Allergen Immunotherapy

April 8, 2017
AAOM Annual Conference
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University of South Florida
Morsani College of Medicine
Tampa, Florida
Sunrise in Tampa, Florida, U.S.A.
Disclosures

• Worked as Merck consultant for USA Federal Drug Administration filing of sublingual Timothy grass tablet and participate in Merck clinical trials. No consultation after 2015.

• No other disclosures for this lecture.
Outline

I. Historical perspective of allergen immunotherapy
II. Allergic reactions
III. Subcutaneous (SCIT) versus sublingual immunotherapy (SLIT)
IV. Side effects
V. How should SCIT versus SLIT be utilized?
Outline

I. Historical perspective of allergen immunotherapy

II. Allergic reactions

III. Subcutaneous (SCIT) versus sublingual immunotherapy (SLIT)

IV. Side effects

V. How should SCIT versus SLIT be utilized?
## History of Allergen Immunotherapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Observation/Finding</th>
<th>Credit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>First double-blind study of efficacy of SCIT to treat ragweed-induced allergic rhinitis</td>
<td>Francis Lowell, William Franklin</td>
</tr>
</tbody>
</table>

45. A Double Blind Study on the Specificity of Injection Therapy With Aqueous Extracts in Ragweed Pollenosis

F. C. Lowell, M.D., William Franklin, M.D., with the technical assistance of Marsha Williams, Boston Massachusetts

In the light of previous experience, special attention was given to the selection of patients and the method of scoring symptoms. As expected, the criteria used for selection markedly restricted the number of patients available for study.

Detailed notes maintained throughout the year of 1962 provided the means of selecting 24 patients who, in addition to meeting other qualifications, had a clear exacerbation of allergic rhinitis during the ragweed season of 1962 and who, during a period at some other time of year, had no symptoms and had taken no medication. All were receiving injections of ragweed pollen extract in a mixture containing other allergenic extracts. The patients were paired on the basis of severity. Early in March 1963, ragweed pollen extract was withdrawn from the mixture received by one member of each pair (group A) and treatment with this was continued in the other member (group B). Strict experimental control was maintained throughout.

Both groups exhibited minimal symptom and medication scores up to mid-August. From the last week in August until the last week in September, symptoms and medication scores taken together or separately for group A, clearly and consistently exceeded those of group B.

It was concluded that 1) in conformity with earlier studies, injections of pollen extract are effective in ragweed pollenosis; 2) that this effect is specific; and 3) that it is lost in part or entirely within about five months after injections are stopped.
William Franklin, M.D.            Age 105
## History of Allergen Immunotherapy

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<tr>
<th>Time</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1967-1987</td>
<td>Identification and assay of immunoglobulin E as the reaginic antibody and function of a cytokine, IL-4, in its synthesis; presenting new vistas for exploring applications of cellular and molecular immunological phenomena to allergen immunotherapy through regulatory control of IgE.</td>
<td>Kimishiga and Teruko Ishizaka; William Paul</td>
</tr>
</tbody>
</table>

Kimishige Ishizaka (b. 1925) (standing) and Teruko Ishizaka (b. 1926)

Simons FE. Ancestors of Allergy. Global Medical Communications Ltd., New York, 1994
## History of Allergen Immunotherapy

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<tr>
<th>Time</th>
<th>Observation/Finding</th>
<th>Credit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978</td>
<td>Venom immunotherapy versus placebo and whole-body extract efficacious to treat Hymenoptera hypersensitivity</td>
<td>K Hunt, MD Valentine, AK Sobotka, AW Benton, FJ Amodio, LM Lichtenstein</td>
</tr>
</tbody>
</table>

### History of Allergen Immunotherapy

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</thead>
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Extracts to vaccines and first reference to efficacious sublingual immunotherapy for allergic rhinoconjunctivitis
<table>
<thead>
<tr>
<th>Time</th>
<th>Observation/Finding</th>
<th>Credit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Anti-IgE therapy introduced in U.S.A. – to treat severe asthma. Also efficacious to treat allergic rhinitis, peanut allergy and, in 2014, chronic idiopathic urticaria.</td>
<td>Multiple investigators</td>
</tr>
</tbody>
</table>

History: 2003 - Present

• SLIT introduced (more in Europe than USA)
• Oral allergen immunotherapy a reality but not yet FDA approved for food allergy
• Epicutaneous allergen immunotherapy under investigation for food allergy
• Recombinant and modified allergen vaccines and adjuvants used and being developed for allergen immunotherapy
Outline

I. Historical perspective of allergen immunotherapy
II. Allergic reactions
III. Subcutaneous (SCIT) versus sublingual immunotherapy (SLIT)
IV. How should SCIT versus SLIT be utilized?
V. Side effects
Gel and Coombs classification of hypersensitivities.

