The Evolution of Food Allergy Therapy: Past, Present, and Future

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Disclosures

• Member, Joint Task Force on Allergy Practice Parameters

• Member of Nutricia, DBV, Aimmune, Kaleo and Monsanto specialty advisory boards and has received honorarium

• Co-chair, Nestle international consensus panel on the use of hydrolyzed formula and received honorarium

• Member, CSACI Food Allergy in Schools Guideline Panel

• Member of the Medical Advisory team for the Allergy and Asthma Foundation of America and the International Association for Food Protein Enterocolitis (nonfinancial)

• Has received honorarium from Thermo Fisher, Symbiotix, Hybrid Health, ClinicalMind, Vindico, Before Brands, multiple state allergy societies for CME/non-CME presentations

• Consultant to Aimmune, Intrommune, Thermo Fisher

• Receiving support from K08-HS024599 (Agency for Healthcare Quality and Research)

• Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food committees

• Co-chair, AAAAI Primary Prevention of Food Allergy Working Group; Co-chair, AAAAI Oral Immunotherapy Office-based Practice Working Group

• Member ACAAI Annual Meeting Planning Committee, Chair, GI/Food Allergy Track chair; Chair, Food Allergy Committee

• ACAAI representative to consensus statement on interim consensus on early peanut introduction guidelines

• Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy

• Associate Editor, Annals of Allergy, Asthma, and Immunology

• Editorial board: Allergy and Rhinology; Medscape Pediatrics; Infectious Diseases in Children

• Member, Scientific Advisory Council, National Peanut Board

• Member, EAACI Task Force on Nutrition and Immunomodulation
Goals

Understand OIT, EPIT and their present potential benefits

Understand potential alternative approaches to treating food allergy

Understand the complexities of the choice to consider enrollment in therapy

OIT, oral immunotherapy.
A Delicate Balance

Treating/curing food allergy

Maximizing how we can live with food allergy
Choosing Treatment vs Avoidance

• Caregivers are faced with many decisions
  – May focus on the perceived benefit vs accidental death
  – May prefer to avoid therapy that becomes burdensome
  – May prefer to avoid costly therapy, or not care about cost
  – May have realistic or unrealistic expectations
  – May feel that doing “something” is better than avoidance

• Have to define their expectations and goals

• We can’t judge or prescribe—we are guides

• But, we must inform what would work best
  – If that is even possible!
Fast-tracked Approaches to Treatment

Oral and Epicutaneous Immunotherapy
OIT: What Do We Know?

- OIT involves slow medically supervised re-feeding of increasing doses of one’s allergen
- Many achieve some degree of desensitization
  - Threshold increased for most, but not all, but few develop sustained unresponsiveness
  - No indication of the duration of therapy, or how long the effects last
- Fairly equal effects were seen with milk, egg, peanut in ability to achieve desensitization
- Markers of allergen sensitivity diminish significantly
  - See shift in allergen-specific IgE >IgG₄ and part of allergen recognized
- See variable effect of immune cell shut down
  - No consistent biomarker pattern shown, but are many targets of interest

References:
- Blumchen et al, J Allergy Clin Immunol 2010; 126: 83-81
- Jones SM et al, J Allergy Clin Immunol 2009; 124: 252-300
- Skripak et al, J Allergy Clin Immunol 2008; 122: 1154-60
- Narketi et al, J Allergy Clin Immunol 2009; 124: 610-12
- Varshney et al, J Allergy Clin Immunol 2011; 127: 654-60
- Kim et al, J Allergy Clin Immunol 2011; 127: 640-6
- Fleischer et al, J Allergy Clin Immunol 2013; 131: 119-27
### “Typical” OIT Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry challenge</strong></td>
<td>Build to 12 mg-50 mg</td>
</tr>
<tr>
<td><strong>Rapid desensitization</strong></td>
<td>Build up to ~300 mg-800 mg (varies), increase dose in office every 2 weeks</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Placebo group crossover</td>
</tr>
<tr>
<td><strong>Interim challenge</strong></td>
<td>? interrupt therapy, test sustained nonresponse</td>
</tr>
<tr>
<td><strong>End of maintenance challenge</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Continuation or discontinuation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>End of study challenge</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Process Details

