Sublingual Immunotherapy for Allergic Disease

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Disclosures

• Zero, Zip, None

Learning Objectives

• Describe the indications for allergen immunotherapy
• Understand the contraindications and potential risk with allergen immunotherapy
• Compare various allergen immunotherapy delivery methods

Allergy Definition

• An allergic reaction is the body's immune system reacting inappropriately to a foreign substance, such as pollen. The immune system perceives the benign substance as dangerous, thereby triggering a reaction.

Putting Allergies in Perspective

The Growing Shortage of Allergists

The demand for allergists will increase 35% by 2020, while at the same time the number of medical students choosing the specialty tumbles. The ACAAI predicts "a shortfall of more than 2,100 allergists with no solution in sight."

"By the year 2020, there will not be enough allergists to handle the increased amount of patients suffering from allergies." - American College of Allergy, Asthma & Immunology
Treatment

• Avoidance
• Symptom management with medications
• Immunotherapy

Immunotherapy

• The only therapy available that alters the natural course of the disease.
• May prevent the progression from mono- to polysensitization
• May prevent the development of asthma
• Decreased symptoms often persist after IT is discontinued

Allergen Immunotherapy: Indications

• Patients with allergic disease with specific IgE antibodies to clinically relevant allergens documented by *in vitro* or skin tests
• Factors to consider when prescribing immunotherapy:
  – Effectiveness of medications and avoidance measures
  – Side effects/costs of medications vs. immunotherapy
  – Possible special benefit in children as preventative therapy

Allergen Immunotherapy Indications

**Allergic rhinoconjunctivitis**
- Positive allergy test results correlate with symptoms
- Symptom control is inadequate despite avoidance measures and medications
- Patient wishes to avoid cost or adverse effects of medications

**Allergic asthma**
- Positive allergy test results correlate with symptoms
- Asthma control is inadequate while patient is taking daily preventive medications
- Symptoms occur nearly year round
- Allergic rhinitis coexists with allergic asthma

**Stinging insect hypersensitivity**
- There is evidence of systemic (not local) reaction
- There is an urticarial reaction (in those older than 16 years)
- Patient has a high risk of exposure


Allergen Immunotherapy

• Terms: Immunotherapy, “Allergen Vaccine”, “Desensitization”, “Hyposensitization”, “Allergy shots”
• Oldest continuously practiced form of medicine (100 years)

Allergen Immunotherapy

• Exposing patients to a specific allergen in order to: promote tolerance to a specific allergen with the ultimate clinical goal of causing a sustained decrease in allergic symptoms.
• Allergen immunotherapy is distinct from available pharmacologic treatments. Its aim is sustained alteration in immune response beyond discontinuation of treatment.
**Allergen Immunotherapy: Clinical Trials**

- **Benefits:**
  - Reduced symptoms
  - Reduced medication use
  - Reduced treatment cost
  - Clinical remission (?)

- **Indications**
  - Allergic rhinitis
  - Asthma
  - Stinging insect hypersensitivity

- Multiple allergens studied

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**Potential Pitfalls**

- Incorrect diagnosis
- Selection of allergen(s) was inadequate ("missing allergen")
- Maintenance dosage and duration of vaccine therapy not high or frequent enough
- Environmental control measures inadequate
- Poor adherence with treatment schedule
- Other co-morbid medical conditions or interfering medications (hypothyroidism, hormones, beta-blockers, etc.)

