Immunotherapy in Food Allergy

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Faculty Disclosure for
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For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from: None
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I will be discussing products that are investigational or not labeled for the use under discussion.
OBJECTIVES

- Understand that there are several new forms of food allergen immunotherapy

- Discuss positive and negative findings of food IT and their use in clinical trials

- Discuss usefulness of food allergen oral immunotherapy and current status of investigations
Current Immunotherapy Categories for Food Allergy

- Oral immunotherapy
  - with and without a period of withdrawal
  - with and without adjunctive therapy
  - with and without extensively heated protein
- Sublingual immunotherapy
  - with and without follow on OIT
- Epicutaneous immunotherapy

Sicherer, S. 2011
Nowak-Wegrzyn and Sampson, 2011
Questions 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

  - 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
Table 1  Summary of human clinical trials of immunotherapy for food allergies

<table>
<thead>
<tr>
<th>Types of immunotherapy</th>
<th>Types of food allergies</th>
<th>Study designs</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIT</td>
<td>Peanut allergy</td>
<td>DBPC</td>
<td>A 67–100 % decrease in symptoms induced by peanut challenge. The rate of systemic reactions with rush immunotherapy was 13.3 %.</td>
<td>[21]</td>
</tr>
<tr>
<td>SCIT</td>
<td>Peanut allergy</td>
<td>Open label</td>
<td>Although injections of peanut extract increase the tolerance of patients with peanut allergy, that also result in repeated systemic reactions in most patients.</td>
<td>[22]</td>
</tr>
<tr>
<td>SCIT</td>
<td>Pollen-food allergy</td>
<td>Open label</td>
<td>Injection of birch pollen extracts effectively reduces clinical apple sensitivity and skin reactivity in most cases after only 1 year of treatment (84 % vs. 0 %).</td>
<td>[24]</td>
</tr>
<tr>
<td>SCIT</td>
<td>Pollen-food allergy</td>
<td>Open label</td>
<td>Eighty-seven percent of pollen SCIT-treated patients could eat more apple or hazelnut without allergic symptoms/signs. The average tolerated quantity increased from 12.6 to 32.6 g apple after 1 year</td>
<td>[25]</td>
</tr>
<tr>
<td>OIT</td>
<td>Cow’s milk allergy</td>
<td>DBPC</td>
<td>The median cumulative dose inducing a reaction in the treatment group was 5140 mg, while that was 40 mg in the placebo group.</td>
<td>[28]</td>
</tr>
<tr>
<td>OIT</td>
<td>Cow’s milk allergy</td>
<td>RCT</td>
<td>After one year, 36 % of children in the treatment group had become completely tolerant, while none of the controls could tolerate milk intake.</td>
<td>[29]</td>
</tr>
<tr>
<td>OIT</td>
<td>Cow’s milk allergy</td>
<td>RCT</td>
<td>Full tolerance to cow’s milk (200 ml) was achieved in ten of 30 patients in the treatment group and partial tolerance in one.</td>
<td>[30]</td>
</tr>
<tr>
<td>OIT</td>
<td>Egg allergy</td>
<td>Open label</td>
<td>Seven subjects completed the protocol; all tolerated significantly more egg protein than at study onset.</td>
<td>[31]</td>
</tr>
<tr>
<td>OIT</td>
<td>Egg allergy</td>
<td>Open label</td>
<td>All six patients who completed the entire protocol developed clinical tolerance to egg during the study.</td>
<td>[32]</td>
</tr>
<tr>
<td>OIT</td>
<td>Peanut allergy</td>
<td>Open label</td>
<td>All subjects (n=4) tolerated at least ten whole peanuts (approximately 2.38 g protein) in postintervention challenges.</td>
<td>[33]</td>
</tr>
<tr>
<td>OIT</td>
<td>Peanut allergy</td>
<td>Open label</td>
<td>Of the 29 subjects who completed the study, 27 ingested 3.9 g peanut protein during food challenge. Most adverse reactions resolved spontaneously or with antihistamines.</td>
<td>[34]</td>
</tr>
<tr>
<td>OIT</td>
<td>Peanut allergy</td>
<td>DBPC</td>
<td>All peanut OIT subjects (n=16) ingested the maximum cumulative dose of 5000 mg (approximately 20 peanuts), whereas placebo subjects (n=9) ingested a median cumulative dose of 280 mg.</td>
<td>[35]</td>
</tr>
<tr>
<td>SLIT</td>
<td>Peach allergy</td>
<td>DBPC</td>
<td>After 6 months of SLIT, the treatment group tolerated a significantly higher amount of peach (3- to 9-fold). No significant changes were observed within the placebo group.</td>
<td>[37]</td>
</tr>
<tr>
<td>SLIT</td>
<td>Hazelnut allergy</td>
<td>DBPC</td>
<td>Mean hazelnut quantity provoking objective symptoms increased from 2.29 to 11.56 g (treatment group) vs. 3.49 to 4.14 g (placebo group).</td>
<td>[38]</td>
</tr>
<tr>
<td>SLIT</td>
<td>Peanut allergy</td>
<td>DBPC</td>
<td>After 12 months of SLIT, the treatment group safely ingested 20 times more peanut protein than the placebo group (median, 1,710 vs. 85 mg).</td>
<td>[39]</td>
</tr>
<tr>
<td>SLIT</td>
<td>Pollen-food allergy</td>
<td>Open label</td>
<td>Pollen SLIT reduced respiratory symptoms to birch pollen, but not apple-induced oral allergy syndrome.</td>
<td>[40]</td>
</tr>
<tr>
<td>EPIT</td>
<td>Cow’s milk allergy</td>
<td>Open label</td>
<td>In the active group, although not statistically significant, EPIT tended to increase cumulative tolerated dose at the end of study.</td>
<td>[43]</td>
</tr>
</tbody>
</table>

