Sublingual Immunotherapy: A New Player in Allergy Management

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Grand Rounds
10/31/2014

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

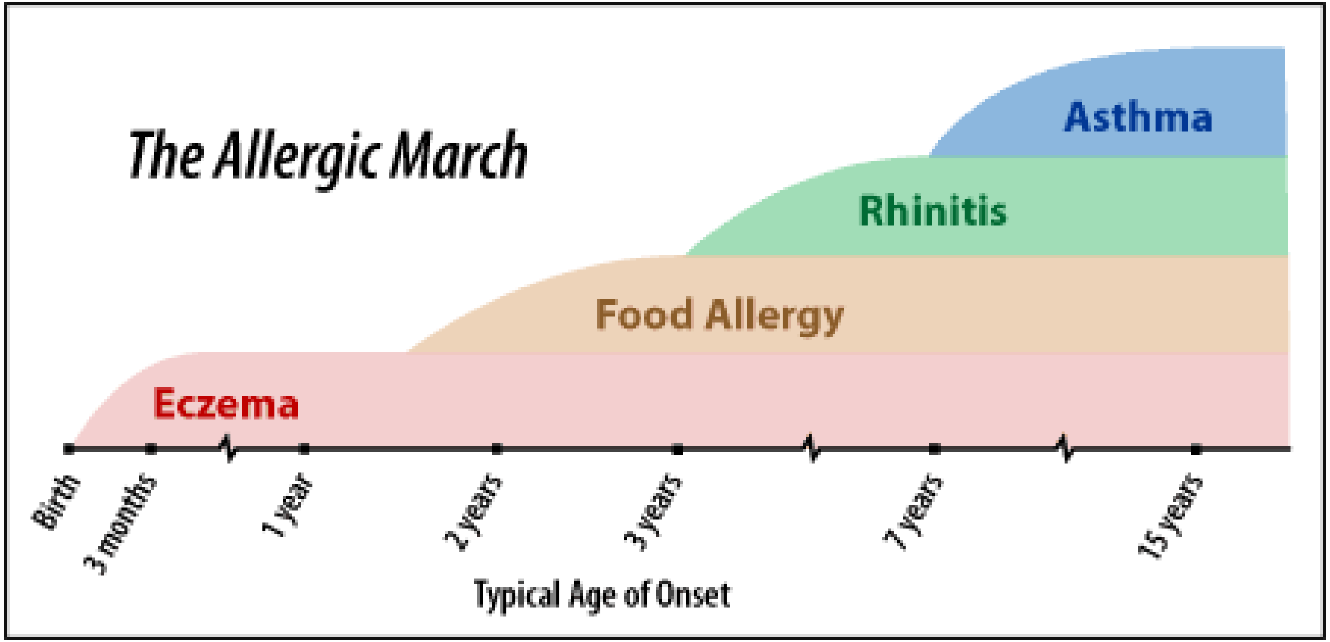
OSU Otolaryngology-Head and Neck Surgery

- 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

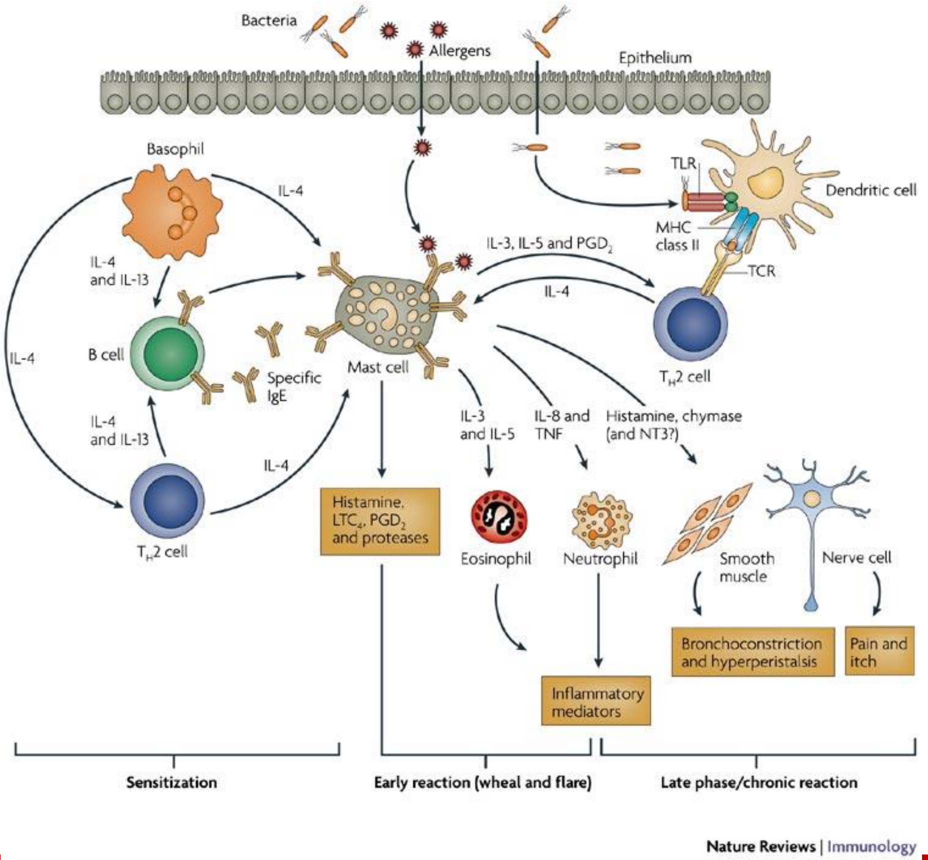


Immunology Overview

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



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Immunology of Allergic Disease: The Team

