Peut-on prévenir les allergies à l’arachide?

Gideon Lack
Conflits d’intérêt

- In relation to this presentation I declare that observational studies [but not interventional studies] have benefited from the National Peanut Board Funding [USA]

- I am on the Scientific Advisory Board of DBV Technologies and am a shareholder
Overview

1. Background & Study Design
2. Clinical Outcomes
3. Immunological Outcomes
4. Public Health Implications
5. Conclusions
Background

Prevalence of Peanut Allergy in Children 4 - 18yrs

Median of peanut protein / week

Peanut Protein Consumption 8 - 14 months

LEAP Study Design

Recruitment: 2006 ----- 2009
n = 640 infants with severe eczema and/or egg allergy

n = 319
Intervention group; SPT-Positive Stratum (n=47)

n = 321
Control Group; SPT-Positive Stratum (n=51)

n = 272
Intervention group; SPT-Negative Stratum (n=272)

n = 270
Control Group; SPT-Negative Stratum (n=270)

Age at clinic visits: 4-11 months 12 months 30 months 60 months
Peanut-specific IgE levels at Baseline by group

Recommended Dietary Interventions

- **Consumption**: 2 g of peanut protein 3 times per week for duration of study.

- Bamba or peanut butter from infancy, whole peanuts could be added after 3 years of age

- **Avoidance**: Avoid peanut consumption
Actual Peanut Consumption

- Consumption of peanut protein median per week (IQR)
  - Avoidance group 0.0 g (0.0-0.0)
  - Consumption group 7.7 g (6.7-8.8)
- Equivalent to:
Peanut Protein in Bed Dust at 60 months of age

The box in these plots represents the median and IQR. The whiskers represent the furthest point within 1.5 times the IQR from the box.

p-value <0.01
Clinical Outcomes

• Peanut Allergy Prevalence
  o Primary and Secondary Prevention
  o Primary Outcome by Race
## Evaluation of Peanut Allergy Outcomes at 60 Months

<table>
<thead>
<tr>
<th>Peanut Allergy Outcome Known</th>
<th>SPT-Negative</th>
<th>SPT-Positive</th>
<th>Combined</th>
<th>% each group</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral food challenge</td>
<td>521</td>
<td>96</td>
<td>617</td>
<td>96.4%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Diagnostic algorithm</td>
<td>9</td>
<td>2</td>
<td>11</td>
<td>1.7%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peanut Allergy Outcome Unknown</th>
<th>SPT-Negative</th>
<th>SPT-Positive</th>
<th>Combined</th>
<th>% each group</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-evaluable</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Missing</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Total No. participants</td>
<td>542</td>
<td>98</td>
<td>640</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
To eat or not to eat . . .
Intention-to-Treat Analysis

SPT-Negative Cohort
(N=530)
P<0.001

86% Relative Reduction
Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)

- Avoidance Group: 13.7%
- Consumption Group: 1.9%

P<0.001

86% Relative Reduction

SPT-Positive Cohort (N=98)

- Avoidance Group: 35.3%
- Consumption Group: 10.6%

P=0.004

70% Relative Reduction
Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)

- P<0.001
- Avoidance Group: 13.7%
- Consumption Group: 1.9%

SPT-Positive Cohort (N=98)

- P=0.004
- Avoidance Group: 35.3%
- Consumption Group: 10.6%

Both Cohorts (N=628)

- P<0.001
- Avoidance Group: 17.2%
- Consumption Group: 3.2%

86% Relative Reduction  70% Relative Reduction  81% Relative Reduction
Intention-to-Treat Analysis (worst-case imputation)

12 missing outcomes
- 5 in the consumption group
- 7 in the avoidance group
Primary and Secondary Prevention for Different Levels of Sensitisation (SPT and/or Specific-IgE)

