Updates in Food Allergy

April 11, 2014

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Agenda

- Introduction to Food Allergy
- Immunological Mechanisms
- Unmet Needs
- Clinical Trial Results

Do You Have Food Allergies?

Definition of Food Allergy

- Defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. (Boyce et al., Nutrition Res., 2011)

- Should not be confused with ‘intolerance’

Allergy Vs. Intolerance

Food intolerance

- Non immune related
- Low IgE antibodies
- Random
- Will tolerate small amounts
- Can mimic food allergy
- Generally not life threatening

Food allergy

- Immune related
- IgE antibodies in blood stream
- Reproducible
- Reacts systematically
- More typical symptoms
- Can lead to anaphylaxis and death

SAFAR Fast Facts

- Million people in the U.S. with food allergies
- Days per year children & families live in fear of life-threatening food exposure
- # of effective treatments available for food allergies
- $ Billions spent on food allergy patient care in the U.S. per year
- Only food allergy research center west of the Mississippi
- Only food allergy research center in the World working on cure for multiple food allergies

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**Incidence & Prevalence of Food Allergies in U.S. - Increasing and Associated with Near-Fatal Events**

Note: 2007 CDC/National Health Interview Survey (NHIS) was used to estimate the prevalence of food allergy among children in the United States.

**Prevalence**

- Most common in first few years of life
- 90% of food allergies are caused by 8 most common allergenic foods

**Top 8 Allergens**

PEANUT
TREE NUT
WHEAT
EGG
MILK
COCONUT MILK
FISH
SHELLFISH

**Prevalence and Trends**

- 8% of U.S. children suffer from allergies
  - Of which, approx. 40% have a history of severe reactions
- 25.2% peanut---21.1% milk---(17.2%) shellfish
  
  Gupta et. al., Pediatrics, 2011
- +18% in prevalence among children from 1997 to 2007
  
  Branum et. al., Pediatrics, 2009
- 3-4% of adults have food allergies
  
  Sicherer & Sampson, JACI, 2010
- Spontaneous resolution vs. persistence of allergies
  
  Milk, Egg, Wheat, and Soy vs. Peanut, Tree Nuts, Fish, and Shellfish

**Food Allergy is an Immune Disease**

**Immune Response Behind IgE-mediated Food Allergy**

- Presentation of food allergen-derived epitope
- Polarization of naive T cells to T_{H2}
- Class-switching in B cells
- Basophil with FcεRI bound to IgE
- Degranulation: Release of histamines, leukotrienes, prostaglandins
- Manifestation of clinical symptoms

**Anaphylaxis**

- 30,000 cases every year in the U.S.
  - Results in 150 deaths
- Risk factors for fatal anaphylaxis:
  - Teens and Young Adults
  - Uncontrolled Asthma
  - No EpiPen
  - Strong Allergens
Skin-Prick Test

Estimation of Allergen-Specific IgE

Double-Blind Placebo-Controlled Food Challenge

How Related Are Food Allergies to Other Allergies?

How causes food allergy? Why is the prevalence on rise?

Exposure in utero

Current Diet

Gut Microbiota

GMOs

Hygiene

Detergents

What Causes Food Allergy?

• Proteins

• Not fat (oil) and not carbohydrate (sugar)

• Major allergenic foods (>90% of allergy)
  – Children: milk, egg, soy, wheat and as in adults
  – Adults: peanut, nuts, shellfish, fish

• Single food allergy, then have up to 30% chance of multiple food allergies

Critical Questions

Correlation: Nut Consumption During Pregnancy and the Risk of Developing Nut Allergy

• Avoid eating peanuts, tree nuts during pregnancy
  American Academy of Pediatrics, Pediatrics, 2000

• Do not restrict maternal diet; no significant association between avoidance and protection from developing allergy
  Greer et. al., Pediatrics, 2008

• Flip-flopping of recommendations for more than a decade
  Gupta, JAMA Pediatrics, 2014