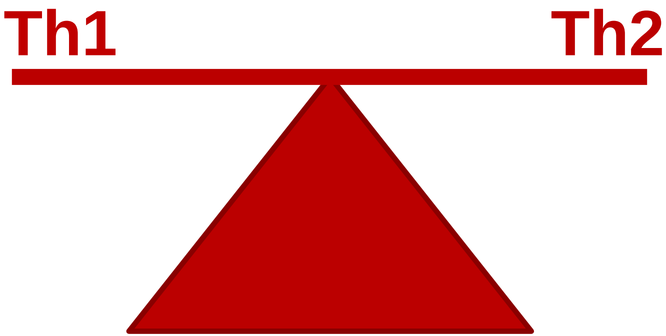
- Antigen/Allergen: usually protein epitope
  - Allergen is antigen that induces sIgE response
  - Requires prior exposure called sensitization
- Mast cells/Basophils
  - Second exposure elicits degranulation and release of histamine
- Eosinophils
- Antigen Presenting Cells (APC): MHC II
  - Monocytes/dendritic 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

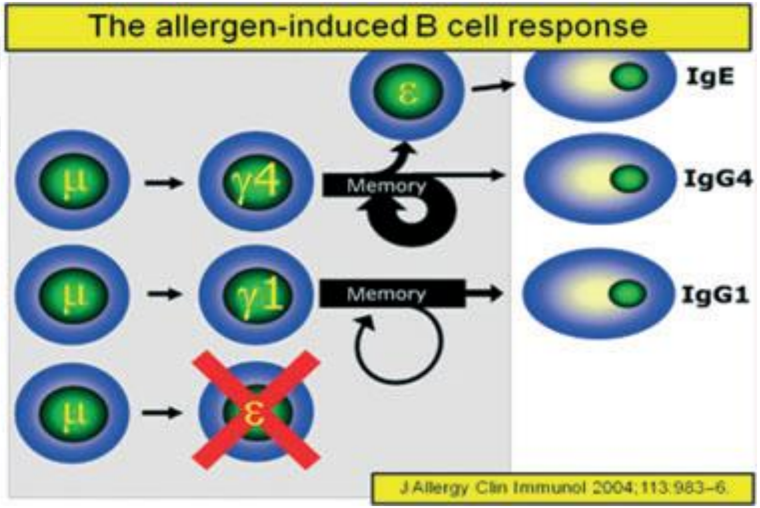
Immunology of Allergic Disease

Immunology of Allergic Disease



Immunotherapy brings about balance by shifting the allergic immune response from a dominant Th2 response by increasing Th1 activity

sIgG4



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).

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

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

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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

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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

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AAOA Standard SLIT Escalation

Vial #1	
1 drop	Day 1
2 drops	Day 2
3 drops	Day 3
4 drops	Day 4
5 drops	Day 5

Vial #2	
1 drop	Day 1
2 drops	Day 2
3 drops	Day 3
4 drops	Day 4
5 drops	Day 5

SLIT Tablets: Greer

Oralair
(Grass Pollen Allergen Extract)

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

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

SLIT Tablets: Merck

GRASTEK®
Timothy Grass Pollen Allergen Extract
Tablet for sublingual use 2800 BAU

RAGWITEK®
Short Ragweed Pollen Allergen Extract
Tablet for sublingual use 12 Amb a 1-U

- 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

Scadding G et al. J Asthma 2009;46:322-324

SLIT *Decreases*

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

Eifan AP et al. Expert Opinion Biol Ther 2013; 13:1543-1556
Tari MG et al Allergol Immunopathol 1994;22:209-216

SLIT *Increases*

sIgG

- sIgG1 up to 2 yrs after
- sIgG4 (studies vary)
- sIgA
- IL-10
- TGF-β
- Treg induction

Eifan AP et al. Expert Opinion Biol Ther 2013; 13:1543-1556
Tari MG et al Allergol Immunopathol 1994;22:209-216

SCIT v. SLIT

Chart excerpt from Clinical Practice Guideline: Allergic Rhinitis 2014 In Print

	SCIT	SLIT
Safety	Deaths:1 per 2.5 million	No reported deaths
Rate of systemic reactions	0.06%-0.9%	0.056%
Dosing	In physician office	At home after first dose in office; not standardized
FDA status	FDA approved	SLIT drops not FDA approved SLIT tablets approved for limited allergens
Socioeconomic	CPT code Most insurances cover	No CPT code SLIT drops not covered SLIT tablet coverage TBD

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

Chelladurai Y et al J Allergy Clin Immunol Pract 2013;1:361-369
Dretzke J et al. J Allergy Clin Immunol 2013;131

Safety of SLIT

- AAAI/ACAAI 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
  - Anaphylaxis12:1

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?

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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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