Nutricia Paediatric Food Allergy Expert Meeting
6th December 2016

10.25am  Immunotherapy for Food Allergy
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Nutricia Paediatric Food Allergy Expert Meeting

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Immunotherapy for food allergy

Dr Helen A Brough PhD
Consultant and Honorary Senior Lecturer
in Paediatric Allergy

MRC & Asthma UK Centre in Allergic Mechanisms of Asthma

NHS
Keypad Question 1: Are you introducing baked egg or milk in children with plain egg or milk allergy?

- Yes
- No
Keypad Question 2: Are you performing immunotherapy to unheated cow’s milk, egg or peanut in your patients?

☐ Yes

☐ No
Keypad Question 3: Is immunotherapy to unheated cow’s milk, egg or peanut ready for standard clinical practice?

- Yes
- No
Immunotherapy for food allergy

- Methodology and terminology
- Cow’s milk (baked and unheated)
- Egg (baked and unheated)
- Peanut
- Multiple allergen

- Adverse events and safety considerations
- Quality of life
Methodology

- Routes of administration
  - Subcutaneous
  - Oral
  - Sublingual
  - Epicutaneous

- Protocols
  - Stage 1: Rush immunotherapy – over days
  - Stage 2: Up dosing – over weeks
  - Stage 3: Maintenance dosing – over years / for life
Mechanism of oral immunotherapy

Freeland DMH et al. Curr Opin Immunol; 2016:119-123
Efficacy - Terminology

- **Desensitisation**
  - Reversible state
  - Effector cells less reactive
  - Increases threshold of reactivity
  - Once immunotherapy is discontinued, previous clinical reactivity returns

- **Tolerance or ‘sustained unresponsiveness’**
  - Patients can eat as much of the allergen as they want
  - Patients can stop and start eating the allergen
  - Patients have no need for regular therapy
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 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
  - Eliciting dose <0.8ml

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

36% tolerated 150ml+
54% tolerated 5-150ml
10% withdrawn: abdominal/respiratory symptoms

Strict CM avoidance (n=30)

After 1 year

DBPCFC
Unable to tolerate 5ml

Adverse events

Almost all experienced adverse events in the active group (mostly cutaneous or abdominal)

- Rush phase: 2 required adrenaline
- Home dosing: 1 required adrenaline

Control group:

- 20% experienced mild accidental reactions

OIT cow’s milk – oral tolerance?

Milk allergic children (6-17 years)
All underwent CM SLIT for 4/52
Tolerated SLIT dose 3.7mg

SLIT (n=10)
Goal dose 7mg
OFC 8g
1/10 tolerated
OFC 8g
0/10 tolerated

1 year

OIT (n=10)
Goal dose 2mg
OFC 8g
8/10 tolerated
OFC 8g
5/10 tolerated

6 weeks off

OIT (n=10)
Goal dose 1mg
OFC 8g
6/10 tolerated
OFC 8g
3/10 tolerated

6 weeks off

# Systematic review of milk OIT

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
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<tbody>
<tr>
<td>Children not able to tolerate 75 mL of milk at baseline</td>
<td></td>
<td></td>
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<tr>
<td>Longo et al (2008)</td>
<td>23.00 (1.42-373.46)</td>
<td>14.20</td>
</tr>
<tr>
<td>Martorell et al (2011)</td>
<td>8.07 (2.77-23.50)</td>
<td>20.51</td>
</tr>
<tr>
<td>Pajno et al (2010)</td>
<td>22.50 (1.45-349.14)</td>
<td>14.37</td>
</tr>
<tr>
<td>Salmivesi et al (2012)</td>
<td>13.24 (0.88-198.67)</td>
<td>14.49</td>
</tr>
<tr>
<td>Skripak et al (2008)</td>
<td>8.00 (0.52-123.68)</td>
<td>14.38</td>
</tr>
<tr>
<td>Subtotal (I-squared = .0%, P=.917)</td>
<td>10.26 (4.41-23.83)</td>
<td>77.95</td>
</tr>
</tbody>
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Children able to tolerate 75 mL of milk at baseline

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<th>Study</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Morisset et al (2007)</td>
<td>1.48 (1.07-2.04)</td>
<td>22.05</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, P= )</td>
<td>1.48 (1.07-2.04)</td>
<td>22.05</td>
</tr>
</tbody>
</table>

Overall (I-squared = 87.6%, P=.000)

8.01 (1.39-46.03) 100.00

NOTE: Weights are from random effects analysis.
Quality of life - cow’s milk OIT

- 30 children (3-12 years) with CMPA had OIT
- QoL assess before and 2 months after OIT

- Parent and child food allergy questionnaire
  - Improved emotional impact: parent and child >4 yrs
  - Improved food anxiety: parent and child >4 yrs
  - Improved dietary limitations: all