• Very recent research shows decrease in the risk of developing nut allergies with peripregnancy nut intake
  Frazier et. al., JAMA Pediatrics, 2014
Negative effect on psychosocial well-being of patient and family members, poorer overall growth (Henson & Burks, Semin. Immunopathol., 2012)

Significant economic burden: Food allergies cost of $24.8 billion annually ($4184/child/year) (Gupta et. al., JAMA Pediatrics, 2013)

Currently, no definitive treatment available!
- Strict avoidance of allergenic foods
- Nutritional counseling
- Access to emergency care (EpiPen, Auvi-Q)

Questions from patients about therapy for Food Allergies
- What dose will protect me from ever having an allergic reaction again?
- How long do I have to be on therapy to be successful (in the patient’s mind, “cured”)?
- Will I ever be cured? If so, how long will it last?
- Will I be able to eat ad lib or do I need to take the food every day?
- Can I take therapy for one food and get protection for my other food allergies?
- Will I have allergic reactions during the therapy?
- How does it work?
- Is there anything I can do to make it work better?

Answer: Excellent questions… We are getting there, and we have a series of studies to perform to provide safe and effective therapy for food allergy patients.

History of Immunotherapy for Food Allergies
- 1908: Schofield, et al. Lancet. - 13 yo boy with egg allergy treated with small increasing amounts of egg to desensitization
- 1930-1940: 3 articles from fish to mixture OIT for food allergies
- 1941-1983: nothing reported in the literature
- 1984: Patriarca, et al. for mixed food allergens
- 1998: Patriarca, et al. First OIT study with a control group
- 2004: Meglio, et al. First OIT study for cow’s milk allergen
- 2005: Enrique, et al. First SLIT study for hazelnut allergen
- 2006: de Boisseau, et al. First SLIT study for milk allergen
- 2008: Skripak, et al. First OIT study with a placebo group
- 2009: Jones, et al. First OIT study for peanut allergen
- 2011: Nadeau, et al. First OIT study with omalizumab therapy for milk
- 2012: Keet, et al. First study to use SLIT then OIT for milk
- 2013: Fleischer, et al. First SLIT study with peanut allergen

How Does Food Allergen Immune Therapy Work?
Longitudinal Changes Over Time During Immunotherapy

Is Food Allergen OIT effective?

Does OIT for the treatment of food allergies have a relative benefit compared to allergen avoidance?

- 4 meta analyses are not conclusive on relative benefit
- Conclusion: more research with proper controlled studies are needed
- Randomized, controlled Phase 2 and 3 studies are needed

Summary of All Food OIT Trials to Date: Is Food Allergen OIT safe?

- Up to 98% of participants in OIT studies will have allergic reactions during the course of an OIT study
- Up to 10% of these reactions can occur during home dosing
- Up to 4% of these reactions are severe in nature and need epinephrine intramuscular injection
- Eosinophilic Esophagitis
- Estimated 20% drop out rate due to non compliance or untoward side effects

Adding Adjunct Therapy to OIT

- There is no effective, FDA-approved treatment for food allergy, except to avoid the offending foods and to have ready access to self-injectable epinephrine.
- Recently, oral desensitization has been used to treat patients with food allergy; the process is slow and associated with frequent allergic reactions.
- By adding adjunct therapy, like anti IgE or Chinese Herbal Medicines or others (anti-TSLP?), can we achieve safer and/or more effective therapy outcomes?
Demographics: Rush Multi Subjects

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in yrs. (range)</td>
<td>7.4 (4.5-15.4)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Clinical reaction</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Number of foods dosed</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>4</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>5</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Peanut baseline allergy test (if included in mix) (median and range)</td>
<td></td>
</tr>
<tr>
<td>SPT in mm</td>
<td>13 (1.5-26)</td>
</tr>
<tr>
<td>Specific IgE in kUa/L</td>
<td>31 (1-192)</td>
</tr>
<tr>
<td>Lowest amount triggering reaction in DBPCFC in mg protein</td>
<td>15.5 (1.6-200)</td>
</tr>
<tr>
<td>Highest baseline allergy test (median and range)</td>
<td></td>
</tr>
<tr>
<td>SPT in mm</td>
<td>17 (6-29.5)</td>
</tr>
<tr>
<td>Specific IgE in kUa/L</td>
<td>06 (2-256)</td>
</tr>
<tr>
<td>Lowest amount triggering reaction in DBPCFC in mg protein</td>
<td>6 (0.1-100)</td>
</tr>
<tr>
<td>Total IgE in kUa/L (median and range)</td>
<td>645 (87-1823)</td>
</tr>
</tbody>
</table>