SCIT subcutaneous immunotherapy, OIT oral immunotherapy, SLIT sublingual immunotherapy, EPIT epicutaneous immunotherapy, DBPC double-blind placebo control, RCT randomized control trial
Influential Factors in Food Allergen Immune Therapy

- Genetics? Age?
- Duration of therapy?
  - Is there a critical time period on therapy for each individual in which immune therapy is better?
- Disease specific?
  - Will the safety and efficacy of immune therapy be different if there are concomitant atopic conditions?
- Allergen specific?
  - Will the mechanism of immune therapy be different depending on the Allergen? Peptide? Epitope?
  - Will the mechanism of immune therapy allow for “bystander” effects? Related vs. non-related allergens?
  - Will conformation of the protein play a role?
- Dose specific?
  - Will the mechanism of immune therapy depend on the dose of the agent used in immunotherapy? Can we use adjuvant therapy to increase the dose to examine the role of anergy? What is the best maintenance dose? Can it be decreased after a period?
- Organ specific? What is the gastrointestinal response to IT?
- Route of dosing?
  - EPIT, SLIT, SCIT, OIT, other

How does Food Allergen Immune Therapy work?

Possible mechanisms of Food Allergen Therapy over time

Roles of B cells: IgG₄ increase, IgE decrease?, IgA increase?

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 and conclude more research with proper controlled studies are needed
- Randomized, controlled Phase 2 and 3 studies are needed

Sampson, H. 2013
Sicherer, S. 2011
Berin, C, Mayer, L. 2013
Akdis, C. 2012
Lack G., 2008
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

Kim and Burks, 2012
Sampson, H. 2013
Sicherer, S. 2011
Berin, C, Mayer, L. 2013
Akdis, C. 2012
Lack G., 2008
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?

- Staden, et al. *Allergy* 2007 demonstrated that 36% of their subjects treated with milk or egg OIT no longer were allergic to egg or milk following 2 months off immunotherapy,
  BUT 35% of the children in the untreated control group also developed ‘tolerance’ in the same period of time.

- Savilahti, et al. 2012 Review of milk OIT show 23-60% untreated control group ‘tolerance’ rate
Food Allergen OIT with a withdrawal period to test “tolerance”

Provided by Dr. Wesley Burks, Univ. of North Carolina
About 50% able to sustain unresponsiveness after 1 mo withdrawal
Single Center Peanut OIT Phase 1 study with a withdrawal period Stanford University

Results:

- 35% 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)
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?
Monoclonal anti-IgE antibodies, like omalizumab, selectively bind to the Cε3 domain of IgE with high affinity. Each IgE molecule has two antigenic sites for anti-IgE, and so can be bound by two drug molecules simultaneously. These form small, soluble, biologically inert IgE/anti-IgE complexes that are cleared from the circulation.
Baseline visit
Start omalizumab (wk 0)

Desensitization
(1000 mg milk powder dose, 2000 mg cumulative)

Weekly up dosing and continued omalizumab

Maintain daily milk dose at home
Off omalizumab
Maintenance dose was 2000 mg

DBPCFC*

Home daily milk ≥ 8 oz

Week 0-9
Week 9
Week 9-16, escalation phase
Week 16-24
Week 24-27
Week 24-52

*DBPCFC=double blind placebo controlled food challenge

Nadeau, K, Schneider, L, Hoyte, L, Borras, I, and Umetsu, D. JACI. 2011
This study is the first published study to use omalizumab in combination with oral desensitization. 9 of 11 patients with milk allergy treated with omalizumab and oral milk desensitization achieved the primary objective, and tolerated desensitization to a dose of 2,000 mg/day within 7-10 wks. The 9 patients then passed a DBPCFC, and began tolerating >240 ml (>8 oz) of milk/day in their diet. These results suggest a potential value for using omalizumab during rapid oral desensitization for food allergy.

