Breakthroughs in Food Allergy: Keeping Nutritious Foods at the Table

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What is Oral Tolerance

• Specific suppression of cellular and humoral immune responses to an antigen by means of prior administration through the oral route
What is Food Allergy

• Failure to develop oral tolerance
• Disruption in previously established oral tolerance
  – Requires an initial encounter with the antigen
Normal Immune Response

• Food presented to the GI tract
  – Largest immunologic organ
    • Populated with lymphocytes
  – Daily exposures to bacteria and ingested protein
• Dietary protein antigen interacts with Antigen Presenting Cells (APCs)
• APCs activate regulatory T cells which results in suppressing the immune response
Abnormal Immune Response

- Food specific antibodies are formed
- Antibodies bind to receptors on the mast cell and basophils
- Exposure to sensitized food occurs
- Food antigen binds to the food specific antibody resulting in a release of mediators
  - Histamine
  - Prostaglandins
  - Leukotrienes
  - Cytokines
- Allergic symptoms occur
Risk Factors for Food Allergy

• Genetic predisposition
  – First degree relative

• Early life factors
  – Maternal and infant diet
  – Presence of co-morbid eczema
  – Immunological stimuli

• Hygiene Hypothesis
History of Food Allergy Treatment

- Reported as early as 1930 as a “rush inoculation”
- 1992 treatment of peanut allergy reported with rush immunotherapy
- 1997 peanut allergy treatment with injections of aqueous peanut extracts
Rationale for Treatment

• Tremendous burden and stress
• Prevalence and incidence rising
• New data reveal that egg and milk appear to be outgrown later in life
• Only 10 to 20% outgrow peanut and tree nut allergy
• Improve quality of life
Why is Research Needed?

• Increasing numbers of people affected by food allergy
  – Adults: 2 to 3%
  – Infants/children 6 to 8% (250,000 births)
• Major allergens common in the western diet
• Food induced allergic reactions #1 reason for ER visits due to anaphylaxis
• Only treatment is avoidance
• Attempts at prevention unsuccessful
Basis of Research

• Alter the immune system’s response to food allergens

• Include different focuses of immunotherapy
  – Cytokine-modulated
  – Allergen-peptide
  – “Engineered” (mutated) allergen protein
Goals of Research

- Increase the threshold of the food protein to which the person is allergic
- Reduce the severity of a reaction
- Induce long lasting tolerance
Food in Schools and Child Care Settings

• Sampson’s landmark study in 1992 in JACI
  – Significant delays in epinephrine administration (average time of 75 minutes)
  – Inadequate management plans
  – Deficiencies in recognizing reactions

• Should foods be banned?
  – Inhalation exposures
    • Only case reports (self reports or questionnaires)
    • Aroma of peanut (no protein)
  – Craft projects

• Cleaning of hands and table surfaces
  – Hand washing with soap and water or commercial wipes
    • Alcohol based hand sanitizers not effective

• Risk of exposure
  – Younger the child greater the risk
  Perry et al JACI 2004
Sublingual Route (SLIT)

- Administration of a liquid antigen extract under the tongue for a specific duration
- Two modalities of administration
  - Hold antigen and swallow (SLIT)
    - Dose held for various amounts of time (30sec – 4 min) before swallowed
  - Hold antigen and spit (Sublingual – Spit)
Mechanism of SLIT

• Contact with oral mucosa is critical
  – Sublingual discharge vs sublingual swallow
  – Local Langerhan-like dendritic cells important
  – Allergen-specific IgE – results variable, may be decreased
  – Allergen-specific IgG/IgG₄ – results variable, may be increased somewhat
  – Allergen-specific IgA – unknown

Akdis Allergy 2006
SLIT

• Side effects less than what has been seen with OIT

• Majority of side effects involve oral pruritus and tingling
  – These symptoms usually resolve with eating an ice popsicle, ice chips, or drinking cold liquids

• Systemic reactions can occur, but less likely
Food Allergy Treatment: SLIT

• Mempel, et al. reported in JACI 2003 treatment of severe anaphylaxis to kiwi fruit with SLIT