- **Pre-study**: Variable duration
- **Day 1**: Can persist for a few months to 2 years

**Notes**


**References**

PALISADES Entry Characteristics

- 90% were ages 4-17 years
- 72% had history of anaphylaxis
- 53% had asthma
- 66% with multiple food allergies
- 43% had peanut sIgE > 100 KU/L
- Median entry OFC challenge tolerance was 10mg (1/30th peanut)
**PALISADES Main Results**

**Intention to treat population**

- NNT of 1.58 (ARR 63.2%) for primary endpoint
- NNT of 2.08 (ARR 48%) for secondary endpoint
- 44% with sIgE > 100 kU/L tolerated 1000mg

**Per Protocol Population (“completers”)**

- NNT of 1.23 (ARR 82%) for primary endpoint
- NNT of 1.66 (ARR 60%) for secondary endpoint
- 58% sIgE > 100 kU/L overall tolerated 1000mg

NNT in the 18-55y age group was 1.43, but placebo response was 15.4% (~3.5x the younger age group)

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Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck
PALISADES End OFC Characteristics

### Key Findings
Compared to placebo, the AR101 group:
1. Developed fewer moderate and severe symptoms;
2. Required more peanut exposure for the onset of symptoms;
3. Was more likely to complete the challenge;
4. Needed less epinephrine

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**Epinephrine Use**

<table>
<thead>
<tr>
<th></th>
<th>AR101</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>268 (91%)</td>
<td>54 (47%)</td>
</tr>
<tr>
<td>1</td>
<td>25 (8%)</td>
<td>43 (37%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (1%)*</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>300</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

*One patient at 600 mg and two patients at 1000 mg

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1. p < 0.0001 for overall between-group difference
• 9 SAE in 8 participants (2.2%), 1 SAE in placebo, no fatalities
• 4 events considered related
• 5 events led to discontinuation
• 1 case of anaphylaxis in early maintenance (high baseline sIgE)
• 1 case of EoE developed, patient withdrew
• 14.5% experienced investigator reported systemic hypersensitivity reactions, 98% of which were considered mild or moderate
Teng et al. demonstrated efficacy of 18 months of a novel peanut OIT + Lactobacillus Rhamnossus CGMCC combination in a 2015 double blind, randomized controlled study.

Initial effect demonstrated successful desensitization in 26/29 PPOIT patients and 2 week sustained unresponsiveness in 23/28 of these patients.

Probiotic dose the equivalent of “20 tubs” of yogurt/day!

Now, following 48 of the original 56 participants for 4 years after discontinuation of OIT.

N=24 PPOIT and n=24 placebo patients followed after exit food challenge.

No set protocol for peanut ingestion in the PPOIT group.

At 4 years, both groups asked to discontinue peanut ingestion for 8 weeks and repeat challenge.

PPOIT and 4-Year Outcomes

- Noted 16/24 PPOIT vs. 1/24 subjects were regularly ingesting peanut ad libitum (NNT 1.6)
- Half of the PPOIT subjects were eating >2g/week (46% 1x/wk, 29% 1-2x/wk, 17% 3x or more/wk, with 16/20 PPOIT subjects consuming peanut “regularly”, and 20/24 reporting no reactions since stopping PPOIT therapy
- N=27 agreed to the 8 week additional discontinuation. Of these 7/12 PPOIT vs. 1/15 placebo tolerated the challenge and resumed eating peanut (NNT=1.9)
- 7/12 who underwent PPOIT ate peanut ad lib for 4 years, then agreed to stop eating peanut for another 8 weeks demonstrated sustained unresponsiveness. This pattern mimics a non-allergic individual’s consumption!
- Study issues: no initial challenge for the 2015 study, some degree of drop out, small #’s
- The implications of this effect, if replicated, may completely change the game