Nadeau, K, Schneider, L, Hoyte, L, Borras, I, and Umetsu, D. JACI. 2011
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

Srivastava, et al. JACI 2012. Gave FAHF2 in mice sensitized to peanut, codfish, and egg and it blocked anaphylaxis.
Extensive Heating (denaturing proteins) For Food Allergy Immunotherapy

- Why?
  - Extensive heating denatures conformational epitopes and
  - 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 (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?
Results of CM SLIT/OIT Study in patients with CM Allergy

Combined SLIT/OIT for cow’s milk allergen

Baseline CM Oral Food Challenge
Median Dose at reaction ~40 mg

Initial SLIT in all groups – then
1. Continued SLIT
2. A (low) OIT
3. B (higher) OIT

n=30 cow’s milk allergic children, all started on slit, all went to 3.7 mg of milk protein, then randomized to get 7 mg milk slit, 1 g oit, or 2 g oit, then on maintenance for 60 weeks, then tested with challenge.

Cow’s milk SLIT was well tolerated in safety parameters
Up to 79x increase in the level of milk tolerated after 15 months in higher OIT group

Keet, et al. JACI 2012
Can EPIT provide a safer way to induce desensitization among patients with food allergy?
N=19, a 3-month DBPCFC pilot study was conducted in infants and children with milk allergy. Skin reactions as main adverse event. Preliminary data suggest good safety profile. 12x average increase in the level of milk tolerated after 3 months.

Dupont et al. JACI 2010
## Immunotherapy Comparison for CM Food Allergies

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

- The IgE-binding epitopes of recombinant food allergen proteins can be modified, for example, by site-directed mutagenesis, to reduce the allergenicity.
- Synthetic peptides containing immunodominant T cell epitopes from an allergen can induce T cell nonresponsiveness.
- DNA vaccine encoding specific modified allergens can provide in vitro synthesized allergens persistently and induce prolonged humeral and cellular immune responses.
- Some adjuvants such as heat-killed Listeria monocytogenes (HKLM), CpG motifs, and mannoside could be used with modified allergens during immunotherapy to enhance the type I helper T cells and/or regulatory T cells responses.


There is no cure at the current time.
Drop out rates during clinical OIT studies are between 5-30%
Although most reactions are mild, up to 4% have been reported to be severe (requiring epinephrine).
Adjunct therapies or EPIT or SLIT might offer safer alternatives
Most allergic reactions occur during home dosing
Patients and families must be frequently educated
Random allergic reactions occur 3-4 yrs after OIT started.
Viral infections, temperature, other allergies, exercise, menstruation—all can modulate the threshold for an allergic reaction during ingestion of food therapy
Reaction medications must still be available at all times
Overall Summary POINTS for Food Allergy IT

- OIT, SLIT, EPIT are promising HOWEVER…..
- Food Allergen IT is experimental and in its early phases
- There is still much to learn as to dosing and frequency and length of time on therapy
- SAFETY is paramount
- Work with appropriate regulatory agencies and institutional boards
- Trained staff should perform DBPCFCs and DEs in a hospital setting
- Reach out to centers and PIs with experience
- Constant (i.e. 24/7) availability of trained staff to patients
- Short term and long term follow up are important
- Food Allergy is an exciting and promising field and there are many unanswered questions to continue to address via rigorous controlled studies.
Sublingual immunotherapy for peanut allergy: A randomized, double-blind, placebo-controlled multicenter trial

David M. Fleischer, et al.

After 44 weeks of SLIT, 14 (70%) of 20 subjects receiving peanut SLIT were responders compared with 3 (15%) of 20 subjects receiving placebo (P < .001). In peanut SLIT responders, median SCD (succesfully consumed dose) increased from 3.5 to 496 mg. After 68 weeks of SLIT, median SCD significantly increased to 996 mg.

Conclusions: Peanut SLIT safely induced a modest level of desensitization in a majority of subjects compared with placebo.

Longer duration of therapy showed statistically significant increases in the SCD. (J Allergy Clin Immunol 2013;131:119-27.)
Allergen-specific IgG₄ antibodies increase over the duration of OIT

Levels for Peanut-specific IgG4 antibodies were assessed from the sera of subjects at baseline and at various time points during therapy. Adjusted mean antibody levels demonstrate an increase in IgG4 over time between from immune tolerant (at 27 mo, n=7, at 30 mo, n=3 remained immune tolerant), non tolerant (at 27 months, n=13, at 30 mo, n=17), vs. placebo (n=20) subjects.

(P < 0.05 *)