Egg
Extensively heated (baked) egg

- 70% egg allergic children tolerate baked egg
- 18.5% required adrenaline for systemic reactions
  - 66% had asthma and 14% previous anaphylaxis to egg
- 74% children with plain egg anaphylaxis tolerate 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)

Oral desensitisation to egg

- **Methods**
  - Children (5-18 years) with confirmed egg allergy
  - RCT: Active: 40, placebo: 15
  - Rush, up-dosing, maintenance (2g egg powder= 1/3 egg)
  - Excluded children with anaphylaxis and asthma

- **Adverse effects**
  - Active: 25% of doses, placebo: 4% of doses
  - Active: 78% oropharyngeal, placebo: 20% oropharyngeal symptoms
  - After 10 months active group: 8% of doses
  - No severe reactions

Desensitisation vs. sustained unresponsiveness

- Children who passed egg challenge at 24 months could consume egg ad libitum at 30 and 36 months
- None of placebo group were tolerating egg

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 liberalised cooked egg in diet whilst continuing maintenance doses of raw egg

Vasquez-Ortiz M et al. Paed Allergy Immunol 2015; 26(3)291-294
FAQLQ-PF raw egg OIT

No significant improvement in total score

Frequency of OIT-related allergic reactions had inverse correlation with post-OIT FAQLQ

Vasquez-Ortiz M et al. Paed Allergy Immunol 2015; 26(3)291-294
Peanut

1 peanut = 200-250mg peanut protein
Cure for deadly peanut allergy 'within three years', say doctors

By DAVID DERBYSHIRE
UPDATED: 00:10, 22 February 2010

A permanent cure for deadly nut allergies could be less than three years away, British doctors said yesterday.

In a breakthrough that offers hope to hundreds of thousands of sufferers, researchers say they have 'effectively cured' 21 children of the dangerous condition.

They are so confident of the treatment - which uses tiny doses of peanut flour to build up a child's resistance to the food - they are starting a £1 million clinical trial on more than 100 children.

The researchers also say the same therapy could be used on other allergies - such as milk and egg.

One child in 50 in Britain suffers from peanut allergy and the numbers are rising fast. Reactions can range from mild itching and rashes to dangerous swelling of the airways, breathing problems and severe asthma.

On average seven children die from it each every year. It is the most common serious allergic reaction, affecting around 450,000 people.

The pioneering treatment was developed at Addenbrooke's Hospital, Cambridge, where it was tested on 23 children between seven and 17. All but two have been 'cured'.

© NASONS NEWS SERVICE

Michael Frost aged 9 has been nut allergy de-sensitized
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

Anagnostou K et al. Clin Exp Allergy; 2011: 41(9):1273-81

- 95% children tolerated peanut dose above threshold
Adverse events

- Updosing associated with allergic symptoms in 19/22 (86%)

- 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

Anagnostou K et al. Clin Exp Allergy; 2011: 41(9):1273-81
FAQLQ-PF for ages 7-12 years

1. Emotional impact
2. Food anxiety
3. Social and dietary limitations

Active group -1.6
Placebo group -1.4

Anagnostou K et al. Lancet 2014; 383:1297-304
Desensitisation: 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

**FIG 2.** Food challenge results. Shown are the cumulative amounts of protein successfully ingested before onset of symptoms in TSs (blue circles) and TFs (red circles). Each circle represents 1 subject.
Predictors of success

24/39 (62%) patients included achieved desensitisation

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

7 allergic effects, 8 personal reasons

Vickery BP et al. JACI 2014;133:468-75
Peanut OIT in preschool children

- DEVIL study: 37 children aged 9-36 months

- Selection criteria:
  - Recent peanut allergic reaction and positive sIgE /SPT
  - Peanut sIgE >5kU/L - no known ingestion
  - Positive OFC
  - Excluded life-threatening anaphylaxis / uncontrolled asthma

- Study groups
  - Low dose (300mg/day) peanut OIT for 2.5 yrs
  - High dose (3000mg/day) peanut OIT for 2.5 yrs
  - 154 peanut allergic controls similar age and severity

Peanut OIT in preschool children

- Desensitisation in 81% (DBPCFC 5g peanut protein)
- Sustained unresponsiveness (1 month) in 78%
  - DBPCFC + 5g Peanut butter
- No difference between low and high dosing groups
- OIT 19-fold higher rates of peanut consumption
- Successful OIT associated with lower baseline pslgE

How to assist tolerance induction?

