Oral Immunotherapy and food allergy – ready for clinical practice?

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Outline
- Efficacy – egg / milk / peanut allergy
- Quality of Life
- Safety
- Resources

Egg

- 70% (64/91) egg allergic children tolerate baked egg:
  - Muffin heated at 180 °C for 30 minutes
  - Thin waffle heated at 260 °C for 3 minutes
  - 18.5% required adrenaline for systemic reactions
  - 66% had asthma and 14% previous anaphylaxis to egg
  - 74% children with plain egg anaphylaxis tolerated baked egg
- Children incorporating baked egg into diet
  - 15-fold more likely to tolerate regular egg (scrambled egg)
  - Faster resolution of regular egg allergy (4 vs. 6-7 years)


Extensively heated (baked) egg

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Oral desensitisation to egg

- Children (5-18 years) with confirmed egg allergy
- 22 months of OIT then 4-6 weeks egg avoidance
- Excluded children with anaphylaxis and asthma
- Maintenance dose 2gm egg (1/2 egg daily)

Cow’s milk
Extensively heated cow’s milk
- 75% of children with CMA tolerate baked milk
- Children tolerant to baked milk at baseline 28-fold chance of tolerating unheated milk
- Children that incorporated baked milk into diet were 16 times more likely to tolerate unheated milk


OIT to severe cow’s milk allergy
Milk allergic children [5-17 years]
- History of severe reaction
  - Milk sIgE >85kU/L
  - Eluting dose <0.8ml

2 phase 50% (n=30)
- 10 days IP: 1 CM; 9 AA up to 20ml
- 1ml/2 days home increase

36% tolerated 150ml+
34% tolerated 5-150ml
10% withdrawn: abdominal/respiratory symptoms

After 1 year
Strict CM avoidance (n=30)
DBPCFC Unable to tolerate 5ml


OIT cow’s milk – oral tolerance?

Milk allergic children [5-17 years]
All underwent CM SIT for 4/52
Tolerated SIT dose 3.7mg

SIT (n=10)
Goal dose 7mg
6 weeks off
1/10 tolerated
6/10 tolerated
1 year

OIT (n=10)
Goal dose 2mg
6 weeks off
8/10 tolerated
3/10 tolerated
1 year

OFC (n=10)
Goal dose 1mg
6 weeks off
8/10 tolerated
6/10 tolerated
1 year


Systematic review of milk OIT

<table>
<thead>
<tr>
<th>Study</th>
<th>Children able to tolerate 7.5% of milk at baseline</th>
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<tbody>
<tr>
<td>Longo et al (2008)</td>
<td>30/30 (100%)</td>
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<tr>
<td>Makita et al (2011)</td>
<td>4/4 (100%)</td>
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<tr>
<td>Oettl et al (2010)</td>
<td>24/24 (100%)</td>
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<tr>
<td>Truelove et al (2012)</td>
<td>12/12 (100%)</td>
</tr>
<tr>
<td>Bork et al (2006)</td>
<td>6/6 (100%)</td>
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<td>Lii et al (2004)</td>
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<tr>
<td>Overall 3 studies: EF 78% (2/2/2)</td>
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SIT (n=10)
Goal dose 7mg

OFC 8g
8/10 tolerated
6 weeks off

OFC 8g
6/10 tolerated
6 weeks off

OFC 8g
0/10 tolerated
6 weeks off


Peanut

Ara h 1
Ara h 2
Ara h 8
Ara h 9
Ara h 3

Cure for deadly peanut allergy ‘within three years’, say doctors
Peanut oral immunotherapy

- 22 children with confirmed peanut allergy (4-18 years)
- Included children with a history of anaphylaxis
- Children ate 5-7 peanuts daily

<table>
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<tr>
<th>Successful peanut challenge (%)</th>
<th>Low dose challenge</th>
<th>High dose challenge</th>
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<tbody>
<tr>
<td>12 peanuts</td>
<td>6 weeks</td>
<td>10 months</td>
</tr>
<tr>
<td>32 peanuts (6.6g)</td>
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- 21/22 (95%) children tolerated peanut dose above threshold

Predictors of success

- Lower peanut specific IgE
  - Fewer symptoms with updosing (<27.3kU/L)
  - Higher chance of passing challenges (<11.3kU/L)
- No difference between groups:
  - Low peanut threshold for allergic reactions
  - History of anaphylaxis
  - Age
  - Asthmatic

Can peanut OIT lead to tolerance?

- 24/39 (62%) children underwent OIT successfully
- 12/24 (50%) passed OFC after 1 month off

Predictors of success

- 24/39 (62%) patients included achieved desensitisation
- 7 allergic effects
- 8 personal reasons

- 5 with peanut sIgE <2kU/L underwent 5 gm SORC
  - 100% passed challenge
- 8 with peanut sIgE <15kU/L underwent 5 gm SORC
  - 75% passed challenge
- 12 with peanut sIgE >15kU/L underwent 5 gm SORC after 5 years
  - 8% passed challenge

How to assist tolerance induction?

