th1 response
- Increased Treg response

SLIT **Decreases**

- sIgE long term
- Post seasonal rise in IgE
- Ag-specific T helper cells
- Eosinophils
- Serum IL-13

SLIT Increases

- slgG1 up to 2 yrs after
- slgG4 (studies vary)
- slgA
- IL-10
- TGF-β
- Treg induction

<table>
<thead>
<tr>
<th>SCIT v. SLIT</th>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Deaths: 1 per 2.5 million</td>
<td>No reported deaths</td>
</tr>
<tr>
<td>Rate of systemic reactions</td>
<td>0.06%-0.9%</td>
<td>0.056%</td>
</tr>
<tr>
<td>Dosing</td>
<td>In physician office</td>
<td>At home after first dose in office; not standardized</td>
</tr>
<tr>
<td>FDA status</td>
<td>FDA approved</td>
<td>SLIT drops not FDA approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SLIT tablets approved for limited allergens</td>
</tr>
<tr>
<td>Socioeconomic</td>
<td>CPT code Most insurances cover</td>
<td>No CPT code SLIT drops not covered SLIT tablet coverage TBD</td>
</tr>
</tbody>
</table>
Most RCTs for SLIT are monotherapy or single antigen studies
Efficacy of SLIT: Allergic Rhinitis

- Seasonal and Perennial AR in adults
  - Cochrane Review and meta-analysis 2010
  - Decreased allergy symptoms
  - Decreased medications
  - >6 months of treatment

- Seasonal allergic rhinitis in children
  - Larenas-Linneman review 2013
  - Penagos et al meta-analysis 2006
  - Similar outcomes after >18 mos treatment
Efficacy of SLIT: Allergic Rhinitis

- Perennial allergic rhinitis in children
  - Larenas-Linneman review 2013
  - Low-moderate quality evidence for HDM SLIT
Efficacy of SLIT: Asthma

- Adult Asthma
  - Calamita et al Meta-analysis 2006
  - Evidence not strong for improving asthma symptom
  - 6 /25 RCTS showed some improvement in pulmonary function (FEV1, PEFR)

- No strong evidence for prevention of asthma or new sensitivities in adult
Efficacy of SLIT: Asthma

- **Childhood Asthma**
  - Penagos et al 2008 Meta-analysis
  - Larenas-Linneman 2013 review of 29 studies
  - Decreased symptoms and medication use
  - Most evident in HDM v. pollen IT

- **Prevention of new sensitizations and asthma**
  - Marogna et al 2008, RCT, with or without intermittent
  - 3.1% v 34.8% developed new allergy after 3 years
  - Mild persistent asthma OR 0.4 favoring SLIT v meds
Efficacy of SLIT v. SCIT

- Chelladurai et al 2013, 8 trials
  - Low grade evidence SCIT > SLIT for asthma
  - Moderate grade evidence SCIT > SLIT for rhinoconjunctivitis

- Dretzke et al 2013
  - SLIT and SCIT better than placebo
  - Trend toward SCIT being better

Dretzke J et al. J Allergy Clin Immunol 2013;131
Safety of SLIT

- AAAI/AACAI SLIT Task force 2006
  - 66 studies, 1,181,654 doses
  - No fatalities
  - 0.056% systemic reaction rate
  - Most reactions local reactions

- 2012 SCIT v. SLIT Meta-analysis
  - 36 RCTs, 22 SLIT, 14 SCIT
  - Anaphylaxis 12:1

Cox et al J Allergy Clin Immunol 2006
Dibona et al J Allergy Clin Immunol 2012
Safety of SLIT

- Gidaro et al 2005, 25 DBPCTs
  - Low dose (1-50x SCIT) n=587
  - High dose (50-100x SCIT) n=850
  - Approx. 199,000 doses
- No anaphylaxis
- 76% local reactions v. 23% minor systemic reactions
- Systemic reactions low dose = high dose
Summary

- SLIT is *not* a new form of immunotherapy
- SLIT is not a replacement for SCIT but rather another treatment option
- SLIT is highly safe
- SLIT side effects are mostly limited to local reactions/irritation in mouth
- SLIT is available in FDA approved tables for grass and ragweed pollens
Summary

- SLIT drops are not FDA approved and lack standardization of dose and treatment schedules
- Strong evidence suggests that SLIT controls SAR, PAR and asthma symptoms in adults as well as SAR and asthma symptoms in children
- SLIT also prevents new sensitizations and asthma risk
- There is evidence that also supports benefit in PAR in children of low to moderate quality
Summary

- More studies needed comparing SCIT to SLIT but challenging due to variation in SLIT dosing and treatment schedules

- Is there a role for single antigen therapy versus multi-antigen therapy in allergic patients?
WHAT’S THAT?
IT’S AN OLD PHONE.
WEIRD. HOW DOES IT TAKE PICTURES?
Question 1

- The role of immunotherapy is to reduce the TH2 driven IgE response by increasing TH1 activity and ultimately IgG4

  - A. True
  - B. False
Question 1

- The role of immunotherapy is to reduce the TH2 driven IgE response by increasing TH1 activity and ultimately IgG4
  - A. True
  - B. False
Question 2

- SLIT is now FDA approved in both drops and tablet formulations
  - A. True
  - B. False
Question 2

- SLIT is now FDA approved in both drops and tablet formulations
  - A. True
  - B. False - SLIT is only FDA approved in tablet formulations for grasses and ragweed
Question 3

- SLIT has been shown to decrease symptoms of allergic rhinitis and asthma
  - A. True
  - B. False
Question 3

- SLIT has been shown to decrease symptoms of allergic rhinitis and asthma
  - A. True
  - B. False
Thank You

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