Safety: Allergic Reactions with Rush Multi OIT

<table>
<thead>
<tr>
<th>Initial escalation day</th>
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<tbody>
<tr>
<td>Escalations performed</td>
</tr>
<tr>
<td>Reactions</td>
</tr>
<tr>
<td>Mild (Grade 1)</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
</tr>
<tr>
<td>Severe (Grade 3)</td>
</tr>
<tr>
<td>Epinephrine use</td>
</tr>
<tr>
<td>Dose escalations</td>
</tr>
<tr>
<td>Doses administered</td>
</tr>
<tr>
<td>Reactions</td>
</tr>
<tr>
<td>Mild (Grade 1)</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
</tr>
<tr>
<td>Severe (Grade 3)</td>
</tr>
<tr>
<td>Median reaction rate [range]</td>
</tr>
<tr>
<td>Epinephrine use</td>
</tr>
<tr>
<td>Home dosing</td>
</tr>
<tr>
<td>Doses administered</td>
</tr>
<tr>
<td>Reactions</td>
</tr>
<tr>
<td>Mild (Grade 1)</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
</tr>
<tr>
<td>Severe (Grade 3)</td>
</tr>
<tr>
<td>Median reaction rate [range]</td>
</tr>
<tr>
<td>Epinephrine use</td>
</tr>
</tbody>
</table>

Phase 1: Rush Multi Immunotherapy: Preliminary Safety

Phase 1: Rush Multi Immunotherapy: Preliminary Efficacy

A Desensitization Journey

Rush Multi OIT: Blood & SPT Results for Peanut Baseline vs. Post-OIT
Clinical Conclusions of Phase 1 Chinese Herbal Medicine Study

Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study

Jie Wang, MD; Sung Ho P. Paul, PhD; Nan Yang, PhD; Emmy Ko, MD; Joyce Lee, MD; Sally Noone, RN; Hugh A. Sampson, MD; and Xin-Min Li, MD


Srivastava, et al. JACI 2012. Gave FAHF2 in mice sensitized to peanut, codfish, and egg and it blocked anaphylaxis.

Ross, J, et al. AAAAI 2014, n=68, Poster, current Phase II study

Extensive Heating (Denaturing Proteins) For Food Allergy Immunotherapy

- Why
  - Extensive heating denatures conformational epitopes
  - Majority of milk allergic patients can tolerate baked milk

- How
  - Kim et al. JACI 2011 compared the frequency of milk allergy resolution after the regular ingestion of baked milk products vs. strict avoidance
    - n=89 milk-allergic children
    - 74% tolerated a challenge to baked milk at study entry
    - Of these, 60% vs 22% placebo tolerated unheated milk in 5 yrs..


Sublingual Immunotherapy for Food Allergies

Sublingual Immunotherapy (SLIT) for peanut-allergic children and adults

(1) Initial pilot study – Adolescents and adults - Laubach, Burks, et al. JACI, 2008
Bird et al. JACI 2009

(2) 2nd-blinded study – Children – Bird et al. AAAAI 2010,
Kim et al. AAAAI 2010

(3) 3rd study (CoFAR-NIH) – Adolescents and adults – 3 year study Fleisher, et al. JACI 2013

Can SLIT provide a safer way to induce desensitization among patients with food allergy?

Epicutaneous Immunotherapy for Food Allergies

Can EPIT provide a safer way to induce desensitization among patients with food allergy?