Type I
IgE Mediated
Classic Allergy

Type II
IgG/IgM Mediated
RBC lysis

Type III
IgG Mediated
Immune complex Disease

Type IV
T cell
Delayed Type Hypersensitivity
Type I or Immediate Hypersensitivity

• Mediated by IgE attached to mast cells.

• Is involved in the pathogenesis of allergic rhinitis and conjunctivitis, allergic asthma, allergic eczema, Hymenoptera hypersensitivity, food allergy, and drug allergy.
Allergens

• Allergens are antigens that can stimulate a type I hypersensitivity response.

• Allergens bind to IgE attached primarily to mast cells which causes degranulation and release of preformed and newly generated chemical mediators.
Some Common Allergens

- Aeroallergens: dust mites, pollens, animal danders, molds
- Foods: peanuts, tree nuts, and shellfish
- Venoms: honeybee, wasps, fire ants
- Drugs: penicillin
- Latex
Characteristics of allergens

- Small 15-40,000 MW proteins.
- Specific protein components
  - Often enzymes.
- Low dose of allergen triggers symptoms
- Mucosal exposure.
- Most allergens promote a Th2 immune.
Allergens

Example: Der P1

Der P1 is an allergen from the fecal pellets of the dust mite.
IgE Production and Subsequent Involvement in Allergic Disease

Sensitization

Allergen

Antigen presenting cell

MHC class II protein and epitope

Th2-cell + B-cell

Production of antigen-specific IgE

Mast cell degranulation

Mediators

Re-exposure

Environment

Submucosa

Clinical effects asthma, hayfever, urticaria
IgE-Dependent Release of Inflammatory Mediators Leading To Early/Acute Asthma Symptoms

Immediate Release
Preformed Mediators:
- Histamine
- TNF-α
- Proteases
- Hydrolases
- Proteoglycans (Heparin)

Over Minutes
Lipid mediators:
- Prostaglandins
- Leukotrienes
- Thromboxanes

Over Hours
Cytokine production:
- ILs-3, 4, 5, 6, 8, 9, 11, 13
- TNF-α, MIP1, MCP

Mucus Production
Mucosal Edema
Bronchoconstriction
Chemotaxis

Chronic Inflammation

Asthma Symptoms
Outline

I. Historical perspective of allergen immunotherapy
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Subcutaneous Immunotherapy (SCIT)

SCIT involves the subcutaneous injections of gradually increasing quantities of allergens to which a subject is allergic until the optimal dose is reached. This increases the patient’s tolerance (immune tolerance) to said allergen thereby minimizing symptoms and signs of the disease.
The percentage of children after 3 years of immunotherapy with and without asthma among those without asthma before treatment (N=151). The absolute numbers of children are shown above the bars.

Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy

Initial Placebo Trial

Current Trial

<table>
<thead>
<tr>
<th>Pollen Count (grains/m³)</th>
<th>Study group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>May</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Maintenance</th>
<th>Discontinuation</th>
<th>None (control)</th>
</tr>
</thead>
</table>


SCIT
Sublingual Allergen Immunotherapy (SLIT)

SLIT involves the sublingual administration of optimal doses of allergens to which a subject is allergic. This increases the patient’s tolerance (immune tolerance) to said allergen thereby minimizing symptoms and signs of the disease.
3-Year Sustained Effect With Persistent Effect for at Least 2 Years Post-treatment

Total Combined Score (TCS)

<table>
<thead>
<tr>
<th></th>
<th>Treatment Period</th>
<th>No Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCS Score</td>
<td>Placebo</td>
<td>MK-7243</td>
</tr>
<tr>
<td>Season 1</td>
<td>34%*</td>
<td></td>
</tr>
<tr>
<td>Season 2</td>
<td>41%*</td>
<td></td>
</tr>
<tr>
<td>Season 3</td>
<td>34%*</td>
<td></td>
</tr>
<tr>
<td>Follow-Up Season 1</td>
<td>27%*</td>
<td></td>
</tr>
<tr>
<td>Follow-up Season 2</td>
<td>23%*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05

