Novel Treatments for Food Allergy

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Today's Presenter

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Background: Food Allergy

- Prevalence:
  - ~5.9 million school age children
  - 18% increase since 1997
- Why more food allergy?
  - Peanuts, tree nuts, milk, egg, soy, fish, shellfish, wheat
  - Most common cause of anaphylaxis in children
  - Most common cause of fatal food anaphylaxis
- Standard of care:
  - Avoidance of food allergens
  - Self-injectable epinephrine/antihistamines
- No proactive therapy available

Food Allergy Immunotherapy Goals

- Goals of treatment are two-fold
  - Clinical desensitization
    - Tolerate more food on treatment than before starting
  - Eventual clinical tolerance
    - Off treatment can tolerate food — how long off treatment?
    - No good definition of tolerance — issue in all of allergic diseases

Clinical Research Basics

- Phases
  - Phase 0
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4
- Design
  - Randomized
  - Blind
  - Placebo-controlled

Approaches to Food Allergy Immunotherapy
Potential Effect of Heated Milk & Egg

- 100 milk-allergic pediatric subjects enrolled
  - mean age: 6.7 yrs; range: 2.6 – 17.3 yrs
- Challenged sequentially to baked muffin, waffle & uncooked milk (~1.3 g milk protein / baked product)
- Milk challenges:
  - 9 (~10%) "outgrown" – tolerated all challenges
  - 68 (77%) Heated Cow’s Milk (HCM) tolerant – baked-milk products only
  - 23 (23%) Allergic – could not tolerate milk in any form

Nowak-Wegrzyn, Sampson et al. JACI 2008

Potential Effect of Heated Milk & Egg

- ~75% of allergic children tolerate extensively heated product in a food challenge
- Associated with reductions in:
  - Specific IgE
  - Prick Skin Test
  - Basophil activity
  - Lymphocyte - Treg cell activity
- Accelerated tolerance development
- Questions –
  - effective dose
degree of heating
role of the food matrix

Nowak-Wegrzyn, Sampson et al. JACI 2008
### Approaches to food allergy immunotherapy

<table>
<thead>
<tr>
<th>Allergen-specific</th>
<th>Allergen non-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral IT (OIT)</td>
<td>Chinese herbs (CSE)</td>
</tr>
<tr>
<td>Sublingual IT (SLIT)</td>
<td>Herbs and eliciting factor expressing isoforms</td>
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</tbody>
</table>

### Differences
- **Dose:** mg vs. mcg, route, digestion

### Oral Immunotherapy (OIT) – Eggs & Peanut

- **Multiple clinical studies on OIT conducted worldwide**
- **Evidence from 2 clinical OIT studies**
  - CoFAR egg OIT - Jones, Burks, Sampson et al.
    - NEJM July 2012
  - Peanut OIT - Varshney, Jones, Burks et al.
    - JACI March 2011

### OIT – CoFAR3 Egg Study

- **Clinical findings in OIT study of food allergy**
  - CoFAR egg OIT - Jones, Burks, Sampson et al. NEJM July 2012
    - 55 subjects (> 5 yrs) – 40-egg OIT, 15-placebo
    - Multiple centers involved in the study
    - Investigators and families did not know if they received study drug or placebo
    - Treatment through 48 weeks

### Oral IT (OIT)
- swallowed with food

### Sublingual IT (SLIT)
- sublingually then swallowed

### Differences
- **Dose:** mg vs. mcg, route, digestion

### Methods of Immunotherapy

**OIT**

**SLIT**

### Oral Immunotherapy (OIT) – Eggs & Peanut

**Clinical desensitization**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Egg OIT</th>
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<tr>
<td>5 gm desensitization challenge (10 Month)*</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>10 gm desensitization challenge (22 Month)*</td>
<td>0/15 (0%)</td>
</tr>
</tbody>
</table>

*P < .001

**Off OIT 4 weeks**

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<th>Placebo</th>
<th>Egg OIT</th>
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<tbody>
<tr>
<td>10 gm desensitization challenge (23 Month)**</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>10 gm tolerance challenge (36 Month)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*P < .001
**P < .025
Clinical findings in OIT study of peanut allergy

- **Peanut OIT** — Varshney, Jones, Burks et al. JACI March 2011
  - 25 subjects – 16 - active treatment; 9 – placebo (3 withdrew)

Clinical results - UNC and Arkansas studies

- 19 subjects with peanut allergy completed an OIT protocol
  - Oral food challenge (OFC) 4 weeks after stopping OIT
    - evaluate clinical tolerance (sustained unresponsiveness)
  - Peanut OIT - range of 33-70 months
    - Rates of successful tolerance induction?
  - 11 subjects now eat peanut ad lib without symptoms

Approaches to food allergy immunotherapy

- **Allergen-specific**
  - Immunotherapy by heated milk or egg, etc.
  - Sublingual corticosteroids with peanut
  - Oral IT
  - Oral OIT combined with oral IgG
  - Subcutaneous IT
  - Equine dermonecrotic IT

- **Allergen-nonspecific**
  - *Chinese hamster FEV-2
  - Anti-agglutinins
  - Pollinosis and pediatrics
  - Anti-IL-5
  - Low-grade immune response