<table>
<thead>
<tr>
<th>SPT-Negative &amp; IgE Negative</th>
<th>SPT-Negative &amp; IgE Positive</th>
<th>SPT-Positive &amp; IgE Negative</th>
<th>SPT-Positive &amp; IgE Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention Group</td>
<td></td>
<td>Secondary Prevention Groups</td>
<td></td>
</tr>
<tr>
<td>n=378</td>
<td>31.6%</td>
<td>21.4%</td>
<td>40.5%</td>
</tr>
<tr>
<td>p-value = 0.008</td>
<td>p-value &lt;0.001</td>
<td>p-value=0.16</td>
<td>p-value =0.006</td>
</tr>
<tr>
<td>6.0%</td>
<td>4.3%</td>
<td>0.0%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

Prevalence of Allergy

Avoidance Group | Consumption Group | Avoidance Group | Consumption Group | Avoidance Group | Consumption Group | Avoidance Group | Consumption Group |
---|---|---|---|---|---|---|---|
6.0% | 1.0% | 31.6% | 4.3% | 21.4% | 0.0% | 40.5% | 12.8% |
Primary Outcome by Race

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Mixed</th>
<th>Asian</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>460</td>
<td>87</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Prevalence of Allergy

- **Avoidance Group**
  - White: 13.0%
  - Mixed: 30.8%
  - Asian: 44.4%
  - Black: 23.1%

- **Consumption Group**
  - White: 3.2%
  - Mixed: 2.1%
  - Asian: 0.0%
  - Black: 0.0%
Figure 2

Options

Gender:  [ ] Both  [ ] Male  [ ] Female

Race:  [ ] All  [ ] White  [ ] Others

Baseline peanut specific IgE

APPLY  Selected age value: 0

Help

Use the option boxes to the left to change the parameters of the participant charts below; click "Apply" to regenerate plots. Click on the grey headers (for example, "Gender") to expand or collapse portions of the display to assist reading. You can also right-click on a plot to save it as an image.

To view the R source code that generates this figure click [here].
To return to the List of Figures, click [here].
If the report image does not load within three minutes, click retry to resend the request.

User Defined Figure

**SPT-negative Stratum**
- n=530
- p-value<0.001

**SPT-positive Stratum**
- n=98
- p-value=0.004

**Both Strata**
- n=628
- p-value<0.001

<table>
<thead>
<tr>
<th></th>
<th>SPT-negative Stratum</th>
<th>SPT-positive Stratum</th>
<th>Both Strata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoidance Group</td>
<td>Consumption Group</td>
<td></td>
</tr>
<tr>
<td>n=542</td>
<td>13.3%</td>
<td>3.7%</td>
<td>16.9%</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

|        | Avoidance Group     | Consumption Group    |             |
| n=500  | 13.9%                | 0.4%                 | 3.2%        |
| p-value| 0.001                | 0.001                | 0.001       |

|        | Avoidance Group     | Consumption Group    |             |
| n=589  | 13.9%                | 0.4%                 | 3.2%        |
| p-value| 0.001                | 0.001                | 0.001       |

|        | Avoidance Group     | Consumption Group    |             |
| n=640  | 13.3%                | 3.7%                 | 16.9%       |
| p-value| 0.001                | 0.001                | 0.001       |

Data Available At
[www.itntrialshare.org](http://www.itntrialshare.org)
Safety

- Serious Adverse Events (SAEs)
- Adverse Events (AEs)
- Hospitalisation Rates
- Participants Who Discontinued Peanut
- Challenge Safety
<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Avoidance</th>
<th>Consumption</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>101</td>
<td>89</td>
<td>0.41</td>
</tr>
<tr>
<td>No. with at least one SAE</td>
<td>70 (21.8%)</td>
<td>61 (19.1%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Ever hospitalised</td>
<td>52 (16.2%)</td>
<td>50 (15.7%)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Avoidance</th>
<th>Consumption</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>4,287</td>
<td>4,527</td>
<td>0.02</td>
</tr>
<tr>
<td>No. with at least one AE</td>
<td>99.4%</td>
<td>99.7%</td>
<td>0.45</td>
</tr>
</tbody>
</table>
AE data available in an **interactive graphic at:**
http://graphics.rhoworld.com/studies/leap/aes/explorer/