Courtesy of Merck

SLIT
Systematic Review of Double-Blind Randomized Clinical Trials of SCIT and SLIT With Inhalant Allergens Show Similar Efficacy

Symptom-Medication Scores

Standardized Mean Difference (SMD)

Better  No difference between active and placebo  Worse

-1  0  1

SCIT:
SMD=-0.48
95% CI [-0.67;-0.29]

SLIT:
SMD=-0.40
95% CI [-0.55;-0.25]

SCIT= subcutaneous immunotherapy; SLIT= sublingual immunotherapy.
Change from baseline to the end of the grass pollen season 2009 (FY2) in specific IgG₄ was significantly higher in the Grass AIT group than in the placebo group (p<0.0001).

TY=treatment year; FY=follow-up year.
The Clinical Effect of MK-7243 May Be Similar to or Better Than Pharmacotherapies Used for Treatment of Seasonal Allergic Rhinitis

<table>
<thead>
<tr>
<th></th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>Type of SAR Treatment</th>
<th>Symptoms Evaluated (2 Weeks)</th>
<th>Improvement vs. Placebo (95% CI, Range†)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MK-7243‡</strong> Pooled Analysis</td>
<td>6</td>
<td>3501</td>
<td>Allergen immunotherapy</td>
<td>Nasal/ocular</td>
<td>22% (17%, 26%)</td>
</tr>
<tr>
<td><strong>Meta-analysis§</strong></td>
<td>38</td>
<td>12,926</td>
<td>Antihistamine</td>
<td>Nasal/ocular</td>
<td>9%¶ (-24%, 23%)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nasal corticosteroid</td>
<td>Nasal</td>
<td>26%¶ (-16%, 43%)†</td>
</tr>
<tr>
<td><strong>Meta-analysis‖</strong></td>
<td>11</td>
<td>3924</td>
<td>Antihistamine</td>
<td>Nasal/ocular</td>
<td>7%¶ (2%, 9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nasal corticosteroid</td>
<td>Nasal</td>
<td>17%¶ (7%, 23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leukotriene antagonist</td>
<td>Nasal</td>
<td>5 %¶ (3%, 7%)</td>
</tr>
</tbody>
</table>

† Range (min, max) is provided due to lack of information in the publication.
‡ Percent relative improvement vs. placebo in total combined score during peak grass pollen season.
SAR=seasonal allergic rhinitis.
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I. Historical perspective of allergen immunotherapy

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AAAAAI/AACAAI SCIT Deaths 2008-2017

- 3/6 years vs 3 to 4/year previously

- SAR, 0.1% of injection visits, 82 to 85% of practices

Bernstein DI. Personal communication.
AAAAI/ACAAI Survey 2008-2014
Systemic allergic reaction rate/ 10,000 injection visits
Post-Marketing SLIT Adverse Event Reports

• 3927 adverse events in 1268 patients reported following GRAZAX licensure in 2006
• 116 reported as severe adverse events
• 27 serious systemic allergic reaction cases
  • 16 after first dose
    • 14 within 20 minutes
    • One within 6 hours
    • Time unspecified in one report
  • Two on Day 2
  • Day 9, 28, and 47 (3 subjects)
• 35 serious local reactions with throat symptoms
AAAAl/ACAAI SLIT SAR

• 2 World Allergy Organization Grade 3 in 1,350 patients on commercial SLIT.

• No fatal or near-fatal reactions

Bernstein DI. Personal communication.
Patient Selection, SCIT or SLIT

- Subcutaneous immunotherapy: It will be used primarily to treat multi-sensitized individuals such as allergic patients in Florida.
Vaccines for Allergic Florida Patient

The patient is symptomatic and allergic to many allergens

- For example:

  **Vaccine A**
  - Trees: oak, cedar, Australian pine, bayberry
  - Grasses: Bahia, Bermuda
  - Weeds: short ragweed, pigweed, lamb’s quarter
  - Cat

  **Vaccine B**
  - Dust mites: *D. pteronyssinus, D. farinae*
Patient Selection, SCIT or SLIT

- Sublingual immunotherapy: It will be used to treat seasonal allergy. It can be used to treat northern grass and ragweed seasonal allergy. Dust mite SLIT for perennial dust mite allergy.