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**Key Principles**

- **Indications:**
  - Allergic rhinitis/conjunctivitis or allergic asthma with symptoms not well controlled by medications or avoidance measures or require high medication doses, multiple medications, or both to maintain control

- **Adverse effects of medications**

- **Desire to avoid or reduce the long-term use of medications**

- **Stinging insect allergic reaction**

- **Asthma, however, must be controlled**

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**Proteolytic Enzymes**

- Separate allergens with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens

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**Key Principles**

- When writing a prescription, consider:
  1. cross-reactivity of allergens
  2. Optimization of the dose of each allergen
  3. Enzymatic degradation of allergens

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**Key Principles**

- Know allergen cross-reactivity to limit the number of allergens in the immunotherapy prescription

- In general, there is a high cross-reactivity if in same genus, a lesser degree if same family, and rare cross-reactivity between families (although several exceptions exist).
Effective SCIT Target Doses

<table>
<thead>
<tr>
<th>Allergen Extract</th>
<th>Target Dose</th>
<th>Mean concentration of major allergen in 1mL stock extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. pteronyssinus</td>
<td>7.0 ug Der p 1* or 500-2000 AU** 228 ug/mL of 30,000 AU</td>
<td></td>
</tr>
<tr>
<td>D. farinae</td>
<td>10 ug Der f 1* or 500-2000 AU** 168 ug/mL of 30,000 AU</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>15 ug Fel d 1* or 1000-4000 AU** 43 ug/mL of 10,000 AU</td>
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</tr>
<tr>
<td>AP Dog</td>
<td>15 ug Can f 1*,** 140 ug/mL of 1:100 w/v</td>
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<tr>
<td>Short ragweed</td>
<td>6-12 ug Amb a 1* ,** or 1000-4000 212 ug/mL or 1:10-1:20 wt/vol or 100,000 AU</td>
<td></td>
</tr>
<tr>
<td>Timothy grass</td>
<td>20 ug Phl p 5* ,** or 1000-4000 BAU 680 ug/mL of 100,000 BAU</td>
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<tr>
<td>Standardized grass</td>
<td>1000-4000 BAU** 10,000-100,000 BAU</td>
<td></td>
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</tbody>
</table>

*Joint Task Force Practice Parameters for Allergen Immunotherapy JACI 2007  
**Joint Task Force Practice Parameters for Allergen Immunotherapy JACI 2003  
***Joint Task Force Practice Parameters for Allergen Immunotherapy JACI 2003

Key Principles

- Once at maintenance dose, can space out injects to every 2 weeks -> every 3 weeks -> monthly
- Expect clinical response when on maintenance dosing (within first year)
- Maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions
- Might not always be the initially calculated effective dose
- Duration 3-5 years or longer

Immunotherapy Reagents

- Standardized allergenic extracts (BAU or AU): cat, dust mite, short ragweed, grass, Hymenoptera
- Non-standardized allergenic extracts (weight-to-volume or PNU)

Pregnancy and Immunotherapy

- Continuation during pregnancy appears safe
- Initiation during pregnancy not recommended
- Continue current dose and do not increase (or only increase very slowly)
- If history of systemic reactions, consider holding injections
- Settipane, et al, in study of offspring of atopic pregnant women undergoing immunotherapy:
  - 31% of children developed asthma or allergic rhinitis
  - 45% of children of controls developed asthma or allergic rhinitis

Estimated Costs of Treatment of Allergic Rhinitis

<table>
<thead>
<tr>
<th>Treatment Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total 5 Year Cost</th>
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<tbody>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
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<td>$1960</td>
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<tr>
<td>(single injection)</td>
<td>$800</td>
<td>$290</td>
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<td>Medications</td>
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<td>$6000</td>
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<tr>
<td>(oral &amp; topical)</td>
<td>$1200</td>
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<td>$1200</td>
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</tr>
</tbody>
</table>
Cost-Effectiveness of SLIT in Adults

- 2230 patients (16 to 45 years) 60% rhinitis only; 40% rhinitis and asthma
- Improvement in symptoms with SLIT in 399 of 1000 patients and prevented asthma in 229 of 1000 patients compared with drugs alone
- SLIT is less costly and more effective than pharmacotherapy alone