Immunotherapy Comparison for CM Food Allergies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Milk IT Dose</th>
<th>Increase in Tolerated Dose</th>
<th>Time of Dose Increase</th>
<th>Desensitized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT</td>
<td>7 mg</td>
<td>7x</td>
<td>60 wks...</td>
<td>1/10</td>
</tr>
<tr>
<td>OIT</td>
<td>1g</td>
<td>64x</td>
<td>60 wks...</td>
<td>3/10</td>
</tr>
<tr>
<td>OIT</td>
<td>2g</td>
<td>79x</td>
<td>60 wks...</td>
<td>5/10</td>
</tr>
<tr>
<td>EPIT</td>
<td>skin</td>
<td>12x</td>
<td>12 wks...</td>
<td>3/9</td>
</tr>
</tbody>
</table>

Can the Effects of Food Allergen OIT Last?

- Can desensitization last?
  - If we test how well the food allergen is tolerated in long term follow-up periods of daily OIT, does the patient maintain the same level of desensitization?

- If we test for withdrawal to the food allergen after a period of OIT, how long can sustained unresponsiveness last?
  - Burks, Jones, Wood et al. NEJM 2012— 6-8 weeks withdrawal egg 28% sustained UR
  - Vickery, et al. JACI 2014— 4 weeks withdrawal peanut 50% sustained UR
  - Syed, et al. JACI 2014— 3 months withdrawal peanut 35% sustained UR

- AAAAI 2014
  - Jones, et al. Long lasting Egg OIT: N=40, 4-6 weeks off OIT, then add 1b unbaked egg, 55% sustained UR at 4 yrs...
  - Nowak-Wegrzyn, et al. Long term baked Milk: N=85, 72% tolerant to unheated milk after about 7 yrs...
Single Center Peanut OIT Phase 1 Study with a Withdrawal Period--Stanford University

Desensitization, Tolerance, and Non-Tolerance

DBPCFC DBPCFC^*  

Patients on 4g OIT maintenance (desensitization)  
n=20 for 24 months all became SPT neg  
n=20 controls  

Tolerant if no clinical reactivity upon DBPCFC^*  
Non-tolerant if any clinical reactivity upon DBPCFC^*  
3 months of peanut avoidance  

Results:  
20% of subjects had no clinical reactivity upon rechallenge (after 3 months of withdrawal)  
15% of subjects had no clinical reactivity upon rechallenge (after 6 months of withdrawal)  

Syed, et al.

In-Vivo Epigenetic Results

Methylation patterns are associated with NT vs IT

Syed, et al. 2014 JACI

Conclusion

- OIT is in experimental stages and is under investigation. Safety risks are paramount to address during therapy studies.
- There continue to be many unanswered questions to study:  
  - Can OIT lead to ‘tolerance’? What are the best markers of tolerance?  
  - There are clinical impacts from studying ‘tolerance’ vs. ‘desensitization’  
  - Subjects that should continue frequent dosing of therapy vs. those allowed to withdraw and eat ad lib  
- There are scientific impacts from studying ‘tolerance’ vs ‘desensitization’  
  - Identifying immune indicators to improve monitoring safety and efficacy for patients  
  - Data suggest to date that allergen-specific T cells and B cells play a role in desensitization/tolerance; however further studies on cells, tissues, and function (trafficking/immunosuppression/Ab inhibition assays) are needed

Food Allergy research is an opportunity to make a major impact in our field; however, we need randomized, controlled clinical studies with close monitoring for short term and long term follow up phases.

With Appreciation to Subjects and their Families and the Extended SAFAR Team

SAFAR Clinical Research  
Nadeau Laboratory

Thank you to:  
Dr. Wesley Burks  
Dr. Steve Gold  
Dr. Nicole Jones  
Dr. Holden Mössner  
Dr. Hugh Simpson  
Dr. Lynda Schneider  
Dr. Dale Umetsu  
Dr. Kedrin Wang  
Dr. Robert Wood

Thank You

Funded By:

Stanford Allergy for Food Allergy Research

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