- NOTE: Impossible to treat subjects with multiple allergen sensitivity with sublingual drops (using SCIT extracts). Cannot reach optimal doses.
Specific Allergen Immunotherapy Risk & Benefit (grass pollen)

Efficacy ++  
Safety +

SCIT

Efficacy +  
Safety ++

SLIT

Patient choice is important
I. Historical perspective of allergen immunotherapy
II. Allergic reactions
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Case Report

• 15 year old male with severe fall induced allergic rhinoconjuntivitis in Lancaster, Pennsylvania

• Has failed over-the-counter and intranasal antihistamines, intranasal glucocorticoids (nose bleeds), and other pharmacotherapy

• 2 years ago had honeybee sting-induced anaphylaxis (hypotension and trouble breathing)

• PMH, SH, FM, ROS negative or noncontributory
• Physical examination in June normal
• Prick-puncture skin test (PPST) revealed markedly positive skin text to ragweed with minimal or no reactivity to other allergens
• PPST negative to all Hymenoptera
• Intradermal skin tests (IDST) 4+ at 0.01 μg/ml to honeybee
• Other tests negative
• Appropriate controls positive and negative
• He has heard of SLIT and wants to begin it. You agree.
• You advise him as follows:
  1. That he should carry an autoinjector of epinephrine and know how and when to use it
  2. You start him on SLIT 12 or more weeks before the ragweed season which begins in Lancaster about August 15
  3. You start him on honeybee venom immunotherapy (VIT).
4. You instruct him that he will receive his VIT injections and his first SLIT dose in your clinic and, thereafter, ragweed SLIT at home.

5. He will continue to carry an epinephrine autoinjector for both SLIT and VIT.
Follow-Up

- He achieves a maintenance honeybee dose of 100 μg of venom and his maintenance injection interval is increased to every 6 weeks after 1 year.
- He receives SLIT for 12 or more weeks before each ragweed season for 3 years with marked resolution of his seasonal allergy the first year and subsequent years.
- You decide to stop ragweed SLIT.
- His honeybee skin test remains positive and because of the historical severe anaphylactic reaction, he continues on VIT.
Comparison of SCIT and SLIT Allergen Immunotherapy

**SCIT**
- Injections in office
- Safety
  - Poor adherence
  - Duration, 3-5 yrs

**SLIT**
- Cost
- N.G., R and D.M. tabs
- FDA approved
- Poorly defined dosing with liquid extracts
- Mixing unrelated Ag’s not proven efficacy

600 pages, 75 authors, 38 chapters
Thank you
IgE Synthesis and Biology

Thomas B. Casale, MD
Professor of Medicine
Chief, Allergy/Immunology
Creighton University
Omaha, NE
Summary of IgE Synthesis Events

- Th2
- Basophil
- Mast Cell

**Signal 1**: ε mRNA
- Germ-line Transcription

**B Cell**
- CD40 Engagement via Physical Association
- CD40 Engagement (and other co-stimulatory molecules)

**Signal 2**: B-cell Activation & Class Switch Recombination

- CD154

**B Cell**
- IgM
- IgE
IgE Structure

- Extra constant region, unique to IgE
- Sites for attachment to mast cells and basophils
- Sites for attachment to antigen
- Carbohydrate
- Variable regions
- Constant regions
- Disulfide bonds

S Dreskin 2008. Board Review
**IgE Levels**

- **Least abundant Ig:**
  - ~150 ng/ml vs. 10 mg/ml for IgG (~66,000 fold less)
  - Increase from birth through age 10
  - Preschool levels do not correlate well with those at older ages

- Largely produced by plasma cells in the mucosal-associated lymphoid tissue

- **T1/2 of plasma IgE = 1 to 5 days**
- **T1/2 of mast cell-bound IgE ~ 2 weeks**
IgE and Allergic/Respiratory Diseases

- Increased serum IgE associated with:
  - Atopic Dermatitis
  - ABPA
  - Asthma prevalence (w/ and w/o atopy)
  - Persistent wheezing in children
  - Airway hyper-responsiveness

Epidemiologic and empirical evidence confirms a clear relationship between IgE and both pathogenesis and symptoms of respiratory disease.

High-and Low-Affinity IgE Receptors

High Affinity
FcεRI
10^{-10}

Low Affinity
FcεRII
10^{-7}
Binding of IgE to FcεRI

IgE binds to α chain. β and γ chains are involved in signal transduction.