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (mg)</th>
<th>Duration</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al</td>
<td>2009</td>
<td>Open label</td>
<td>29</td>
<td>1-16</td>
<td>1800</td>
<td>36 mo</td>
<td>93% passed 3.9-g peanut OFC</td>
</tr>
<tr>
<td>Blumchen et al</td>
<td>2010</td>
<td>Randomized open label</td>
<td>23</td>
<td>3-14</td>
<td>500</td>
<td>7-d Rush escalation, 8-wk maintenance period</td>
<td>64% reached maintenance of 500 mg of peanut</td>
</tr>
<tr>
<td>Varshney et al</td>
<td>2011</td>
<td>Randomized, placebo controlled</td>
<td>19</td>
<td>3-11</td>
<td>2000</td>
<td>48 wk</td>
<td>84% passed 5000-mg peanut OFC</td>
</tr>
<tr>
<td>Anagnostou et al</td>
<td>2011</td>
<td>Open label</td>
<td>22</td>
<td>4-18</td>
<td>800</td>
<td>32 wk</td>
<td>64% tolerated 6.6-g OFC</td>
</tr>
<tr>
<td>Anagnostou et al</td>
<td>2014</td>
<td>Randomized, controlled</td>
<td>39</td>
<td>7-16</td>
<td>800</td>
<td>26 wk</td>
<td>62% tolerated 1400-mg challenge</td>
</tr>
<tr>
<td>Vickery et al</td>
<td>2014</td>
<td>Open label</td>
<td>24</td>
<td>1-16</td>
<td>Up to 4000</td>
<td>Up to 5 y</td>
<td>50% SU to 5000-mg OFC after 4-wk avoidance</td>
</tr>
<tr>
<td>Narisety et al</td>
<td>2014</td>
<td>Randomized, placebo controlled</td>
<td>16</td>
<td>7-13</td>
<td>2000</td>
<td>12 mo</td>
<td>OIT &gt; SLIT in OFC threshold, low rate of SU</td>
</tr>
<tr>
<td>Factor et al</td>
<td>2012</td>
<td>Open, uncontrolled</td>
<td>93</td>
<td>5-18</td>
<td>450 (3 M&amp;M)</td>
<td>24 wk</td>
<td>90/100 pts able to tolerate 450 mg, showed improvement in pt FAQLQ score. Clinic-based study</td>
</tr>
<tr>
<td>Wasserman et al</td>
<td>2014</td>
<td>Open label</td>
<td>352</td>
<td>Median 5-9 y</td>
<td>415-8000</td>
<td>Variable, Weeks-yrs</td>
<td>Real-life experience of 5 practices. 281/352 (80%) reached maintenance. 10% of pts required epi (36/352)</td>
</tr>
<tr>
<td>Tang et al</td>
<td>2015</td>
<td>Randomized, placebo controlled</td>
<td>62</td>
<td>1-10</td>
<td>2 g with 2x10^2 CFU L. rhamnosu</td>
<td>18 mo</td>
<td>23/28 (82.1%) vs 1/28 (3.6%) achieved SU at 2-5 wk post-discontinuation. 26/29 achieved desensitization.</td>
</tr>
<tr>
<td>Vickery et al</td>
<td>2016</td>
<td>Randomized, placebo controlled</td>
<td>40</td>
<td>9-36 mo</td>
<td>300 vs 3000</td>
<td>Up to 3 y</td>
<td>17/20 in 300-mg and 12/17 in 3000-mg arm achieved SU at 4 weeks (29/37 total)</td>
</tr>
</tbody>
</table>
# Published Egg and Milk OIT Studies

## Table II. Egg OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (g)</th>
<th>Duration (mo)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan et al</td>
<td>2007</td>
<td>Open label</td>
<td>7</td>
<td>1-16</td>
<td>0.3</td>
<td>24</td>
<td>57% Passed 8-g OFC</td>
</tr>
<tr>
<td>Vickery et al</td>
<td>2010</td>
<td>Open label</td>
<td>8</td>
<td>3-13</td>
<td>0.3-3.6</td>
<td>18-50</td>
<td>75% Passed OFC 1 mo after stopping OIT</td>
</tr>
<tr>
<td>Burks et al</td>
<td>2012</td>
<td>Randomized, placebo controlled</td>
<td>40</td>
<td>5-11</td>
<td>1.6</td>
<td>22</td>
<td>75% Passed 10-g OFC but SU in only 28% at 6-8 wk later</td>
</tr>
</tbody>
</table>

