Potential Treatments for Food Allergy

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  • NIH
  • ITN
  • DBV
• Advisory Boards
  • Sanofi
  • Stallergenes
Current Treatments for Food Allergy and Their Limitations

1. Strict avoidance
   - Very difficult to accomplish
   - Major impact on quality of life
   - Significant nutritional risks

2. Wait for the allergies to be outgrown
   - Peanut, tree nut, seed, fish, shellfish allergies usually lifelong
   - Milk, egg, wheat, soy, ? others now more persistent (~20% persist into adulthood and are often very severe)

3. Treat reactions when they occur
   - Reactions can be severe and even fatal

Potential Approaches to the Treatment of Food Allergy

- Anti-IgE antibodies (Xolair)
- Chinese herbal formulas
- Immunotherapy
  - intact allergen
  - modified allergens
    - peptide vaccines
    - mutated recombinant vaccines
- homologous proteins
- plasmid vaccines
- Ingestion of extensively heated milk and egg
Ingestion of “Heat-Denatured” Milk or Egg

- Milk (and egg) allergic children can be divided into several groups:
  - Group 1: Severe, more persistent, react to all forms of milk or egg
  - Group 2: Less severe, easier to outgrow, do not react to extensively heated (baked) products, esp at lower doses
  - Children in group one may eventually move into group two
- In those children in group 2, it may be safe to introduce milk or egg in a baked form without doing harm, and possibly helping to increase tolerance
- Breaks the old dogma of strict avoidance until outgrown

Immunotherapy for the Treatment of Food Allergy

- In food allergy, the risks of traditional subcutaneous immunotherapy appear to far outweigh the benefits
- Alternative approaches are under investigation that may change this equation
  - Modification of the allergens
  - Different routes of delivery
    - Oral (OIT)
    - Sublingual (SLIT)
    - Epicutaneous (EPIT)
Potential Approaches to the Treatment of Food Allergy

Key questions to consider:

• Is it allergen specific or a more general Rx?
• 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?
• Is it feasible for general use?

Sublingual Immunotherapy for Hazelnut Allergy
(Enrique et al, JACI 116:1073, 2005)

• 23 patients with varying degree of hazelnut allergy divided into active and placebo groups
• “Rush” desensitization with 22/23 reaching the planned maximum dose at 4 days

50% could tolerate the entire 20 g challenge
First double-blind, placebo-controlled OIT trial
Children with severe, persistent milk allergy
Dosing
  - Milk powder or placebo powder
  - Day 1 escalation from 0.4 mg to 50 mg (1/3 tsp)
  - Then build-up from 50 mg to 500 mg (=15 ml milk)
Primary outcome: change in threshold dose causing reaction, as determined by oral food challenge
All patients completing treatment with placebo were offered open-label active therapy

General Approach to Immunotherapy Protocols

- Dose Escalation: Daily Dosing with dose increases q 1-2 weeks over 6 - 9 months
- Screening and Baseline Challenge (1g)
- Initial treatment escalation day (max 50 mg)
- Home Maintenance x 1 – 3 years (doses 500 mg to 4000 mg)
- 6-12 Months
- 18+ Months
- Repeat Challenges (10 grams)
  Many studies also include a final challenge off therapy to distinguish desensitization from tolerance
Milk Dose Threshold

<table>
<thead>
<tr>
<th></th>
<th>Pre-MOIT</th>
<th>Post-MOIT</th>
<th>Δ from baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (n=18)</td>
<td>40</td>
<td>6,140</td>
<td>6,100</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Placebo (n=7)</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Milk OIT Safety Measurements