## LEAP Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Peanut Avoidance (n=321)</th>
<th>Peanut Consumption (n=319)</th>
<th>AE Rate by group</th>
<th>Difference Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>99.1%</td>
<td>99.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>65.7%</td>
<td>73.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>62.6%</td>
<td>62.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>49.5%</td>
<td>47.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>46.4%</td>
<td>48.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>29.0%</td>
<td>33.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>29.3%</td>
<td>22.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>16.2%</td>
<td>15.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>9.3%</td>
<td>6.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2.8%</td>
<td>4.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4.0%</td>
<td>2.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3.7%</td>
<td>1.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>2.5%</td>
<td>2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>1.9%</td>
<td>1.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1.9%</td>
<td>1.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>0.0%</td>
<td>1.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>0.3%</td>
<td>0.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>0.0%</td>
<td>0.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>0.6%</td>
<td>0.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>0.6%</td>
<td>0.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0.0%</td>
<td>0.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>0.3%</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>99.4%</strong></td>
<td><strong>99.7%</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety - Peanut challenges

• **Baseline challenge**
  – 2 g peanut protein or if sensitized to peanut, 3.85 g.
  – Challenge foods well accepted, no incomplete challenges due to feeding or choking issues.
  – 7 positive challenges
  – Reactions:
    • Predominantly cutaneous
    • No epinephrine required

• **Month 60 challenge**
  – 5 g peanut protein open challenge or 9.35 g DBPCFC
  – 57 positive challenges
  – Reactions:
    • Respiratory and/or cardiovascular signs 14 (24.5%)
    • IM epinephrine administered to 9 (16%)
Immunological Outcomes
Per-protocol Analyses
Levels of IgG4 and IgG

Peanut Avoidance

Peanut Consumption

Peanut-Specific IgG
(µg/liter, log₁₀)

Peanut-Specific IgG₄
(µg/liter, log₁₀)

Age at Visit (mo)
Peanut Wheal Size by Age

Age p-value <0.001
Increasing Wheal Size with Age and SCORAD

SCORAD p-value <0.001

Age p-value <0.001
Factors that Could Increase Treatment Efficacy at a Population Level

• Apply intervention before SPT grows above 4mm; there is a narrow window of opportunity

• Early intervention:
  – For infants with no eczema
    • Introduce peanut without screening as of 4 months of age and once weaning has been established
  – For infants with eczema
    • Screen using SPT
    • Introduce peanut under supervision if SPT <5mm
LEAP Study Conclusions

• **Peanut consumption** beginning in the first year of life **prevents peanut allergy** in a high-risk population.
  • 86% reduction in the **SPT-negative stratum**
  • 70% reduction in the **SPT-positive stratum**
  • Both primary and secondary prevention effective
  • Prevention is **effective in all races**
  • Peanut consumption in high-risk children is **safe**
LEAP Study Conclusions

- Many children are sensitized or already allergic (SPT >4mm) early in life.

- **Early intervention** in infancy may further increase efficacy by reducing the number of children with SPT > 4mm prior to intervention.

- **Prevention of allergy** is associated with an early and sustained rise in IgG and IgG4 and a later and progressive suppression of high levels of peanut-specific IgE production.
LEAP-On Study

**Primary Endpoint** - proportion of participants with peanut allergy at 72 months of age

- **LEAP Study**
  - Consumption
  - N=319
  - Avoidance
  - N=321

- **LEAP-On Study**
  - 87% (n=558) enrolled on LEAP-On
  - Avoidance

**Comparison at 72 months of the observed rates between Groups A and B**
- **Persistent Tolerance**
- **Transient Desensitisation**

As of Jan 2015: 92% have completed LEAP-On final visit
Research Support

• Immune Tolerance Network

• National Institute of Allergy and Infectious Disease

• Food Allergy Research & Education

• The **MRC & Asthma UK Centre**; The UK Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy’s & St. Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust.

• Food Standards Agency UK

• Rho Federal Systems Division
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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Acknowledgements – Participants & Families

- Families helped us achieve:
  - 98.4% retention over 5 years,
  - 92% compliance with intervention,
  - OFC in 96%,
  - Near complete blood draws at all time points