## Table III. Milk OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (g)</th>
<th>Duration</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglio et al</td>
<td>2004</td>
<td>Open label</td>
<td>21</td>
<td>6-10</td>
<td>200 mL</td>
<td>6 mo</td>
<td>72% Desensitization to 200 mL of cow’s milk daily</td>
</tr>
<tr>
<td>Longo et al</td>
<td>2008</td>
<td>Randomized, open label</td>
<td>30</td>
<td>5-17</td>
<td>150 mL</td>
<td>10-d Rush escalation, 1 y of maintenance</td>
<td>36% Tolerant (2-150 mL) and 54% partially tolerant (5-150 mL)</td>
</tr>
<tr>
<td>Skripak et al</td>
<td>2008</td>
<td>Randomized, placebo controlled</td>
<td>13</td>
<td>6-17</td>
<td>500 mg</td>
<td>23 wk</td>
<td>Median OFC threshold increased from 40 to 5,140 mg after OIT</td>
</tr>
<tr>
<td>Narisetty et al</td>
<td>2009</td>
<td>Open label (follow-up)</td>
<td>13</td>
<td>6-16</td>
<td>500-4,000 mg</td>
<td>3-17 mo</td>
<td>Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)</td>
</tr>
<tr>
<td>Pajno et al</td>
<td>2010</td>
<td>Randomized, placebo controlled</td>
<td>15</td>
<td>4-10</td>
<td>200 mL</td>
<td>18 wk</td>
<td>67% Tolerant to 200 mL of cow’s milk</td>
</tr>
<tr>
<td>Martorell et al</td>
<td>2011</td>
<td>Randomized, placebo controlled</td>
<td>30</td>
<td>2-3</td>
<td>200 mL</td>
<td>1 y</td>
<td>90% Showing complete desensitization</td>
</tr>
<tr>
<td>Keet et al</td>
<td>2012</td>
<td>Randomized, placebo controlled</td>
<td>20 for OIT</td>
<td>6-17</td>
<td>1,000-2,000 mg</td>
<td>60 wk</td>
<td>70% Desensitized to 8-g OFC, SU in 40% after 6 wk</td>
</tr>
<tr>
<td>Wood et al</td>
<td>2015</td>
<td>Omalizumab DBPC, open-label OIT</td>
<td>57</td>
<td>7-32</td>
<td>3,300 mg</td>
<td>24 mo</td>
<td>80% Desensitized to 10-g OFC, SU in 42% after 8 wk</td>
</tr>
</tbody>
</table>
OIT: Present Knowledge

<table>
<thead>
<tr>
<th>Food</th>
<th>RCT</th>
<th>Severe pts</th>
<th>Infants</th>
<th>Major Sx Free</th>
<th>Desensitization</th>
<th>SU</th>
<th>Mechanism</th>
<th>EoE</th>
<th>Recurrence</th>
<th>Twists</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Yes</td>
<td>Yes</td>
<td>One</td>
<td>No</td>
<td>Yes</td>
<td>4-5 weeks; ad lib in PPOIT</td>
<td>unclear</td>
<td>Yes</td>
<td>NA</td>
<td>algE; PPOIT</td>
<td>III</td>
</tr>
<tr>
<td>Egg</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>4-6 weeks</td>
<td>unclear</td>
<td>None</td>
<td>NA</td>
<td>LRTA</td>
<td>I/II</td>
</tr>
<tr>
<td>Milk</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>algE; LRTA</td>
<td>I/II</td>
</tr>
</tbody>
</table>

