Food Allergen Immunotherapy and Tolerance Induction

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University of Arkansas for Medical Sciences
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# Faculty Disclosure

## FINANCIAL INTERESTS
I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount (including consulting fees, grants, honoraria, investments, etc.) or invest money which may create or be perceived as a conflict of interest.

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>Food Allergy Research and Education</td>
<td>Consultant, Board Member</td>
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## RESEARCH INTERESTS
I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

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<tr>
<td>National Institutes of Health</td>
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<tr>
<td>National Peanut Board</td>
<td>Grantee</td>
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Objectives

• Review oral tolerance and immune mechanisms
• Evaluate current clinical trials for food allergen immunotherapy
• Assess efficacy in food allergy trials
  – Focus on tolerance induction to date
Background

• **Immune tolerance**
  - Defined as non-responsiveness of the adaptive immune system to antigen or the presence of an active regulatory T cell response.

US diet: >150 g/day of dietary protein

Vickery JACI 2011:127:576
Berin JACI 2013:131:14
**Breakdown of Oral Tolerance = Food Allergy**

**Goal = Restoration of Tolerance**

**CURE for Food Allergy**

**Clinical Allergy**

**Desensitization**
- increased reactivity threshold
  - "on therapy"

**Immune modulation**

**Tolerance**
- loss of reactivity
  - "off therapy"

**Prevailing Question:** *What time frame to defines “tolerance”?*
Approaches to Food Allergy Immunotherapy

**Allergen-specific**
- Extensively heated milk or egg diet
- Subcutaneous cross-immunotherapy with pollen
- Oral IT
  - Milk OIT combined with anti-IgE
  - Sublingual IT
  - Epicutaneous IT

**Allergen non-specific**
- Chinese herbs FAHF-2
- Anti-IgE
- Probiotics and prebiotics
- Anti-IL-5
- *Trichuris suis* ova

Potential for entering clinical practice

Clinical trials

Nowak-Wegrzyn JACI 2011:127:558
# Immunologic Differences

## Food Allergy vs. Effective Immunotherapy

<table>
<thead>
<tr>
<th>Immune Parameters</th>
<th>Food Allergy</th>
<th>Effective Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Serum IgG4</td>
<td>↓/-/↑</td>
<td>↑</td>
</tr>
<tr>
<td>Th2 cytokine Prod’n</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>MC/Basophil Reactivity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Treg Activation</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Scurlock Current Opin Allergy Immunol 2010; Akdis JACI 2011:127:18
OIT: Randomized controlled trials

• Three randomized, controlled trials
  – Peanut OIT (n=28), Duke/AR¹
  – Milk OIT (n=20), Hopkins/Duke²,³
  – Egg OIT (n=55), CoFAR – 5 centers⁴

• Median age = 7-9 years

• Maintenance dose and duration:

<table>
<thead>
<tr>
<th></th>
<th>POIT</th>
<th>MOIT</th>
<th>EOIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>4 gm</td>
<td>500 mg (16 gm)</td>
<td>2 gm</td>
</tr>
<tr>
<td>Duration</td>
<td>4 yr</td>
<td>2-3 yr</td>
<td>4 yr</td>
</tr>
</tbody>
</table>

• Assessment of tolerance: POIT and EOIT

¹Varshney JACI 2011:127:654
²Skripak JACI 2008:122:1154
³Narsity JACI 2009:124:610
Oral Immunotherapy Study Design

- **Maintenance**
- **Food Challenge #1 (OFC 1)**
- **Desensitization**
- **Initial escalation day – 6 mg**
- **Dose Escalation**

- **4000 mg**
Oral Immunotherapy Study Design

- **Initial escalation day** – 6 mg
- **Dose Escalation**
- **4000 mg**
- **Maintenance**
- **Meet criteria for assessing tolerance**
- **Off OIT (4-8 wk)**
- **Food Challenge #1 (OFC 1)**
- **Food Challenge #2 (OFC 2)**
- **Desensitization**
- **Food Challenge #3 (OFC 3)**
- **Tolerance**
Immunotherapy and **Desensitization**

