Current and Future Prospects for the Treatment of Food Allergy

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Disclosure

In relation to this presentation, I declare the following real or perceived conflicts of interest:

- **Research Support** from:
  - NIH
  - Aimmune
  - DBV
  - Astellas
  - HAL Allergy
Learning Objectives

• Describe the current treatments under study

• Recognize of the risks associated with these treatments

• Identify potential future treatments under development
Food Allergen Immunotherapy

• The risks of traditional subcutaneous immunotherapy with intact allergens appear to outweigh the benefits

• Alternative approaches are therefore being investigated that may change this equation
  • Modification of the allergens
  • DNA vaccines
  • Adjunctive treatment
    • Adjuvants
    • Medications to reduce adverse reactions
  • Different routes of delivering intact allergens
    • Oral (OIT)
    • Sublingual (SLIT)
    • Epicutaneous (EPIT)
Food Allergen Immunotherapy

Key questions to consider:

- What degree of protection will the treatment provide?
  - Add an element of safety?
  - Allow intro of the food(s) into the diet?
- Does the treatment provide any long term protection (or will continuous treatment be needed)?
- How safe is it? Are the potential benefits worth the risk?
- Is it feasible for general use?
CoFAR Egg OIT Trial: Study Design

- Randomized, placebo controlled, multicenter
- 10 month escalation to 2000 mg maintenance, then 5 OFC to 5 grams of egg protein (“desensitization challenge”)
- Un-blinding, 12-36 additional months of daily maintenance, repeat 10 gram OFC annually
- If OFC successful: stop dosing for 8 weeks and repeat OFC (“tolerance” / SU challenge)
- Primary endpoint: Sustained Unresponsiveness at month 24
## Egg OIT: Oral Food Challenge Results Summary

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Egg OIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 gm desensitization OFC (Month 10)</td>
<td>0/15 (0%)</td>
<td>21/40 (52.5%)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (Month 22)</td>
<td>0/15 (0%)</td>
<td>30/40 (75%)</td>
</tr>
<tr>
<td>10 gm tolerance OFC (Month 24)</td>
<td>0/15 (0%)</td>
<td>11/40 (27.5%)</td>
</tr>
</tbody>
</table>

**Key Results:**

- 75% were desensitized after 22 months of OIT
- 19 out of 30 who were desensitized at 22 months lost protection after avoiding egg for 8 weeks
Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy

Table 1. Food Challenge Defined Clinical Outcomes with Long-term Egg OIT

<table>
<thead>
<tr>
<th>Time from Egg OIT Initiation</th>
<th>Desensitization</th>
<th>Sustained Unresponsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>30/40 (75%)</td>
<td>11/40 (27.5%)</td>
</tr>
<tr>
<td>36 months</td>
<td>32/40 (80%)</td>
<td>19/40 (47.5%)</td>
</tr>
<tr>
<td>48 months</td>
<td>32/40 (80%)</td>
<td>21/40 (52.5%)</td>
</tr>
</tbody>
</table>

In the 22 subjects still dosing in years 3 and 4, 54.5% still reported reactions with dosing.
When compared with subjects not achieving SU, subjects achieving SU had higher IgG4 values (P<.001)
Egg Consumption at Follow-Up (Year 4)

**Concentrated Egg**

![Chart showing Egg Consumption at Follow-Up (Year 4) for Concentrated Egg](chart_concentrated_egg)

**Baked Egg**

![Chart showing Egg Consumption at Follow-Up (Year 4) for Baked Egg](chart_baked_egg)

**Legend**
- **Daily**
- **Several times a week**
- **Weekly**
- **Monthly**
- **Less than monthly**
- **Strict avoidance**
- **Not eating**
Comparison of milk oral and sublingual immunotherapy 
(Keet et al JACI 2012)