• Kerzl et al reported lasting protective effect of SLIT after discontinuation in JACI 2007
Sublingual Immunotherapy (SLIT)

• SLIT – hazelnut allergy in adults
  – DBPC, multi-center study, adults w/ hazelnut allergy (n=22)
  – Sublingual-discharge technique
  – 4 day rush build-up, 8-12 week daily SLIT (66 mg)
  – Primarily OAS patients benefited

• SLIT – peanut-allergic children and adults
  (1) Initial pilot study (Duke)
    - Adolescents and adults
  (2) 2nd-blinded study (Duke)
    - Children
  (3) 3rd study (CoFAR)
    - Adolescents and adults – 3 year study
    Bird et al. J Allergy Clin Immunol 2009
Aims of OIT

• Desensitization
  – Increases the threshold for an allergic reaction to the particular food
  – Starts with multiple doses on the first day followed by single daily doses at home
  – Build-up of dosing over time

• Tolerance
  – Change the food specific immune response of the subject
OIT Studies for PN - Arkansas and Duke

OIT Study Design – 300 mg Dose

- 28/29 ingested 7.8 gm on OIT 300 mg dose
  - 1 had allergic symptoms (one hive, sneeze) - challenge was stopped at 2100 mg due to parental concern

7.8 gram Food Challenge

Initial escalation day

Dose Escalation

300 mg = 1 peanut

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Peanut OIT Subjects

• Enrollment criteria - Any peanut-allergic subject - including history of anaphylaxis (unless accompanied by significant hypotension)

• Age at enrollment: Mean 57 months (range 12-111)
  – Age at first reaction: Mean 15 months (range 8-48)
  – Peanut CAP FEIA: Mean 148 kU/L

• 29 of 33 subjects completed - Duke and Arkansas sites
  – 4 - allergic side-effects more than parents/investigators comfortable

Jones, Burks et al. – J Allergy Clin Immunol – August 2009
Side effects of OIT

• Change in usual state of health
  – Subject’s demeanor
  – Activity level
• Skin
  – Rash
  – Angioedema
  – Urticaria
  – Pruritus
• Gastrointestinal
  – Nausea
  – Vomiting
  – Abdominal pain
  – Diarrhea
• Oral
  – Mouth tingling/itching
  – Hoarseness
• Upper respiratory
  – Sneezing/Itching
  – Rhinorrhea
  – Nasal congestion
  – Cough
• Lower Respiratory
  – Wheeze
  – Shortness of breath
  – Respiratory distress
• Cardiovascular compromise
## Safety of Peanut OIT Dosing

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Initial Escalation Day</th>
<th>Buildup Phase</th>
<th>Home Dosing Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any</strong></td>
<td>93% (77%, 99%)</td>
<td>46% (37%, 56%)</td>
<td>3.5% (2.3%, 5.1%)</td>
</tr>
<tr>
<td>Upper Respiratory</td>
<td>79% (59%, 92%)</td>
<td>29% (20%, 41%)</td>
<td>1.2% (0.6%, 2.5%)</td>
</tr>
<tr>
<td>Skin</td>
<td>61% (41%, 79%)</td>
<td>24% (17%, 32%)</td>
<td>1.1% (0.7%, 1.8%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>68% (48%, 84%)</td>
<td>5.5% (3.2%, 9.2%)</td>
<td>0.9% (0.6%, 1.4%)</td>
</tr>
<tr>
<td>Chest</td>
<td>18% (6%, 37%)</td>
<td>1.7% (0.6%, 5.1%)</td>
<td>0.3% (0.1%, 0.4%)</td>
</tr>
</tbody>
</table>

Risk of Symptom Occurrence with 95% Confidence Intervals

Hofmann et al. JACI 2009
Peanut OIT Dosing
Adverse Reactions

• Patterns of reactions have surfaced –
  – Dosing with fever/illness
  – Suboptimally-controlled asthma
  – Exertional (exercise) symptoms
  – Timing of dose
  – Menses