“increased reactivity threshold on therapy”

- Clinical desensitization and immunologic modulation noted with OIT
  - Milk, egg, peanut
  - Side effects noted in 10-20%
- Clinical desensitization (partial) and some immunologic modulation noted with SLIT
  - Peanut, milk
  - Reduced side effects
- Clinical desensitization (partial) noted with anti-IgE
  - Reduced side effects and time to maintenance with omalizumab pre-treatment for milk OIT
  - Immunologic modulation with anti-IgE + milk OIT

Oral Immunotherapy

Impact on “Clinical Tolerance”

“loss of reactivity off therapy”
Clinical Tolerance Develops after 3 Years of Peanut OIT (PnOIT)

- 27 subjects on open label OIT >33 months (median 44 mo)
- After 33-70 months, the rates of tolerance induction were:
  - **PP Analysis**: 11/19 (58%); **ITT Analysis**: 11/27 (41%)

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**Dose Escalation**

Initial escalation day – 6 mg

**Maintenance**

4000 mg

**Desensitization**

Food Challenge #1 (OFC 1)

Food Challenge #2 (OFC 2)

**Meet criteria for assessing tolerance**

Off OIT (4-6 wk)

**Food Challenge #3 (OFC 3)**

Tolerance

Vickery B. AAAAI 2012
Lower peanut-specific IgE levels at baseline are associated with tolerance.

<table>
<thead>
<tr>
<th>Baseline peanut IgE</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85.45 kU_a/L</td>
<td>81.8% (48.2 - 97.8)</td>
<td>87.5% (47.4 – 100)</td>
</tr>
</tbody>
</table>

AUC = 0.8864
p = 0.005
Over time, the reduction in peanut IgE levels is similar in all subjects, independent of outcome.

** indicates p<0.01
Among tolerant subjects, skin prick tests start small and remain suppressed.
Among tolerant subjects, skin prick tests start small and remain suppressed.
Among tolerant subjects, skin prick tests start small and remain suppressed.

** indicates p<0.01; * indicates p<0.05
POIT Modulates Tregs and Cytokines

**Tregs Activation**

\[ p = 0.05 \]

**Cytokines change with IgG4**

IL-10:IL-13 ratio

Peanut-IgG4

Kulis M. AAAAI, 2011
### Egg OIT – “Sustained Unresponsiveness”

#### Oral Food Challenge Success Rates

<table>
<thead>
<tr>
<th>OFC Performed</th>
<th>Placebo</th>
<th>Egg OIT</th>
<th>Placebo</th>
<th>Egg OIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 gm desensitization OFC (10 mo.)</td>
<td>13</td>
<td>35</td>
<td>0/15 (0%)* (n=13)</td>
<td>22/40 (55%)* (n=35)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (22 mo.)</td>
<td>1***</td>
<td>34</td>
<td>0/15 (0%)* (n=1)</td>
<td>30/40 (75%)* (n=34)</td>
</tr>
<tr>
<td>10 gm OFC off OIT + open egg (24 mo.)</td>
<td>0***</td>
<td>29</td>
<td>0/15 (0%)** (n=0)</td>
<td>11/40 (27.5%)** (n=29)</td>
</tr>
<tr>
<td>10 gm OFC off OIT + open egg (~36 mo.)</td>
<td>N/A</td>
<td>13</td>
<td>N/A</td>
<td>18/40 (45%)# (n=13)</td>
</tr>
</tbody>
</table>

*p<.001; **p=.025; #p<.01; ***OFC performed w/ criteria met

- 1 subject in the 2 yr tolerant group had reaction ~1 yr after OFC upon eating a fried egg; continues ad libitum egg diet; Other tolerant subjects continue on ad libitum egg diet

Supported by NIH-NIAID U19AI066738 and U01AI066560

Jones SM. AAAAI, 2012

Burks/Jones NEJM 2012:367:233
Egg OIT

Change in Skin Prick Tests Over Time

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Egg OIT</th>
</tr>
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<td></td>
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</table>