All subjects began dosing with SLIT, then randomized to further dose escalation to:
- SLIT: 7 mg daily (~1/20 teaspoon) given as 5 squirts x 3
- OIT: 1000 mg (= one oz) or 2000 mg (= 2 oz)
- Primary endpoint desensitization to 8 grams of milk protein after 15 months of treatment
At 15 mo, 10% desensitized with SLIT, 60% with OIT (p<0.001 SLIT vs. OIT)

Keet et al JACI 2012
## Milk SLIT vs OIT: Challenge Summary

<table>
<thead>
<tr>
<th></th>
<th>SLIT/SLIT</th>
<th>SLIT/OIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrew</td>
<td>0/10</td>
<td>2/20</td>
</tr>
<tr>
<td>Passed full desensitization (8 gram) challenge†</td>
<td>1/10</td>
<td>14/18</td>
</tr>
<tr>
<td>Passed one week off therapy</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Passed six weeks off therapy</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Threshold dose at 1 and 6 week follow-up challenges</td>
<td>8000mg</td>
<td>2540 - 8000mg</td>
</tr>
</tbody>
</table>

† p=0.002 SLIT vs. OIT

Keet et al JACI 2012
Milk SLIT vs OIT – Adverse Reactions

• Overall reaction rates were similar (27 – 33% of all doses, escalation and maintenance)
• SLIT reactions were almost entirely local (oral)
• While reactions with OIT were most often local,
  • GI symptoms in 8 – 10% of doses (90% of subjects)
  • Urticaria in 4% (55% of subjects)
  • Lower respiratory in 2 – 3% (40% of subjects)
  • Multisystem reactions in 0.5 – 1% (30% of subjects)
• Antihistamines were needed in 1% of SLIT doses compared to 16% of OIT doses
Summary of OIT Efficacy (>30 studies)

• Most patients can be successfully desensitized

• The level of desensitization is measured in grams of food protein (usually sufficient to introduce the food into the diet)

• The desensitization is transient in most patients without ongoing exposure

• It is possible that sustained unresponsiveness is more common:
  • In younger children (The DEVIL Study, Vickery et al JACI 2017)
  • With co-administration of probiotics (Tang et al, JACI 2015)
• 40 children aged 9 to 36 months randomized to receive OIT at maintenance doses of 300 or 3000 mg

• SU assessed 4 weeks after stopping OIT

• Outcomes were compared with 154 matched standard-care controls.

• 29 of 37 (78%) in the intent-to-treat analysis achieved SU (300-mg arm, 17 of 20 [85%]; 3000 mg, 12 of 17 [71%]) over a median of 29 months.

• Adverse reactions during OIT were common but all were mild to moderate.
Summary of adverse reactions with OIT

- The types and frequency of reactions appear very similar for milk, egg, peanut, and wheat.
- Overall reaction rates are extremely high – affecting virtually all patients – but most reactions are mild.
- Moderate reactions occur in <10% of doses, severe reactions and / or reactions treated with epinephrine occur in <1% of doses.
- However, since so many doses are needed, on a per patient basis, significant reactions are very common.
  - At least twice as common – and more likely 10 – 20 times more common – than would be expected with strict avoidance.
Summary of adverse reactions with OIT

• Chronic GI symptoms are common, and the most common reason to discontinue therapy (10-25%)
• The true incidence of EoE is not clear
• Are the benefits worth the risk?
• Is co-treatment with omalizumab valuable, and worth the cost?
• Most of the answers to these questions will depend on long term outcomes
Conclusions

• In this first randomized, double-blind, placebo-controlled trial of omalizumab in combination with food OIT, we found significant improvements in measurements of safety but not in outcomes of efficacy (desensitization or SU)

• Safety was improved with regard to acute reactions but not GI symptoms

• With or without omalizumab, most subjects could be desensitized to a high dose (10 g) of milk protein over a 24-month period, but half had increased reactivity after an 8-week period of avoidance
Long-Term Follow-up of Milk OIT  
(Keet et al, J Allergy Clin immunol 2013)