F(ab′)_2 –

Holgate S. QJM 1998;91:171-84.
IgE- Mediated Allergic Reactions

Adapted from Bischoff, Nature Immunol, ‘07

Immune cell recruitment and activation

Blood flow coagulation and vascular permeability

Many of these cells have IgE receptor

Secretion and epithelial permeability

Wound healing and fibrosis

Neuroimmune interactions, peristalsis bronchoconstriction and pain

Histamine, LTC₄ and PGD₂

Histamine, LTC₄, Chymase, and heparin

Histamine, PGD₂, and proteases

Bacteria

Epithelium

Neutrophil

Mast cell

Histamine, LTC₄ and PGD₂

TNF

ILs-3, 4, 5, 6, 8, 9, 11, 13, TNF-α, MIP1, MCP

Histamine, PGD₂, and proteases

Blood vessel endothelium

Eosinophil

B-cell

T-reg cell

Blood flow coagulation and vascular permeability

Immune cell activation and recruitment

Fibroblasts

Smooth muscle cell

Nerve cell

Adapted from Bischoff, Nature Immunol, ‘07
IL-10 Activity

- Originates from Ag specific T-cells, activated CD4^+CD25^+ T cells, monocytes, and B cells
- Decreases IL-4 induced B-cell IgE production and increases IgG_4
- Inhibits IgE dependent mast cell activation
- Inhibits eosinophil cytokine production and survival
- Suppresses IL-5 production
ALLERGEN IMMUNOTHERAPY

Hugh H. Windom, M.D.

Clinical Professor
Division of Allergy and Immunology
University of South Florida College of Medicine
Objectives

• Gain an understanding of the mechanism of action of subcutaneous immunotherapy (SCIT)

• Learn the proper way to prepare and administer allergen vaccines

• Compare SCIT to other forms of immunotherapy for allergic respiratory disease
General Principles

• Effective in allergic rhinoconjunctivitis, asthma, and insect allergy. Worth considering in atopic dermatitis.

• Only specific form of therapy for these conditions

• Potentially curative

• May alter the natural history of allergic disease
Mechanism of Allergen SCIT

• Early decrease in mast cell and basophil activity

• Generation of Treg cells (produce IL-10 and TGF-β) and Breg cells (IL-10)

• Modify antibody isotypes, increasing allergen specific IgG4, IgA, and early then in IgE

• Late decrease in tissue mast cells and eosinophils
IL-10 Activity

- Originates from Ag specific T-cells, activated CD4^+CD25^+ T cells, monocytes, and B cells
- Decreases IL-4 induced B-cell IgE production and increases IgG_4
- Inhibits IgE dependent mast cell activation
- Inhibits eosinophil cytokine production and survival
- Suppresses IL-5 production
Patient Selection

- Diagnosis of rhinoconjunctivitis or asthma
- Positive allergy tests (invivo or invitro) that correlate with respiratory disease
- Poorly controlled disease
- Failure to respond or tolerate pharmacotherapy
- Motivated to try allergy shots
Local Allergic Rhinitis

- Local production of nasal sIgE
- Positive nasal Ag provocation test (NAPT), with lavage showing tryptase and ECP
- Negative in vivo and in-vitro allergy tests
Allergen Extracts

A solution of elutable material derived from an allergen source product, e.g. pollens or molds. Each contain multiple antigens (Ag’s).

- Cockroach and animal dander: 10-20 Ag’s
- House dust mites: 20-40 Ag’s
- Pollens: 30-50 Ag’s
- Fungal extracts: as many as 80 Ag’s
Allergen Units

• **Weight/volume (W/V)**
  
  weight of raw material / volume of extraction fluid

• **Protein nitrogen units (PNU)**
  
  1 unit = 0.01 mg of protein nitrogen

• **Bioequivalent allergy or Arbitrary units (BAU = AU)**
Standardized Extracts

Manufactured lots are compared to a reference extract having a known biologic activity.