<table>
<thead>
<tr>
<th></th>
<th>N (% of total doses)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=12)</td>
<td>Placebo (n=7)</td>
</tr>
<tr>
<td>Doses / child, median (range)</td>
<td>189 (155 – 242)</td>
<td>171 (152 – 199)</td>
</tr>
<tr>
<td>Total doses</td>
<td>2,272</td>
<td>1,193</td>
</tr>
<tr>
<td>Total reactions</td>
<td>1,041 (45.8)</td>
<td>134 (11.2)</td>
</tr>
<tr>
<td>Local reactions</td>
<td>804 (35.4)</td>
<td>104 (8.7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>458 (20.2)</td>
<td>16 (1.3)</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>198 (8.7)</td>
<td>28 (2.3)</td>
</tr>
<tr>
<td>Skin</td>
<td>22 (1)</td>
<td>1 (0.08)</td>
</tr>
<tr>
<td>Multiple Systems</td>
<td>29 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Eczema flare</td>
<td>1 patient</td>
<td>1 patient</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>249 (11)</td>
<td>14 (1.1)</td>
</tr>
<tr>
<td>Albuterol</td>
<td>21 (0.9)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>3 (0.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

CoFAR Egg OIT Trial

• Design summary:
  • Randomized, placebo controlled
  • N = 55 (40 active, 15 placebo)
  • No OFC at baseline
  • 10 months escalation to 2000 mg, then OFC ("desensitization challenge")
  • Un-blinding, 12 additional months with daily maintenance, repeat OFC
  • If OFC successful: stop dosing for 6 weeks, repeat OFC ("tolerance" challenge)

Egg OIT Results
"Desensitization" Oral Food Challenge

Oral Food Challenge with 5 grams of egg white performed after ~44 wks of OIT to assess desensitization

<table>
<thead>
<tr>
<th></th>
<th>Withdrawal (not assessed)</th>
<th>Fail w/ Mod Sx or Tx</th>
<th>Fail w/ Mild Sx</th>
<th>Pass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLACEBO (n=15)</td>
<td>2 (13.3%)</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EGG OIT (n=40)</td>
<td>5 (12.5%)</td>
<td>13</td>
<td>1</td>
<td>21</td>
</tr>
</tbody>
</table>

Results Summary: Successful challenge in 0/15 on placebo compared to 21/40 (52.5%) on egg OIT (p<.001)
## Egg OIT: Oral Food Challenge Results Summary

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=participants)</th>
<th>Egg OIT (n=participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 gm desensitization OFC (10 Month)</td>
<td>0/15 (0%)</td>
<td>21/40 (52.5%)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (22 Month)</td>
<td>0/15 (0%)</td>
<td>30/40 (75%)</td>
</tr>
<tr>
<td>10 gm tolerance OFC (24 Month)</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 6 weeks

### Change in Serum Levels of Egg-Specific IgE During OIT

At month 22, egg-specific IgE is lower in the egg OIT group (median=3.8 kUA/L) than placebo (median=14.0 kUA/L) p<0.001
Change in Serum Levels of Egg-Specific IgG4 During OIT.

Levels were compared from baseline to 3, 10, and 24 months of therapy. Significant increases occurred after egg OIT and between treatment groups (*p < 0.001)

Change in Egg Skin Tests During OIT.

Prick skin test sizes from baseline to month 22 decreased more in subjects undergoing egg OIT than placebo OIT (*p=0.02)
CoFAR Peanut SLIT Study  
(Fleischer et al JACI 2013;131:119)

- Design summary:
  - Randomized, placebo controlled, N = 40
  - 2 gram peanut OFC at baseline
  - 10 months escalation to 1.3 mcg, then OFC ("desensitization challenge")
  - Un-blinding, placebo subjects offered escalation to "high dose" SLIT (3.7 mcg)
  - 12 – 24 additional months with daily maintenance, repeat OFC annually
  - If OFC successful: stop dosing for 6 weeks, repeat OFC ("tolerance" challenge)

Peanut SLIT: Oral Food Challenge Baseline to Week 44

- Active versus Placebo P=0.16
- 70% on peanut SLIT were responders compared with 15% on placebo (P < .001)
- Responders defined as tolerating 1 gram OFC or 10-fold increase in threshold over baseline
CoFAR Peanut SLIT Study: Safety and Study Conclusions
(Fleischer et al JACI 2013;131:119)

• No significant changes were seen between the active and placebo groups

• Significant within group changes from baseline were seen with active SLIT for OFC response as well as changes in peanut IgE and IgG4