- Probiotic Lactobacillus rhamnosus + peanut OIT age 1-10 years
- 90% rate peanut desensitisation vs 7% in placebo
- 82% versus 4% sustained unresponsiveness after 2-5 weeks discontinuation

Quality of life

- Peanut allergy known to affect quality of life more than other chronic diseases
- Prevention of allergic reactions to smaller doses of allergen
- Reduction in anxiety and social restriction
1. Emotional impact
2. Food anxiety
3. Social and dietary limitations

Active group -1.6
Placebo group -1.4

FAQLQ-PF raw egg OIT

No significant improvement in total score
Frequency of OIT-related allergic reactions had inverse correlation with post-OIT FAQLQ

Parent burden QoL (FAQL-PB)

Factors influencing parent QoL
- Positive influences:
  - Parents of children older than 10 years
  - Desensitized to more than 4 foods (including peanut, tree-nuts, egg, milk, sesame, shellfish)

- Negative influences
  - Participants with pre-existing asthma
  - Participants with dose related respiratory allergic reactions

Safety of OIT
- During updosing
  - Mostly mild cutaneous, oral and GI symptoms
  - Anaphylaxis in 10-20% of patients
  - Lower respiratory symptoms in asthmatics

- Maintenance phase
  - Co-factors: anaphylaxis to previous tolerated doses
  - Missed doses
  - Adherence to daily preventative doses is poor

Raw egg OIT
- 22 children aged 8-12 years
- OIT top dose (1 egg) in 91%
- Reactions in 82%
  - Adrenaline in 14%
  - Ongoing at 12 month in 46%
- Patients allowed to liberalise egg in diet whilst continuing maintenance doses of raw egg

Vasquez-Ortiz M et al.food allergy immunol 2015 in press

Vasquez-Ortiz M et al. Food allergy immunol 2015 in press
Safety of peanut OIT

- Updosing associated with allergic symptoms in 19/22 (86%)
  - Oral itching
  - Abdominal pain
  - Nasal symptoms
  - Wheezing
  - Nausea and vomiting

- Unexpected allergic symptoms during updosing phase (54%):
  - Mainly oral itching and abdominal pain
  - Treated with antihistamines and inhaled Salbutamol
  - Usually related to intercurrent infection or tiredness

Reduction in peanut allergenicity

- Physical methods (boiling, autoclaving, PUV)
- Chemical methods (acid, magnetic beads)
- Biological methods (breeding, genetic engineering)
- Enzymatic treatment
- Fermentation

- Boiling peanuts
  - Removes Ara h 2,6 and 7
  - Reduced in-vitro IgE and in-vivo clinical reactivity (n=4)

Anti-IgE

- TNX-901 (binds free IgE)
  - Increases threshold OFC 6-fold
  - Concomitant Xolair + OIT facilitates rush desensitisation with fewer adverse effects

What about the guidelines?

- Muraro A et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014; 69 (8): 1026-1043
- "OIT not yet ready for clinical use due to inadequate evidence for therapeutic benefit over risks of therapy"
Summary

- OIT is effective in inducing desensitization (60-85%)
  - Improved efficacy with adjuncts up to 90%
- Oral tolerance induction
  - Only fraction of patients
  - Only when avoidance short (<2 months)
- Safety considerations

OIT ready for standard clinical practice?

- Best safest and most efficacious clinical protocol has not yet been established
- Biomarkers for OIT success and safety
- Motivated, carefully selected and monitored patients willing to accept risk of adverse reactions
- Cost and resources – NHS England / CCG / FDA

OIT ready for standard clinical practice?

- Extensively heated egg and milk - YES
  - Tolerated in 70-75% children
  - Expedites resolution of unheated food allergy
- OIT to egg, milk and peanut - NO
  - Future studies should focus on developing a standardized and safe protocol that is safe and reasonably easy to perform

Learning Early About Peanut Allergy (LEAP Study)

- Randomisation
  - Intervention Group: Peanut consumed 3 times per week (n=320)
  - Control Group: Peanut avoidance (n=320)

- Age groups: 0-11 months, 1 yr, 2.5 yr, 5 yr

- Intention-to-treat Analysis
  - SST-Negative Cohort (n=320)
  - SST-Positive Cohort (n=320)

- Per-Protocol Analysis
  - SST-Negative Cohort (n=320)
  - SST-Positive Cohort (n=320)

- Immunological Network / NHR
  - Food Standards Agency

- www.leapstudy.co.uk
Summary of LEAP study findings

- Primary prevention: 86% reduction
- Secondary prevention: 70% reduction
- Strong evidence that peanut allergy can be prevented – guideline changes are underway
- Children with peanut SPT >/=5mm excluded (9%)

Thank you for your attention

Acknowledgements

- Gideon Lack
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- Martin Penagos
- Allergy Team GSTT
- LEAP Study Team
- EAT Study Team

Peanut OIT tolerance induction?

- 80% lost peanut tolerance after 9 months (Blumchen JACI 2010)

Epicutaneous desensitisation

- Pollen, house dust mite, egg and peanut in mice
- Patch impregnated with allergen onto intact skin
- Patch well tolerated in peanut allergic adults and children:
  - Mild cutaneous symptoms
  - No systemic allergic reactions
  - No worsening asthma control
- Multicentre study in 220 adult and children
Sublingual immunotherapy

- Good efficacy and safe for inhalant allergens
- Multicentre SLIT study for peanut allergy (12-37yrs)
  - 2 to 10 peanuts/day vs. controls
  - 10 months: None passed 5 g (low-dose) challenge
  - 16 months: 5/20 (25%) tolerated at least 5 grams
  - 70% tolerated 10 times more peanut
- Safety:
  - Oropharyngeal symptoms in 1/3 of cases
  - One patient required AA at home for cough and urticaria

Fleischer DM et al JACI 2013

FAQLQ-CF raw egg OIT

Even in children with egg anaphylaxis

- 143 egg allergic children (mean 3.8 years)
  - Previous reaction to plain egg & +ve test or no exposure + >95%PPV sIgE/SPT
  - 63% tolerated baked egg on challenge
  - 14/19 (74%) children with plain egg anaphylaxis tolerated baked egg

Tan et al. CEA 2013

What about Cochrane reviews?