- Are European SOTI data better? Protocols differ significantly?
- SLIT vs OIT—SLIT appears “safer” but less effective than OIT
- Limited long-term follow-up exists, esp. sustained nonresponse
- Some ADR’s worse than one’s baseline, prompt discontinuation
- Cases of EoE have occurred
- Few studies have addressed any patient-oriented outcome
- Will egg or milk be commercially developed?
- Do the differing methods make a difference?
- Newer trials focused on lower maintenance and target, different
- How do new PPOIT data change the landscape?
- **Major hurdles to overcome:**
  - consistent vehicle needed
  - reconcile high dropout rate & % developing symptoms,
  - clarity on mechanism
  - outcomes
Incidence rate ratios of the influence of baseline characteristics on the prevalence of AEs, overall and during the buildup and maintenance phases of OIT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall AEs</th>
<th>Buildup AEs</th>
<th>Maintenance AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>P value</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Sex (female compared with male)</td>
<td>0.7 (0.4-1.2)</td>
<td>.24</td>
<td>0.6 (0.3-1.0)</td>
</tr>
<tr>
<td>Age (per 1-y increase)</td>
<td>1.0 (0.9-1.1)</td>
<td>.89</td>
<td>1.1 (0.9-1.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.9 (0.5-1.4)</td>
<td>.55</td>
<td>0.6 (0.4-1.1)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1.2 (0.6-2.2)</td>
<td>.59</td>
<td>1.2 (0.6-2.3)</td>
</tr>
<tr>
<td>AR</td>
<td>2.9 (1.6-5.0)</td>
<td>&lt;.001*</td>
<td>2.1 (1.2-3.8)</td>
</tr>
<tr>
<td>Peanut SPT wheal size (per 5-mm increase)</td>
<td>1.4 (1.1-1.7)</td>
<td>.005*</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>Log peanut IgE (per log increase)</td>
<td>0.9 (0.7-1.0)</td>
<td>.14</td>
<td>0.9 (0.7-1.0)</td>
</tr>
</tbody>
</table>
FIG 4. Frequencies of AEs resulting in epinephrine use. Patterns of use of epinephrine concurrently with administration of antihistamines, albuterol, oral corticosteroids, or an ED visit (A), and in response to specific symptoms (cough, wheeze, hives, abdominal [Abd] pain, or vomiting) (B). Overlap of AEs with 2 or more given symptoms (ex: cough and wheeze) may be present.
EPIT—Where Do We Stand?

- DBV Viaskin MILES and PEPITES in Phase 2/3
- Far fewer published data vs OIT
  - Early data note that 70% had a 10-fold dose increase, no serious AEs
  - MILES data noted all AEs associated with site urticaria/redness
  - Milk EPIT induced T\(_{\text{regs}}\) protect from anaphylaxis in adoptive transfer
  - Higher numbers of T\(_{\text{regs}}\) were produced in EPIT vs OIT, persisted after EPIT stopped
  - EPIT was not associated with EoE in murine models vs OIT
- Phase III peanut trial showed significant effect for 250mcg patch with good safety
- Phase II milk trial showed significant effect for 250mcg patch also with good safety

PEPITES Design

356 peanut allergic children
31 centers in US, Canada, Australia, Germany, Ireland

Study Population
Highly allergic patients ages 4-11
- > 0.7 kU/L peanut-specific IgE and ≥ 6mm or 8 mm SPT* wheal
- Reactive dose at M0 ≤ 300 mg peanut protein (i.e. approx 1 peanut)

Efficacy Endpoints
Treatment responder definition:
- Assessed using DBPCFC**
- For subjects with a M0 ED*** ≤ 10mg: responder if ED ≥ 300 mg at M12
- For subjects with a M0 ED > 10mg: responder if ED ≥ 1,000 mg at M12

Key secondary endpoints:
- CRD****, changes in peanut slgE and slgG4

OFC protocol

Baseline
- 1 mg
- 3 mg
- 10 mg
- 30 mg
- 100 mg
- 300 mg

Month 12*
- 1 mg
- 3 mg
- 10 mg
- 30 mg
- 100 mg
- 300 mg
- 1,000 mg
- 2,000 mg

PEPITES Entry Characteristics

356 Patients Randomized
- Active: 238
- Placebo: 118

Peanut Eliciting Dose (mg)
- Median: 100
- Mean: ~140

Medical History of Patients
- Asthma: 169 (47.5%)
- Eczema/Atopic Dermatitis: 218 (61.2%)
- Allergic Rhinitis: 199 (55.9%)
- Polyallergic: 305 (85.7%)

[Graph showing Peanut Protein Eliciting Dose (mg) - Vlaskin Peanut 250 µg vs Placebo]
PEPITES Main Results

Response rate was statistically significant, but 15% lower bound of the 95% CI proposed in the SAP submitted to FDA was not reached.