Immunotherapy: Treatment Schedules

**Build-up phase**
- Involves administration of increasing quantities of allergen vaccine subcutaneously

**Types of schedules**
- 1. Conventional / routine
- 2. Daily
- 3. Cluster
- 4. Rush / modified rush

Novel Allergen Immunotherapy

- Sublingual immunotherapy (SLIT):
  - Drops, sprays, or dissolving tablets placed beneath the tongue have studied and used in European countries
  - Dosing of sublingual therapy requires several times the concentrations used for subcutaneous immunotherapy
  - Data from European studies suggest efficacy with a favorable safety profile
  - Most studies of SLIT have been with single allergens and translation of these studies to treatment with multiple allergens needs to be further studied.
  - Few FDA approved formulations in the US

Subcutaneous Vs Sublingual

- Weekly for build up
- Monthly maintenance
- Higher risk systemic reactions
- FDA approved
- Insurance often covers
- Longer experience

- Daily
- At home
- Lower risk systemic reactions
- Not FDA approved except a few
- Insurance does not cover (<$200/3 mo)
- Shorter experience

SLIT – Sublingual Immunotherapy

- 1900’s SLIT use proposed
- 1980’s Proper studies
- 1998 WHO “promising”
- 2009 WAO “viable alternative”
SLIT Delivery

- Rapidly dissolving tablet
- Aqueous or glycerinated drops
- Held under the tongue for typically 1 minute and then swallowed (more efficacious) or spit out
- No food or beverage with nor for 5 minutes following

SLIT Availability

- Grastek - Merck
- Oralair - Stallergens
- Ragwitek - Merck
- Sublingual drops – “Off label” and similar production as SCIT

SLIT Dosing

- 20-200x SCIT Dosing
- Ragwitek (12 Amb a 1 units of short ragweed pollen in one single dose tablet daily)
- Grastek (2800 BAU, 15mcg Timothy grass pollen in one single dose tablet daily)
- Oralair (25mcg, 5 major allergens in 300 IR single dose tablet in 18-65 yrs of age) Ages 10-17 (Day 1: 100 IR tab, Day 2: Two 100 IR tabs, Day 3: One 300 IR tab)

Oralair Indications

- Indicated 10-65 years of age
- AR with or without conjunctivitis
- Sensitization to any of the 5 species of grass contained (Timothy, Orchard, Perennial Rye, Kentucky Blue, Sweet Vernal)

Grastek Indications

- Indicated 5-65 years of age
- AR with or without conjunctivitis
- Sensitization to Timothy or a cross reactive species (Orchard, Perennial Rye, Kentucky Blue/June, Sweet Vernal, Meadow Fescue, or Redtop)

Ragwitek Indications

- Indicated 18-65 years of age
- AR with or without conjunctivitis
- Sensitization to Short Ragweed
Contraindications

- Severe unstable or uncontrolled asthma
- Hx of Severe Systemic Rx
- Hx of any severe local Rx to SLIT
- Hypersensitivity to any of the inactive ingred.
- Hx of EoE
- Cat B (Oralair, Grastek) Cat C (Ragwitek)
- May not be suitable for patients on beta blockers, alpha blockers, ergots, TCA’s, MOA’s & levothyroxine

SLIT Initiation/Duration

- **Oralair**: 16 wks prior to and through season
- **Ragwitek**: 12 wks prior to and through season
- **Grastek**: 12 wks prior to and through season OR may be continued on perennial basis over 3 yrs for sustained effect

- Give first dose in the office
- Rx epinephrine auto-injector

Adverse Effects

- Oral pruritis
- Throat irritation
- Ear pruritis
- Mouth Edema

- **Oralair**: 25, 22, 8, and 8%, respectively
- **Grastek**: 27, 23, 13, 11%
- **Ragwitek**: 17, 11, 10, 10% (mouth parasthesia)

Efficacy

- **Total Combined Score (TCS)**

  \[ TCS = \text{Sum of daily symptom score (TSS)} + \text{daily medication scores (DMS)} \]

- Must be greater than >15% average relative difference for FDA approval and 20% mean reduction to be clinically meaningful by WAO

- **2011 systematic review of 60 randomized trials including 2300 adults and children receiving SLIT, treatment resulted in a standardized mean difference of -0.43.**
- **Most single pollen studies**
- **15 studies in children**
- **No trial reported anaphylaxis**