- Pollens – ragweed and grass (Bermuda, Kentucky bluegrass, rye, orchard, timothy, meadow fescue, redtop, sweet vernal)

- Perennials – dust mites, cat,
Allergen Stability Factors

- Temperature – must be kept refrigerated
- Time – all proteins have a shelf-life
- Diluent – glycerin the best
- Dilution – lower dilutions less stable
- Mixing – increasing protein content of vial improves stability
- Proteolytic enzymes – allergen degradation
Compatibility Rules

Pollens and Dog

Cockroach and Mold

Cat, RW, and Dust mites in either group

Allergen Selection

- Current practice: + test correlating with history
- Using major allergen IgE (component resolved diagnosis - CRD) avoids overlapping seasonality and cross-reacting molecules
- 651 children started on pollen SCIT in Germany, 47% had SCIT recipe reduced using CRD
- Larger wheals correlated better with CRD

Single vs Multiple Allergens

- Polysensitization more common than mono, 50-80% in USA and Europe
  - However, Europeans prefer single allergen therapy while USA uses an average of 8 Ag/pt
- Their reasoning: polysensitization is not necessarily polyallergic
  - Multi-allergen SCIT in polysensitized patients has not been studied properly

Calderon et al. J Allergy Clin Immunol 2012;129:929-34
Dosing of Allergen Extracts

For non-standardized allergens, the recommendations are empirical: 1:100 w/v

Add 1 cc of a 1:10 w/v allergen into 10 cc maintenance vial, 2 cc of a 1:20, etc

Standardized allergens -

When major allergen known: 12-24 ug/ml

If not: 1,000 – 8,000 AU/ml
Dosing of Standardized Allergens

- Der p1: 0.7 ug less effective than 7 ug in reducing bronchial responsiveness to mite inhalation
- Amb a1: 0.6 – 2 ug less effective than 6-12.4 ug
- Fel d1: 0.6 ug = placebo < 3 ug < 15 ug
<table>
<thead>
<tr>
<th>Extract</th>
<th>Concentrate</th>
<th>Volume of Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pollen, Fungi, and Animal</strong></td>
<td>1:10 w/v</td>
<td>0.5 ml</td>
</tr>
<tr>
<td></td>
<td>1:20 w/v</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1:40 w/v</td>
<td>2</td>
</tr>
<tr>
<td><strong>Ragweed</strong></td>
<td>200 ug AgE/ml</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Timothy</strong></td>
<td>100,000 BAU/ml</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Bermuda</strong></td>
<td>10,000 BAU/ml</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>HDM</strong></td>
<td>10,000 AU/ml</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>30,000 AU/ml</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td>10,000 BAU/ml</td>
<td>2</td>
</tr>
</tbody>
</table>

* Using 10 ml vial/0.5 ml shot

Grier T. Ann Allergy Asthma Immunol 2012;108;
Allergen Extract Dilutions

- Grass at 1:10 v/v loses some potency at 6 months; ragweed, dust mites and cat at 1:100 v/v stable for over 12 months

<table>
<thead>
<tr>
<th>Maintenance, 1:1 v/v</th>
<th>1:10 v/v</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1:100 v/v</th>
<th>1:1000 v/v</th>
</tr>
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<tbody>
<tr>
<td>3-6 months</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>
Injection Schedules

Build-up (Walter Reed schedule ideal)

- “standard”
  - rush
  - cluster

Maintenance

- inhalant: q 2 - 6 weeks
- Hymenoptera: q 4 - 12 weeks
<table>
<thead>
<tr>
<th>Schedule I</th>
<th>Schedule II</th>
<th>Schedule III</th>
<th>Schedule IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 ml</td>
<td>0.1 ml</td>
<td>0.05 ml</td>
<td>0.05 ml</td>
</tr>
<tr>
<td>0.2 ml</td>
<td>0.2 ml</td>
<td>0.1 ml</td>
<td>0.1 ml</td>
</tr>
<tr>
<td>0.4 ml</td>
<td>0.3 ml</td>
<td>0.15 ml</td>
<td>0.15 ml</td>
</tr>
<tr>
<td>0.6 ml</td>
<td>0.4 ml</td>
<td>0.2 ml</td>
<td>0.2 ml</td>
</tr>
<tr>
<td></td>
<td>0.5 ml</td>
<td>0.3 ml</td>
<td>0.25 ml</td>
</tr>
</tbody>
</table>
Cluster Schedule

Accelerated dosing protocol
- fewer office visits
- better compliance
- earlier clinical and immunologic response