- 32 patients followed from 2 initial milk OIT studies
- 3 – 5 years after study completion:

<table>
<thead>
<tr>
<th>Milk Consumption</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrestricted</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>At least 1 serving/day but not unrestricted</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>Some uncooked</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Minimal, baked only</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>None (strict avoidance)</td>
<td>5 (16%)</td>
</tr>
</tbody>
</table>
## Symptoms at Follow-up (N=32)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>8</td>
<td>25%</td>
</tr>
<tr>
<td>Occasional symptoms</td>
<td>7</td>
<td>22%</td>
</tr>
<tr>
<td>Frequent symptoms</td>
<td>12</td>
<td>38%</td>
</tr>
<tr>
<td>GI</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No milk consumption</td>
<td>5</td>
<td>16%</td>
</tr>
<tr>
<td>Systemic reaction, # (%)</td>
<td>10</td>
<td>31%</td>
</tr>
<tr>
<td>Used epinephrine, # (%)*</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Keet et al JACI 2013
Milk OIT Follow-up: Conclusions
(Keet et al, J Allergy Clin Immunol 2013)

- Although we had felt that most participants in these two milk OIT trials had had very positive outcomes, 3-5 years later only 25% consume milk without symptoms.

- Over time, some subjects became far more reactive than they had been early in therapy.

- Long term success appears to be related to ongoing milk exposure (key question: why did exposure decrease from what was recommended).

- Long-term follow-up of OIT is essential.
CoFAR6: EPIT for Peanut Allergy

Randomization 1:1:1

Enrollment N=75

Entry OFC positive to cumulative dose of ≤1044 mg peanut protein

250 µg Peanut EPIT

100 µg Peanut EPIT

Placebo

Immune assays: baseline, 12, 24, 52 weeks

Week 52
5044 mg OFC

Week 130
5044 mg OFC [End of study]

In Press JACI 2016
CoFAR6: Defined Endpoints

Primary endpoint

– The proportion of subjects with a treatment success following 52 weeks of blinded treatment

– Treatment success defined as:

  • Passing a 5044 mg OFC at week 52

  OR

  • by a ≥10-fold increase in the successfully consumed dose (SCD) of peanut protein at week 52 compared to baseline OFC (Same as the VIPES trial)
## Peanut EPIT: Treatment Success

<table>
<thead>
<tr>
<th></th>
<th>Placebo N (%)</th>
<th>100 mg N (%)</th>
<th>250 mg N (%)</th>
<th>Total* N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong>*</td>
<td>3 (12)</td>
<td>11 (45.8)</td>
<td>12 (48)</td>
<td>25 (35)</td>
</tr>
<tr>
<td><strong>SCD &gt;1044 mg protein</strong></td>
<td>2 (12)</td>
<td>3 (12.5)</td>
<td>7 (28)</td>
<td>13 (17.6)</td>
</tr>
<tr>
<td><strong>SCD &gt;1044 mg protein + 10-fold increase</strong></td>
<td>2 (8)</td>
<td>2 (8.3)</td>
<td>4 (16)</td>
<td>8 (10.8)</td>
</tr>
</tbody>
</table>

*P=0.005 Placebo vs 100 µg, P=0.003 Placebo vs 250 µg, P=0.48 100 µg vs 250 µg

**P=0.54 Placebo vs 100 µg, P=0.12 Placebo vs 250 µg, P=0.12 100 µg vs 250 µg

***P=0.55 Placebo vs 100 µg, P=0.26 Placebo vs 250 µg, P=0.27 100 µg vs 250 µg
Change in Successfully Consumed Dose: Baseline to Week 52 by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median Dose (mg)</th>
<th>IQR (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>-40, 1.0</td>
</tr>
<tr>
<td>100 µg Peanut</td>
<td>43</td>
<td>0, 140</td>
</tr>
<tr>
<td>250 µg Peanut</td>
<td>130</td>
<td>30, 600</td>
</tr>
</tbody>
</table>