Differentiated Safety Profile

- Favorable tolerability and compliance observed
- 1.1% dropout due to treatment emergent adverse events (TEAEs)
- Most commonly reported adverse events were application site reactions, which were generally mild to moderate
- Mean patient compliance above 95%

NNT 4.6 (ARR 21.7%)

<table>
<thead>
<tr>
<th></th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12.4</td>
<td>29.8</td>
</tr>
<tr>
<td>Viaskin Peanut 250 µg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEPITES Change in Reactive Dose

CRD After 12 Months
(Mean and Median, ITT)*

CRD at Month-12

Mean = 361 mg
Median = 144
Placebo
n = 118

Mean = 905.7 mg
Median = 444
Viaskin Peanut 250 µg
n = 238

p < 0.001
Like in OIT, changes in EPIT may occur over a longer horizon
- Data on mean CRD and response improved through year 2 and 3 of study

MILES Entry Criteria and Design

198 patients randomized
- 152 Children (2-11)
- 46 Adolescents (12-17)

CRD of Cow’s Milk

Mean
- Children: 216.3 mg
- Adolescents: 222.0 mg

Median
- Children: 144 mg
- Adolescents: 144 mg

Medical history of patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>139</td>
<td>70.2</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>139</td>
<td>70.2</td>
</tr>
<tr>
<td>Allergic Rhinitis</td>
<td>144</td>
<td>72.7</td>
</tr>
<tr>
<td>Polyallergic</td>
<td>178</td>
<td>89.9</td>
</tr>
</tbody>
</table>

Study Population
- Children (2-11) and adolescents (12-17)
- Highly sensitive to milk (≥ 10 kU/L milk-specific IgE and ≥ 6 mm SPT* wheal)
- Reactive dose at baseline (M0) ≥300 mg cow’s milk protein (CMP) (~≥9.4 mL of cow’s milk)

Efficacy Endpoints

Treatment responder definition at M12:
- ≥ 10-fold increase in CRD** and at least 144 mg of CMP
- OR CRD ≥ 1,444 mg

Key secondary endpoints:
- Change from baseline in IgE, IgG4

MILES Phase II Results

- For the 300ug dose, NNT was 3.93 (ARR 25.4%)
- Unclear why response at 300ug was optimal
- High placebo rate likely reflects difficulty of treating an allergen that has a favorable natural history
Other Approaches to Treatment

Past, Present, and Future Attempts
Novel Early Attempts

- SCIT was tried in early 1990s with limited early success
  - The study was abandoned after a dosing error leading to death (not the therapy)
    - Showed promise in increasing peanut threshold though this waned
    - Rates of ADRs were not dissimilar to some OIT trials

- Two anti-IgE monoclonal antibodies have been investigated
  - TNX-901 and Omalizumab
  - Peanut DBRCT showed 450-mg TNX dose increased threshold from 1/2 peanut to 9 peanuts
  - Drug was not commercially developed due to an agreement with Tanox and Genentech
  - Phase 2 trial with omalizumab was halted due to safety concerns in the OFC phase, but there was a slight trend toward increased tolerance

- Will either be resurrected?
  - Anecdotal evidence of increased tolerance/desensitization in patients also on Omalizumab
  - What was the true reason we abandoned SCIT to peanut? Was it potential efficacy?

How to Choose a Treatment

Considering the Scope of Health and Economic Benefits and the Process of Shared Decision-Making
Components of a Treatment Decision

- Provider framing and approach
- Scientific knowledge
- Health Benefits (patient reported outcomes)
- Economic Benefits ($$$)
- Patient stated preferences and goals

- Do we as providers know how to approach a patient to help them make a decision?
- Shared decision-making approaches must be embraced

Elwyn et al British Journal of General Practice, 2000, 50, 892-897
Barriers to Treatment

Health Utility

- Health Utility: weighted preference for a health state, assessing willingness to sacrifice lifespan or healthy years for better present health status
- Regional parental study of 29 pediatric health states, included food allergy
- Asked about avoidance vs treatment after mild and severe reaction
- Health utility ~0.91-0.93 for mild and severe reactions for allergen avoidance
- Little desire for risk of treatment compared to practicing avoidance
- Challenge to deliver a cost-effective therapy meeting parent preferences (low cost, low risk)
Barriers to Treatment