• Changed OIT protocol after first open study

• Recommendations may improve safety of investigational protocols

Varshney P, Jones SM, Burks AW et al, JACI 2009
OIT Study Design – 4000 mg Dose

- **Dose Escalation**
- **Maintenance**
  - 4000 mg

- **Stop OIT if criteria met**
  - 1 mo

- **Initial escalation day**

- **10 gram Food Challenge**

- **Tolerance**

- **Desensitization**
  - 300 mg = 1 peanut

**Jones – AAAAI 2010**
Milk OIT - Johns Hopkins and Duke

- 19 milk-allergic subjects - 6 to 17 years
  - 12 active, 7 placebo
  - Build-up day (initial dose, 0.4 mg of milk protein; final dose, 50 mg)
  - Daily doses with 8 weekly in-office dose increases to a maximum of 500 mg
  - Daily maintenance doses for 3 to 4 months

- Median milk threshold dose
  - 40 mg at the baseline challenge

- After OIT
  - DBPCFC -Active - 5140 mg vs. Placebo - 40 mg (P = .0003)
  - End-point titration SPT – Active vs. Placebo (P=.03)

Heated Protein Studies

• Lemon-Mulé et al reported in JACI 2008 the results of a study evaluating tolerance to heated egg in egg allergic subjects

• Nowak-Wegrzyn et al reported the results of JACI 2008 results of a heated milk study in milk allergic subjects
Clinical Considerations for Heated Protein Challenges

• IgE levels
  – Undetectable serum level of ovomucoid specific IgE for egg
  – Milk specific IgE < 5 kUA/L for milk

• Long term effect of the introduction of heated food in diet unknown

• Amount of protein to be offered during the challenge

• Educating parents before offering the choice of a challenge
Consortium of Food Allergy Research (COFAR)

- NIH multi-site funded study
- Participating Centers
  - Duke University Medical Center
  - University of Arkansas Medical Center
  - Mt. Sinai Medical Center
  - Johns Hopkins Medical Center
  - National Jewish Medical Center
“Engineered” Recombinant Proteins

• Identified the peanut allergens Ara h 1-3 (*Arachis hypogaea*) and with the gene produced peanut proteins in the laboratory

• Identified IgE-binding epitopes on Ara h 1 – 3

• Substituted single amino acid within epitope
  – e.g. Ara h 2 – a.a. 27-36 - DRRCQSQLER
  – eliminated or markedly reduced IgE binding
  – T cell response unchanged

• Utilized the “engineered” peanut protein in a mouse model of peanut allergy
  • “new” proteins prevented anaphylaxis in the peanut-allergic mice

• Initial human safety studies through CoFAR started in 2009

Sampson and Burks et al.
Burks J Allergy Clin Immunol 2008 121;1344
Currently Active Protocols

• Recombinant protein: EMP-123 (COFAR)
• Heated proteins: milk (Mt. Sinai)
• Adjunctive treatments
  – Omalizumab + milk OIT (Mt. Sinai)
  – Food allergy herbal formula-2 (Mt. Sinai)
Currently Active Protocols

- Egg OIT (COFAR)
- Heated Egg / OIT to Egg
- Peanut OIT (Duke/Arkansas, Stanford)
- Peanut OIT with probiotics (Australia)
- Peanut SLIT (Duke/COFAR)
- Milk SLIT vs. OIT (Johns Hopkins/Duke)
- SLIT with various food allergens (Missouri)
- EoE (COFAR)
Questions to be Answered

• How do we determine the starting dose?
• How often do we increase the dose?
• What is the amount required for maintenance?
• When do we challenge?
Determining the Starting Dose

- Challenges for determining threshold dose to start
- Minimum dose to maximum dose
- Acceptable amount of subject symptoms
- Safety of home dosing
Maintenance Determination

• Is a maintenance amount necessary or do we keep pushing the dose
• Food serving size
• Time on treatment
• Minimum amount required to be successful
Summary

• Food allergy is believed to be the result of a breakdown in normal oral tolerance induction

• Therapies may offer protection from potentially life threatening reactions

• Paramount goal is to induce life long tolerance
References


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