• Safety overall reassuring:
  • Of 10,855 peanut doses, 63.1% were symptom free; excluding oral-pharyngeal symptoms, 95.2% were symptom free

• Conclusion: Peanut SLIT safely induced a modest level of desensitization in a majority of subjects

Comparison of milk oral and sublingual immunotherapy

• 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)

Keet et al JACI 2012
Milk OIT vs SLIT: Oral Challenge Threshold

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 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 range at 1 and 6 week follow-up challenges</td>
<td>8000mg</td>
<td>2540 mg-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 in all groups (27 – 33% of all doses, escalation and maintenance)
- However:
  - SLIT reactions were almost entirely local (oral)
  - While oral reactions were most common in OIT,
    - GI symptoms in 8 – 10% of doses
    - Urticaria in 4%
    - Lower respiratory in 2 – 3%
    - Multisystem reactions in 0.5 – 1%
  - Antihistamines were needed in 1% of SLIT doses compared to 16% of OIT doses

Summary of adverse reactions with OIT

- The types and frequency of reactions appear very similar for milk, egg, and peanut
- Overall reaction rates are extremely high – affecting virtually all patients – but most reactions are mild
- Moderate reactions occur in <5% of doses, severe reactions and / or reactions treated with epinephrine occur in <<1% of doses
- However, since to 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 (10-15%)
- The true incidence of EoE is not clear
- Are the benefits worth the risk?
- Is co-treatment with omalizumab necessary?
- Most of the answers to these questions will depend on long term outcomes

Long-Term Follow-up of Milk OIT
(Keet et al, J Allergy Clin immunol 2013)

- 32 patients followed from 2 original 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>Symptom Category</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>Occasional symptoms</td>
<td>7 (22%)</td>
</tr>
<tr>
<td>Frequent symptoms</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>GI</td>
<td>7</td>
</tr>
<tr>
<td>Oral</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
</tr>
<tr>
<td>Upper Respiratory</td>
<td>2</td>
</tr>
<tr>
<td>Lower Respiratory</td>
<td>1</td>
</tr>
<tr>
<td>No milk consumption</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Systemic reaction, # (%)</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>Used epinephrine, # (%)*</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

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**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.

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Keet et al, J Allergy Clin Immunol 2013
Epicutaneous Immunotherapy (EPIT)

Design of VIPES & OLFUS-VIPES Studies

**Phase IIb**
- 221 patients, 22 centers, 5 countries*  
  *US, Canada, The Netherlands, France, Poland

**Study Population**
- Age: 6-55 years old
- Peanut allergic patients (> 0.7 kU/L peanut-specific IgE and ≥ 8 mm SPT wheal)
- Highly sensitive subjects: peanut reactive dose at baseline (M0) ≤ 300 mg peanut protein

**Efficacy Endpoints**
- Primary endpoints: 'responder rate' defined as patients reaching ≥ 1000 mg reactive dose or ≥ 10-fold initial reactive dose at M12 food challenge
- Main secondary endpoints: efficacy in patient populations (CRD, LS Mean, and other measures in children, adolescents, adults), change from baseline in peanut sIgE and sIgG4

**Primary Objective**

The primary efficacy endpoint was the percentage of treatment responders in any active group compared to placebo.

Definition of a treatment responder:

- a subject with a peanut protein eliciting dose equal to or greater than 1,000 mg peanut protein based on the results of the DBPCFC after 12 months of treatment
- or a subject with a 10-fold increase or more of the eliciting dose at 12 months, compared to the initial eliciting dose
Treatment Responders at Month 12
Overall, FAS

The Primary efficacy endpoint was met at the 250 µg dose

ED ≥ 1,000 mg at Month 12
Overall, FAS
ED ≥ 1,000 mg and ≥ 10-fold increase at Month 12
Overall, FAS

Cumulative Reactive Dose (CRD) at Month 12
6-55 years of age, FAS
Change from baseline, Adjusted CRD, LOCF imputation

A Clear quantitative dose-response 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