- **Grastek 20% difference adults, 26% adolescents and children**
- **Oralair 19-36%, 22-37%**
- **Ragwitek 27%**
- **Sublingual drops 2013 systematic review included 63 randomized trials and 5131 subjects, no anaphylaxis, moderate benefit albeit lack of standardized methods for evaluation**
SLIT in Children with Asthma Medication Use

- No difference in medication use was observed during observation period
- Significant reduction in medication use in both groups after 1 year
- After Year 2, 68.16% further reduction in the active treatment group compared to first year of treatment ($P = .0066$)
- Medication use significantly lower for active treatment in Years 1 and 2

Comparison with SCIT

- Safety and efficacy assessed in a 3-year double blind placebo-controlled double dummy study
  - 71 adults with birch pollen hay fever
    - Positive skin prick
    - Positive conjunctival provocation test
    - RAST
  - Randomized to SCIT, SLIT, or placebo after baseline season
  - Treatment continued for 2 seasons

Compliance

- Attrition rate of 40% over 4 years (US)
- 46% of 150 children stopped SLIT within 3 months
- SLIT refills 44% Y1, 28% Y2, 13% Y3

Summary: Efficacy of SLIT

- SLIT is an effective method of administering immunotherapy for
  - Allergic rhinitis
  - Allergic conjunctivitis
  - Asthma
- Efficacy has been demonstrated for multiple antigen types in many age groups
- Efficacy is at least comparable to SCIT

Summary: Safety of SLIT

- Safety superior to SCIT
- Demonstrated to be safe in children and at cumulative doses up to 500 X higher than doses used in SCIT
- Majority of adverse events are mild and self-limited
  - Minority of cases require symptomatic medication or dose adjustment
  - Only 2 recent cases of anaphylaxis in adults and 1 in a child
  - No other severe or life-threatening adverse events reported

Questions?
Overall Summary

- SLIT unlikely to replace SCIT
- Rather will be an alternative for patients with unmet clinical needs, including:
  - High-risk patient unable to tolerate SCIT
  - Needle-phobic patients
  - Patients unwilling or unable to make frequent MD office visits
  - Asthmatic patients
  - Children as young as 2 years of age
    - Especially those sensitized to perennial allergens

<table>
<thead>
<tr>
<th>Immunotherapy Prevents the Development of New Allergen Sensitizations</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td></td>
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<tr>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Control group</td>
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<table>
<thead>
<tr>
<th>Dust Mite Immunotherapy Trial for Asthma</th>
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Dust Mite Immunotherapy Trial for Asthma

- Randomized double-blind
- Significant decrease in asthma symptoms
- Decrease in asthma medications
- Decrease in mite-specific immediate and late phase reactions

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<tr>
<th>Cat Immunotherapy Trial</th>
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Cat Immunotherapy Trial

- Double-blind, placebo controlled
- Decrease in specific and non-specific bronchial sensitivity
- Decrease prick skin test reaction
- Decrease eye, nasal and asthma symptoms with cat challenge/exposure
- Improved asthma control

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<tr>
<th>Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy</th>
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</table>
Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Initial Placebo Trial</th>
<th>Current Trial</th>
</tr>
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<tbody>
<tr>
<td>1989</td>
<td>Pollen Count</td>
<td>Visual-Analogue Score</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
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<tr>
<td>1995</td>
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Meta-Analysis of Immunotherapy for Allergic Asthma

- Mites: Smith (n=22), Maung (n=34), Werner (n=51), D’Souza (n=91), Paul (n=18), Newton (n=14), STH (n=16)
- Other Allergens: Frazier (n=27), Ghani (n=10), Sundin (n=39), Valovirta (n=27), Mites Combined (n=286), Other Allergens (n=140), All Studies (n=426)

Prevention of Asthma by Immunotherapy

5-Year Follow-Up

- Immunotherapy: 39 vs 9
- Control: 16 vs 22

Increasing Asthma Prevalence


Reference List