- without more severe or frequent shot reactions

<table>
<thead>
<tr>
<th>Visit</th>
<th>Dose (ml)</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 - 0.2 - 0.4</td>
<td>1:1,000</td>
</tr>
<tr>
<td></td>
<td>(30 minutes apart)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.1 - 0.2 - 0.4</td>
<td>1:100</td>
</tr>
<tr>
<td>3</td>
<td>0.05 – 0.1</td>
<td>1:10</td>
</tr>
<tr>
<td>4</td>
<td>0.15 - 0.2</td>
<td>1:10</td>
</tr>
<tr>
<td>5</td>
<td>0.3 - 0.4</td>
<td>1:10</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>1:1</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>“ “</td>
</tr>
<tr>
<td>8</td>
<td>0.15</td>
<td>“ “</td>
</tr>
<tr>
<td>9</td>
<td>0.2</td>
<td>“ “</td>
</tr>
<tr>
<td>10</td>
<td>0.3</td>
<td>“ “</td>
</tr>
<tr>
<td>11</td>
<td>0.4</td>
<td>“ “</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>“ “</td>
</tr>
</tbody>
</table>
Importance of Rapid Buildup

My database of 203 SCIT patients from 2005-2011:

- 21% dropped in 1st year, 33% failed to reach 3 years
- Of those reaching maintenance in 4 months, only 4.4% quit < 1 year, 16% <3 years
- Unfortunately, only 1/3 hit maintenance < 4 mo.

Kwarcinski TJ, et al. Poster Session, FL Allergy Asthma Immunol S
Maintenance Therapy

• Frequency of injections is spread out to q 2-4 weeks

• If no clinical benefit in 18 months, d/c SCIT

• Medications are reduced to minimum necessary to maintain clinical benefit

• Discuss completing course at 3-5 years
  - 239 pt. study showed 3 = 5 yrs
  - I allow shots q6 wks. in yrs. 2-3, 8 wks. in yrs. 4-5

Tabar AI, et al.. J Allergy Clin Immunol 2011;127:5
<table>
<thead>
<tr>
<th>Dilution</th>
<th>V/V Label</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>1:1</td>
<td>Red</td>
</tr>
<tr>
<td>10-fold</td>
<td>1:10</td>
<td>Yellow</td>
</tr>
<tr>
<td>100-fold</td>
<td>1:100</td>
<td>Blue</td>
</tr>
<tr>
<td>1,000-fold</td>
<td>1:1,000</td>
<td>Green</td>
</tr>
<tr>
<td>10,000-fold</td>
<td>1:10,000</td>
<td>Silver</td>
</tr>
</tbody>
</table>
Efficacy Studies - Mold

- Fungal spores can exceed that of pollen by 1,000-fold, >1 million different species have been identified, & patient demand for Rx is high
- Variation in potency between manufacturers >100 fold by ELISA inhibition
- Standardized cladosporium and alternaria mainly studied, whereas aspergillus and penicillum are major indoor molds
- No extract available for many ascospores and basidiospore (mushroom)
Duration of Benefit – 12 year F/U

22 grass sensitive rhinitics on SCIT for 3 yrs (1989-91) compared to control group:

• 6 years after d/c therapy
  - significant clinical benefit, reduced onset new sensitivities, decreased grass skin test responsiveness

• 12 years after d/c therapy
  - symptom score and med. use lower, skin test responsiveness returned, new sensitivities less (58% vs. 100%)

Eng PA, Allergy 2006;61:198-201
No Markers of Efficacy

• In vivo – skin test allergen challenge

• Immunologic surrogate marker
  - ↓ specific IgE level
  - ↓ sIgE/total IgE ratio
  - ↑ IgG₄
  - ↑ serum IgA₁ and IgA₂
  - ↑ TGF-β
Early Intervention in the Pediatric Population

• May prevent sensitization to new allergens

• May prevent progression to asthma
Immunotherapy Reduces New Sensitization in Children

- 138 asthmatics 5-8 yo monosensitized to dust mites
- 75 (54%) placed on 3 years of allergen immunotherapy
- graph shows % of kids with onset of new allergic sensitivities over 3 years

Six Year Follow Up

Same results at 6 years of follow up (annual skin test and in-vitro specific IgE):

**New Sensitivities**

SCIT treated children: 17/69 (24.6%)

Control children: 36/54 (66.6%)

Panjo GB, Clin Exp Allergy 2001;31:1392-
Preventive Allergy Treatment

- 6-14 yo with grass and/or birch rhinitis (n=151)
- 1/2 (n=79) placed on 3 years of allergen immunotherapy
- graph shows % of kids with onset of asthma over 3 years

Follow up of the PAT-Study

147 subjects 16-25 y.o., 10 years after starting 3 yrs of grass/birch SCIT

- Improvements in rhinitis symptoms and conjunctival provocation test persisted

- Significantly less likely to develop asthma in treated group, OR 2.5 (1.1 - 5.9), 16/64 (25%) vs. 24/53 (45%) in controls; unchanged from results when SCIT was d/c