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

Sublingual immunotherapy

- Good efficacy and safe for inhalant allergens

- Multicentre SLIT study for peanut allergy (12-37 yrs)
  - 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 AAI at home for cough and urticaria

Fleischer DM et al JACI 2013
Epicutaneous desensitisation

- Patch impregnated with allergen onto *intact* skin
  - Peanut
  - Cow’s milk
  - Egg

- Patch well tolerated in peanut allergic adults and children:
  - Mild cutaneous symptoms
  - No systemic allergic reactions
  - No worsening asthma control
VIPES Phase IIb clinical study

- 221 peanut allergic adults, adolescents + children
  - EPIT daily application of 50ug, 100 ug, 250 ug vs. placebo

- Treatment responders after 12 months:
  - DBPCFC eliciting dose>1g peanut protein (4 peanuts)
  - >10 fold increase in DBPCFC eliciting dose

- 53% treatment responders children using 250mg dose
  - Not significant in adults/adolescents
  - Not significant for lower doses

- Follow-on study for 24 months
  - Children using 250mg dose treatment responders 70%
Phase III multicentre clinical studies

- **PEPITES (Peanut EPIT Efficacy & Safety Study)**
  - 330 children aged 4-11 years
  - Daily application of 250ug patch for 12 months
  - Definition of treatment responder
    - Baseline eliciting dose <10mg: TR tolerates 300mg
    - Baseline eliciting dose >10mg: TR tolerates 1000mg

- **REALISE (REAL Life Use and Safety of EPIT)**
  - 335 children aged 4-11 years
  - Blinded treatment of peanut EPIT 250 ug for 6 months
  - Open label for 36 months of active treatment

- Results pending
Multiple-allergen oral immunotherapy
Multiple-allergen oral immunotherapy

- Age range: 4-46 years (median 9 years)

- Baseline DBPCFC
  - Peanut, tree-nut, sesame, cow’s milk, egg
  - Peanut OIT: 15, Peanut + other food OIT: 15

- Reaction rates per dose 3-4%
  - Both multi-OIT and single OIT
  - Most reactions mild (2 AAI required)

OIT vs mOIT desensitisation

mOIT Quality of life

- Caregiver HRQL was assessed using a validated Food Allergy Quality of Life - Parental Burden (FAQL-PB) Questionnaire

- mOIT led to improvement in caregiver HRQL
  - relieved the psychosocial and economic burden FA imposed on caregivers of food-allergic children

Factors influencing parent QoL

- Positive influences:
  - Parents of children older than 10 years
  - Desensitized to >4 foods (peanut, tree-nuts, egg, milk, sesame, shellfish)

- Negative influences:
  - Participants with pre-existing asthma
  - Participants with dose related respiratory allergic reactions
Summary: 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
EoE following food SLIT/OIT

Lucendo AJ et al. Ann Allergy Asthma immunol 113(2014) 624-629
Approaches to improve safety

- Predosing with antihistamine
- Gradual versus rush updosing
- Longer escalation of maintenance phases
- Reduction of peanut allergenicity
- Use of adjuncts
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

Zhou Y et al. Int J Food Science 2013
Anti-IgE

- TNX-901 (binds free IgE) increases threshold OFC 6-fold
- Xolair + OIT (peanut & milk)
  - Reduces side effects
  - Higher starting dose
  - Faster up-dosing
  - Even in high risk patients

Leung D et al. NEJM 2003;348:986-93
Nadeau KC et al. JACI 2011;127(6):1622-1624
Wood RA JACI 2016; 137: 1103-1110
Schneider LC et al. JACI; 132: 1368-1374
What about the guidelines?

- Muraro A et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014; 69 (8): 1026-1045


- ‘OIT not yet ready for clinical use due to inadequate evidence for therapeutic benefit over risks of therapy’

- EAACI Guidelines for Allergen Immunotherapy (AIT) for IgE-mediated food allergy due to be published in 2017
Summary

- OIT effective for desensitization (60-85%)
  - Improved efficacy with probiotics up to 90%

- OIT is more effective than SLIT and EPIT

- Sustained unresponsiveness
  - Only fraction of patients
  - Only when avoidance short (<2 months)

- Reasonably safe
  - Abdominal symptoms
  - Cofactors
  - Measures to improve safety
Considerations

- Target group (age, severity)
- Non-responders (biomarkers)
- Which dose / route of administration
- How frequent and for how long
- Adverse effects – during up-dosing and maintenance
- Compliance
- Add-on immune modulators

Khoriaty E Allergy Asthma Immunol Res 2013
Sampson H J Allergy Clin Immunol 2013
IT ready for *standard* clinical practice?

- Safest and most efficacious route and clinical protocol needs to be established
- Biomarkers for success, non-responders and safety
- Motivated, carefully selected and monitored patients willing to accept risk of adverse reactions
- Cost and resources – NHS England / CCG
IT 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
  - Need more research to achieve sustained unresponsiveness not just desensitisation
  - In carefully selected patients risk/benefit analysis required – risk of future non-compliance
Thank-you for your attention
Acknowledgements

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