- Cost subject to socioeconomic disparity
- Willingness to pay of $3500/year

The Economics

Total annual cost per child: $4184

Total annual cost in US: $24.8 billion
Decisions to Make Regarding Treatment

- Are the side effects of food therapy worse than living with disease?
- What are the caregiver goals of therapy: cure or treatment?
- What are the caregivers trade-offs and relative value of the therapy compared to avoidance?
- What are the caregiver health beliefs?
- How likely does the caregiver think the chances of success are?
- With multiple potential therapies, is this therapy the best choice?
- What do providers tell caregivers about the chances of success?
- Can guidelines be developed to assist clinicians?
What Motivates Parents to Seek Therapy

Summary of Key Themes

<table>
<thead>
<tr>
<th>Theme 1</th>
<th>Peanut allergy therapy only needs to provide minimal protection with minimal risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. Desire for a buffer</td>
</tr>
<tr>
<td></td>
<td>b. Understanding that therapy wasn't a cure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Theme 2</th>
<th>How the buffer translates to meaningful impact on quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. Decreasing reaction severity</td>
</tr>
<tr>
<td></td>
<td>b. Enhancing social activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Theme 3</th>
<th>Helping others by advancing science</th>
</tr>
</thead>
</table>

Caregiver definitions of what a “buffer” represents, with example quotes

<table>
<thead>
<tr>
<th>Example Definition</th>
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<tbody>
<tr>
<td>The child would tolerate ingestion of a higher amount of total peanut protein than</td>
</tr>
<tr>
<td>their pre-therapy baseline (which was measured as a primary outcome for both the</td>
</tr>
<tr>
<td>OIT and EPIT trials)</td>
</tr>
<tr>
<td>“We’d like him to be bite proof.”</td>
</tr>
</tbody>
</table>

| The child would have less severe symptoms resulting from ingestion than at         |
| pre-therapy baseline;                                                              |
| “So my goal and his goal is that if there's ever accidental exposure...that it's    |
| not gonna end up landing him in the emergency room...It's just if we could just    |
| curb the reactions a little bit and minimize the likelihood of them that's kind of |
| our goal.”                                                                        |
| “We'd like him to be able to accidentally ingest his allergen and not have         |
| anaphylaxis. And that would be, if we could get there I would consider that a      |
| success.”                                                                        |

| Any resulting allergic reaction to peanut would take longer to manifest and peak    |
| (a “slower reaction”), allowing for more time for someone to assess the child       |
| and administer treatment                                                           |
| “We've got a chance if he gets exposed that it doesn't mean he's going to die. It  |
| means we see the symptoms, we catch them quick enough, and hopefully everything    |
| will be okay.”                                                                     |

Study Features

- 45 minute semi-structured interviews transcribed verbatim
- 22 patients interviewed (6 OIT, 16 EPIT)
- Questions probed caregiver motivations/goals for therapy, treatment expectations and trade-offs, family lifestyle, and emotions surrounding life with peanut allergy.

Additional Key Quotes

- “Like there hasn’t been any – and that seems to be the benefit of the patch over OIT, which is that you aren’t ingesting it so you don’t see anaphylaxis from the patch.”

- “Well I think it's gonna help…sort of help safeguard her. That's why we wear seatbelts in the car. It's not just about having a car. It's getting there safely sort of thing.”

- “So our biggest [goal]...was we wanted the freedom to travel without being as concerned about peanuts on airlines... And then the other thing is socially she does really well, but at school she has to sit at the nut-free table, and it's all boys. And so she would really like to be able to sit wherever she wants to sit.”
Rectifying the Health Economics

- Food allergy has large direct and indirect costs that are susceptible to health disparities
- Health utility for avoidance is quite high, and WTP is LOWER than likely annual cost per family
- A family does not have to choose therapy—avoidance is an option!
- How potentially segmented and inelastic is the treatment market?
- What is the most cost-effective strategy, if any?
- Can we determine which patient is the best candidate for a particular therapy?
Conclusions

- Multiple potential approaches to treating food allergy may exist
- None have been proven to date
- Entering into a therapy is a very complex decision
- Highly personal, based on preferences and trade-offs acceptable to caregiver
- Data support high utility for avoidance, low WTP, risk-averse preferences, but that therapy betters QoL
- Cost-effectiveness of therapy will be crucial to determine
- Providers must learn how to coach a shared decision
Thanks! Come Visit Us in Denver

The view from the Food Challenge Unit, Children’s Hospital Colorado.
It looks just like this 300+ days a year!