Mechanistic results - UNC and Arkansas peanut OIT studies

- How Peanut OIT Changes the Body’s Response
  - Regulatory T cells
  - IL-5 (pg/ml)
  - IL-13 (pg/ml)
  - IL-10:IL-13 ratio

Sublingual Immunotherapy (SLIT) – Peanut Studies

- Few clinical studies on SLIT worldwide
  - CoFAR peanut SLIT — Fleischer, Burks, Sampson et al. JACI Jan 2013
  - Peanut SLIT — Kim, Burks et al. JACI 2011
Clinical findings in SLIT study of peanut allergy

- CoFAR peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
  - 40 subjects – adolescents and young adults
    - peanut SLIT or placebo

- SLIT – Peanut Studies

Clinical findings in SLIT studies of peanut allergy

- Peanut SLIT – Kim, Burks et al. JACI 2011

Results: Food challenges and Skin Prick Tests

- Age 1 to 11 years
- peanut IgE ≥ 7 kU/L and clinical history of reaction within 60 min of peanut ingestion
- Subjects randomized to SLIT or placebo on entry
- Underwent 5 g (2500 mg protein) food challenge after 12 months

Critical Knowledge Gaps in OIT/SLIT Research

Summary - consistent results

1. Desensitization - begins within a few days/months of treatment
   - threshold goes up

2. Allergic side effects - primarily gastrointestinal at the beginning
   - viral infections, exercise
   - OFF therapy – recent Hopkins report of worsening symptoms

3. Mechanistic studies - mast cell, basophil, B-cell and T-cell changes

4. Tolerance - not shown in long-term blinded studies

Approaches to food allergy immunotherapy

- Allergen-specific
- Allergen non-specific

- Oral immunotherapy with or without treatment
- Oral challenge
- Placebo challenge
- SLIT challenge

Critical Knowledge Gaps in OIT/SLIT Research

- Preclinical studies
- Preclinical studies
- Clinical trials

Nowak-Wegrzyn IAC March 2011
**VIASKIN ®: How it Works**

**VIASKIN ®: THE NON-INVASIVE GATE TO ACCESS THE IMMUNE SYSTEM**

- Electrostatically charged occlusive polymer
- Dry allergenic proteins
- Epicutaneous absorption of allergenic particles

**Epicutaneous Immunotherapy (EPIT): Cow’s Milk Allergy**

**Phase II pilot randomized placebo-controlled Milk EPIT trial**

- 16 children with severe IgE-mediated cow’s milk allergy
  - 9 treated in Milk EPIT group & 7 children in Placebo group

- Baseline oral milk challenge performed (OFC1):
  - all patients but one had a tolerance level <10 ml of milk. Many did not tolerate even 0.1 ml of milk
  - last patient could tolerate 17 ml

- 3 months of treatment
  - one Diallertest Milk was applied for 48 hours 3 times a week for 3 months

- Second milk challenge performed after the 3 months of treatment (OFC2)

**Example of studies with EPIT in peanut allergy**

**Approaches to Food Allergy Immunotherapy**

**Anti-IgE**

- Anti-IgE monoclonal antibody (Omalizumab) therapy –
  - has been used in 2 trials for peanut allergy

- Hu-901, a novel antibody, to increase the reaction threshold to peanut during a food challenge after treatment
  - approximately 25% of subjects were nonresponders

- A second major study - omalizumab in 26 subjects
  - stopped prematurely because of safety issues that included severe adverse reactions during food challenges
  - increase in tolerability to peanut in omalizumab-treated (44%) versus placebo-treated (20%) subjects

**Anti-IgE**

- Being studied as both monotherapy and as an adjunct to oral immunotherapy (OIT)

- Pretreatment with omalizumab before and during OIT reduced side effects and the time to daily maintenance dosing in a pilot study of 11 patients with milk allergy

Sampson J Allergy Clin Immunol 2011;127:1309-10
Nowak-Wegrzyn JACI March 2011
Nadeau J Allergy Clin Immunol 2011;127:1622-4
Approaches to Food Allergy Immunotherapy

- **D**emonstrated benefits of Chinese herbal therapy in a mouse peanut allergy model – Li - J Immunol 2003
- **H**erbal formula FAHF-2 was developed as a formulation of 9 Chinese herbs to be used in clinical trials
- During an initial phase I study (early study in the FDA approval process)
  - subjects received FAHF-2 tablets or placebo 3 times per day for 1 week
  - treatment was well tolerated, with only minor gastrointestinal symptoms in a few subjects
- A phase II clinical trial (second phase of FDA approval process)
  - in progress in adolescents and adults with allergy to peanut, tree nuts, sesame, fish, or shellfish

Chinese Herbal Therapy

Wang - Ann Allergy Asthma Immunol 2010;105:75-84

Food Allergy Immunotherapy: The Future?

- **L**ife-long?
  - Clinical desensitization versus long lasting tolerance?

- **T**ransient?
  - Do not have ongoing exposure with food allergy

- **M**ajor questions remaining
  - Can we induce long-lasting tolerance at all in food allergy?
  - Can we induce long-lasting tolerance at all in any allergic disease?

Thank you!

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Life-long?

Transient?