Placebo v 100µg
P=0.014

Placebo v 250µg
P=0.003

100 µg v 250 µg
P=0.48

Solid lines represent median values
Hatched lines represent the upper and lower interquartile range
Treatment Response may be Greater in Younger Children (4-11 yrs)

P=0.006, age by treatment interaction with age as dichotomous variable
### Safety of Peanut EPIT: Dosing Reactions

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>100 mg (%)</th>
<th>250 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Reaction (% per dose)</td>
<td>14.4</td>
<td>79.8</td>
<td>79.8</td>
</tr>
<tr>
<td>Patch Site* (Median % doses/subject)</td>
<td>1.6</td>
<td>92.8</td>
<td>96.1</td>
</tr>
<tr>
<td>Patch Site (Grade 2)</td>
<td>1.6</td>
<td>18.7</td>
<td>23.4</td>
</tr>
<tr>
<td>Patch Site (Extension beyond site)</td>
<td>1.6</td>
<td>8.9</td>
<td>16.2</td>
</tr>
<tr>
<td>Non-patch Site</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- Adherence was high – 97%
- No study-related SAEs reported
- No epinephrine use with dosing symptoms
- 1 withdrawal per protocol for grade 3 and 4 patch site reactions

*P<0.01, placebo vs. active EPIT; P=NS, 100 µg vs. 250 µg

**1 subject on 100 µg with systemic hives, treated with oral antihistamines**
## CoFAR6: Patch Site Reaction Scoring

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin Reaction Description</th>
<th>Skin Reaction Example Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Redness only</td>
<td></td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Redness and hard or stiff skin</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Redness and a few bumps</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Redness with many bumps or spreading bumps</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Redness with blisters</td>
<td></td>
</tr>
</tbody>
</table>
Peanut EPIT is associated with modest but significant change in consumed peanut protein (43-130 mg) when compared to placebo after 52 weeks of blinded EPIT

- Greater impact in younger children (4-11 yo)

Adherence to EPIT and trial retention was high (97%)

Peanut EPIT is safe with mild-moderate patch site reactions predominating

Immunologic changes are modest but significant

*Open-label extension to week 130 of active therapy from this study and VIPES will provide additional information on treatment effect*
So Where Do We Go From Here?

- What do patients / families want?
- What do doctors’ want?
- What do these treatments really offer?
  - Degree of protection
  - Duration of protection
  - Long term acceptability
- Is the risk / benefit ratio acceptable?
- Will this be cost effective?
- What are the next steps in research?
Current Status of Food Immunotherapy

• Further study is clearly needed to:
  • Minimize adverse reactions
  • Improve efficacy, ideally including induction of long term protection
  • Identify biomarkers, especially of
    • those at highest risk of adverse reactions
    • those at highest risk to lose protection
  • Long term studies to make certain that these treatments will do more good than harm
**Additional IT Studies Currently Underway**

- Phase 3 studies of peanut patch and low dose peanut OIT
- Milk patch (Phase 2)
- OIT with other foods (e.g. wheat, tree nuts)
- Peanut OIT in 1-3 year olds (IMPACT study)
- Numerous multi-food OIT studies
- DBPC study of peanut OIT and probiotic
- Additional studies with omalizumab (with OIT)
- Studies of Chinese herbs (with and without OIT)
Novel Therapies Underway or in Development

- DNA Vaccine(s)
- SCIT using a chemically modified peanut protein
- Other approaches using modified allergens
- Peanut SLIT with the adjuvant GLA
- Peanut / CPG nanoparticle SLIT
- Trials of other biologic agents, alone or in combination with allergen specific immunotherapy (for prevention or treatment)
  - Omalizumab
  - Dupilumab
  - Anti-TSLP
  - Anti-IL-25
  - Anti-IL-33