- Baseline
- Month 10
- Month 22 Baseline
- Month 10
- Month 22

p=0.02

Egg PST mm

Burks/Jones NEJM 2012;367:233
Egg OIT Decreases Basophil Activation

\[ p < 0.002 \]
Egg OIT

Change in Specific IgE Over Time

Burks/Jones NEJM 2012;367:233
Egg OIT

Change in Specific IgG4 Over Time

![Graph showing change in specific IgG4 over time comparing Placebo and Egg OIT groups. The graph indicates a statistically significant increase in IgG4 levels in the Egg OIT group compared to the Placebo group, with a p-value of <0.001.](NEJM2012_367_233.png)

Burks/Jones NEJM 2012;367:233
Egg OIT
Predictors of Sustained Unresponsiveness

• *When assessing functional tolerance, no parameters can substitute for OFC*

• Among egg OIT subjects:
  – smaller PST size at 22 months correlated with desensitization (p=0.009)
  – small PST size at 22 months correlated with sustained unresponsiveness (p=0.005)
  – change in PST size from baseline to 22 months correlated with sustained unresponsiveness (p=0.01)

Supported by NIH-NIAID U19AI066738 and U01AI066560

Burks/Jones NEJM 2012:367:233
Peanut OIT differentially alters Ara h 1-3 binding patterns
Peanut OIT differentially alters Ara h 1-3 binding patterns (OIT v. controls)
Milk Allergy
A comparison of oral and sublingual immunotherapy

• Combination of SLIT and OIT for milk allergy

• Entry OFC to establish baseline threshold

• Initial SLIT (4 mg) in all groups
  1. Continued SLIT (7 mg)
  2. OIT A (low, 1000 mg)
  3. OIT B (higher, 2000 mg)

• Build-up 14-26 wks, then OFC after 12 weeks and 60 weeks on maintenance; then 1 and 6 weeks off treatment

Keet C. JACI 2012:129:448
Milk Allergy

A comparison of oral and sublingual immunotherapy

Overall greater immunologic impact (IgE, IgG4, PST, basophil activation) noted in OIT vs. SLIT groups

Keet C. JACI 2012:129:448

<table>
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<th>TABLE II. Clinical outcomes</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Withdrew</td>
</tr>
<tr>
<td>Failed full desensitization challenge (T5)</td>
</tr>
<tr>
<td>Failed challenge 1 wk off therapy (T6)</td>
</tr>
<tr>
<td>Failed challenge 6 wk off therapy (T7)</td>
</tr>
<tr>
<td>Considered tolerant</td>
</tr>
<tr>
<td>Total no.</td>
</tr>
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Immunotherapeutic Effect of Heated Milk and Egg

- Confirmed milk and egg allergic children – OFC to baked product
- ~70% tolerate extensively heated food at OFC

• After 3-6 mo of baked goods
  • increased IgG4
  • decreased PST; basophil activity
  • downward trend in IgE

• Heating = enhanced digestibility and reduced absorption

• Suggests: baked products may accelerate tolerance

Regulatory T cells

* p<.01

PP-active group was 3.6 times more likely to tolerate unheated milk.
Development of Tolerance – Baked Egg

PP-active group was 14.6 times more likely to tolerate regular egg
Summary: Tolerance Induction after Food Allergy Immunotherapy

• Breakthroughs
  ▪ OIT is associated with “tolerance” development in a subset of subjects
  ▪ Baked milk/egg are associated with accelerated tolerance development
  ▪ Immune changes support signs of effective immunotherapy
  ▪ Other therapies are emerging

• Work to be done...Questions to be addressed
  ▪ Improve tolerance induction through refining of dosing, safety, improved biomarkers, combination therapy
  ▪ Better understanding of immunologic mechanisms of tolerance and stability of response to therapy (does it last?)
  ▪ Improve understanding of “best fit” therapy for allergen(s), patients
  ▪ Establish consensus on timeframe to define “tolerance”