Asthma Prevention

German cohort study of 2,431 AR patients without asthma started on AIT in 2006

- AIT treated group had decreased incidence of asthma from 2007-12, OR 0.6 (CI 0.42-0.84), or 40% reduction rate

- AIT > 3 years had stronger preventive effect

Safety Aspects of Immunotherapy

- Consent form signed prior to mixing vaccine
- PEFR in patients with asthma
- Question patient prior to injection about previous shot, recent symptoms, new meds., pregnancy
- Abide by observation time periods
Timing of Systemic Reactions

- Survey of A/I practices 2008/9; no fatal rxn’s
- 267 practices provided data on timing of rxn’s
- 86% systemic rxn’s were early (< 30 minutes)
- Same proportion of rxn severity in early vs late
- Epi given more often in office

Cost Savings of SCIT

3rd in series using FL Medicaid claims data, 1997-2009, all ages

- 38% lower costs at 18 months for AR pts. on SCIT vs. matched controls
- Significant savings seen within 3 months of SCIT

Hankins et al. JACI 2013;1311084-91
<3% newly diagnosed AR patients received SCIT

Median # of injections in adults was 6, 13 overall

How much better would the results be with good compliance???

Hankins et al. JACI 2013;1311084-91
FDA Approved Sublingual Tablets (SLIT)

Grass
- Stallagenes: Oralair
- Merck/ALK: Grastek

Ragweed
- Merck/ALK: Ragwitek
SCIT vs. SLIT

A review of 14 trials:

- SCIT more often significantly superior to placebo, and some cases SCIT superior to SLIT

- No study where SLIT superior to placebo when SCIT wasn’t

- No case where SLIT superior to SCIT

Nelson H. JACI In Practice 2014;2:144-9
SCIT vs. SLIT Compliance

- Discontinuation in 15 SCIT studies: 6-84%
- D/C rate in 10 SLIT studies 21-93%
- Italy pharmacy refill rate at year 3 SLIT – 13%
- Netherlands at 3 yrs 23% SCIT, 7% on SLIT

median time to D/C SCIT 1.7 yrs, SLIT 0.6 yrs.
Cox, RFL JACI Pract 2014;2:156-60
Current Status of SLIT

- Efficacy with monotherapy for AR and asthma, atopic dermatitis in selected patients
- Appropriate dosing for grass, ragweed, and dust mite tablets
- Prevention of new sensitization and progression from rhinitis to asthma
- Persistent benefit after stopping
- Better safety compared to SCIT
Beyond SCIT & SLIT

• Alternative route of administration – epicutaneous and intralymphatic

• Chemical treatment of antigen or recombinant technology

• Stimulation of innate immunity toward Treg and Th1 orientation

• Suppression of Th2 response

• Vitamin D or probiotic adjuvants
Intralymphatic SIT

- 3 injections q 4 weeks, ultrasound guided inguinal LN, birch and grass, 7 active/ 8 placebo

- No more painful than SQ injections

- Decreased recall symptoms and better nasal challenge tolerance, ~ same as 3 yrs of SCIT

- No change in IgG₄ or IL-10

Hylander et al. J Allergy Clin Immunol 2013;131:412-20
Allergen Modification

Chemical treatment
- aluminum hydroxide – slows release of Ag
- glutaraldehyde or formaldehyde (allergoid)

Recombinant therapy
- large scale production of peptide fragments of T-cell epitopes
- Fel d 1 most studied, but grass RW, and dust mites are starting
Stimulation of Innate Immunity

Fusion with bacterial DNA sequences CpG that react with toll-like receptors

- resulting cytokines lead to Treg production and Th1 orientation

- initial Amb a 1 study, 6 injections, benefit 2 years

Follow up studies failed
SUMMARY

- Unlike pharmacotherapy, SCIT modulates the allergen-specific immune response and induces long-term remission.
- Reduces the allergic march and the onset of sensitivity to additional allergens.
- Controllable risks under physician supervision.
- Ponder single vs. multi-allergen therapy, ways to improve compliance, and role of SLIT.
No Markers of Efficacy

- Inflammatory markers –
  - ↓ eosinophils
  - ↓ serum or nasal ECP
  - ↓ ICAM-1

- Quality of life questionnaire

Senna G et al Curr Opin Allergy Clin Immunol 2011;11: