DEVELOPMENT OF NEW TECHNIQUES IN SPECIFIC ORAL TOLERANCE INDUCTION

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Professor Cadiz University

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Tolerance Induction:
Today is yesterday's tomorrow.

Is an old problem but result new:

- Increasing prevalence
- Increasing persistent food allergy which have a good forecast in infants
- The involvement of an increasing number of food
- Changes in our lives that make us increasingly take industrially processed foods and outside the domestic sphere

We have lost the control of our food
Treatmet indicated in food allergy

Diet

- Good notice: in some foods and in some ages the evolution at the tolerance is frequent in a high percentage of patients

1. It is easy to prescribe
2. It is effective ¿ 100%?
3. It is safe ¿ ?
4. It is economic ¿ ?
5. It is easy to make ¿ ?
Is it necessary to make anything more than the diet?

Clinic dates about children allergic to cow’s milk
240 childrens

Age: medium 4,6 years (1-12 y)

- 72,9% < 5 y
- 27,1% > 5 y
Persisten allergy = bad evolution

Cow’s Milk Allergy (CMA):
- Isolated: 49,6%
- Associated with other allergies: 50,4%
  - 42,5% Egg
  - 13,3% Fish
  - 15% Nuts
  - 3,3% Fresh fruits
  - 21,7% > 3 food groups

Comorbidities: Asthma: 38,3% (< 5 y: 30,2%; > 5 y: 62,5%) Dermatitis 11,7%

Database: Univ. Hospital PR, 2014
Immunotherapy
Oral tolerance

1908 Schofield Egg
1969 Vaillaud Milk
1984 Patriarca Milk

Pub Med: 1990-2014
Food Allergy & Immunotherapy: 1619
Food allergy & Oral Tolerance: 319
Desensitization or Tolerance induction

Conceptual differences

**Desensitization**: Ability to tolerate the allergens that cause adverse reaction after application of a treatment.
Requires immediate exposure
It is not known how long the interruption of exposure tolerance would be lost
Sometimes it's just an elevation of the threshold dose reactive

**Tolerance**: Permanent state of loss of adverse reaction to a substance with which previously appeared allergic reaction.
Tolerance can be spontaneous or induced

The permanent tolerance is **ALLERGY CURED**
SPECIFIC ORAL DESENSITIZATION INDUCTION (SODI)

Administration of the product (food allergen) which cause the allergic reaction beginning with small amounts until get the normal amount or the highest dosage tolerated.

We try to get an immunological tolerance, reeducating the complex cellular and serologic mechanism, to correct an inadequate reaction.

Our whole life is a history of gradual tolerance towards the environment around us
SPECIFIC ORAL TOLERANCE INDUCTION (SOTI)

WHO?

AT WHAT AGE?

WITH WHAT PROTOCOL?

WHERE?

FOR WHAT FOOD?

WHO SHOULD BE PERFORMED?

WHERE TO GET?

HOW MANY FOOD?

ALWAYS POSSIBLE?
There are many guidelines or protocols:

1. It depends on the means you count

2. It depends of the type of center

3. It depends of the type of patient: age, level of sensitization, disponibility, comorbilities

4. It depends of the type of geographical area and the communications

5. It depends of the circumstances of the center, of the family and of the patient
FOOD ORAL TOLERANCE INDUCTION

- Preference oral and evaluate sublingual start
- COMORBILITIES ASTHMA/DERMATITIS ALWAYS STABLE PATIENTS Treatment for control
- Premedication For and against Antihistamine/ Cromoglicate
- SEQUENCE-INCREASES ALL IN ONE DAY/ WEEKS INCREASES
- START DOSAGE Different by author and type of induction
- Place Consulting/ Hospital/ Home
- Technical and human resources available

SEVERITY OF AWARENESS
VIA

Oral with ingestion, sublingual without ingestion
Subcutaneous

TIME

Slow, very much slow
Short, cluster
Semicluster: first quick and after each week

IS A BESPOKE SUIT

PLACE

Admitted to hospital
With partial admitted
With increases in the hospital
With increases at home
Increases by week, daily....

MEDICATION

Without medication
With premedication: antihistamine, Salbutamol, etc

We make a protocol for “easy” patients versus “anafilactics” and adapted at the circumstances
SPECIFIC ORAL TOLERANCE INDUCTION COW´S MILK

**Table 1. Protocol for oral desensitization with cow’s milk (modified from Patriarca et al. 

<table>
<thead>
<tr>
<th>Days</th>
<th>Daily dose</th>
<th>Days</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 drops of milk in 100 ml of water</td>
<td>Pure milk</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1 drop</td>
<td>65-68</td>
<td>40 drops x 4</td>
</tr>
<tr>
<td>4-6</td>
<td>4 drops</td>
<td>69-72</td>
<td>50 drops x 4</td>
</tr>
<tr>
<td>7-9</td>
<td>6 drops</td>
<td>73-76</td>
<td>60 drops x 4</td>
</tr>
<tr>
<td>10-12</td>
<td>10 drops</td>
<td>77-80</td>
<td>4.5 ml x 3</td>
</tr>
<tr>
<td>13-15</td>
<td>12 drops</td>
<td>81-84</td>
<td>6 ml x 3</td>
</tr>
<tr>
<td>16-18</td>
<td>18 drops</td>
<td>85-88</td>
<td>6 ml x 4</td>
</tr>
<tr>
<td>19-21</td>
<td>1 drop</td>
<td>89-92</td>
<td>7 ml x 4</td>
</tr>
<tr>
<td>22-24</td>
<td>2 drops</td>
<td>93-96</td>
<td>12 ml x 4</td>
</tr>
<tr>
<td>25-27</td>
<td>3 drops</td>
<td>97-100</td>
<td>15 ml x 4</td>
</tr>
<tr>
<td>28-30</td>
<td>4 drops</td>
<td>101-104</td>
<td>20 ml x 4</td>
</tr>
<tr>
<td>31-33</td>
<td>6 drops</td>
<td>105-108</td>
<td>20 ml x 3</td>
</tr>
<tr>
<td>34-36</td>
<td>8 drops</td>
<td>109-112</td>
<td>30 ml x 3</td>
</tr>
<tr>
<td>37-40</td>
<td>10 drops</td>
<td>113-116</td>
<td>40 ml x 3</td>
</tr>
<tr>
<td>41-44</td>
<td>16 drops</td>
<td>117-120</td>
<td>50 ml x 2</td>
</tr>
<tr>
<td>45-48</td>
<td>24 drops</td>
<td>121-124</td>
<td>65 ml x 2</td>
</tr>
<tr>
<td>49-52</td>
<td>32 drops</td>
<td>125-128</td>
<td>80 ml x 2</td>
</tr>
<tr>
<td>53-56</td>
<td>40 drops</td>
<td>129-132</td>
<td>100 ml x 2</td>
</tr>
<tr>
<td>57-60</td>
<td>40 drops x 2</td>
<td>133-136</td>
<td>Maintenance dose: 120 ml of milk (about 1 glass) at least 2-3 times a week</td>
</tr>
<tr>
<td>61-64</td>
<td>40 drops x 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Total daily dosage 120 cc
*Time: 19.4 weeks
*Success: 79.2%
### Experience in Specific Oral Tolerance Induction

#### Food allergy immunotherapy trials

<table>
<thead>
<tr>
<th>Study, y of publication</th>
<th>Targeted food</th>
<th>Modality</th>
<th>Blinded</th>
<th>Total subjects, n (age range)</th>
<th>Duration</th>
<th>Success rate[a] [n (%)]</th>
<th>Withdrawals [n (%)]</th>
<th>Tolerance [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patriarca et al.,[18] 2003</td>
<td>Milk, egg, other</td>
<td>OIT</td>
<td>No</td>
<td>59 (3–55)</td>
<td>2–3 mo</td>
<td>45/54 (83.3)</td>
<td>9 (16.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Meglio et al.,[19] 2004</td>
<td>Milk</td>
<td>OIT</td>
<td>No</td>
<td>21 (6–10)</td>
<td>6 mo</td>
<td>15 (72)</td>
<td>3 (14)</td>
<td>NA</td>
</tr>
<tr>
<td>Staden et al.,[20] 2007</td>
<td>Milk, egg</td>
<td>OIT</td>
<td>No</td>
<td>25 (0.6–12.9)</td>
<td>11–59 mo</td>
<td>12 (48)</td>
<td>9 (36)</td>
<td>9 (36) – off 2 mo</td>
</tr>
<tr>
<td>Buchanan et al.,[21] 2007</td>
<td>Egg</td>
<td>OIT</td>
<td>No</td>
<td>7 (1–7)</td>
<td>24 mo</td>
<td>7 (100)</td>
<td>0</td>
<td>2 (29) – off 3–4 mo</td>
</tr>
<tr>
<td>Longo et al.,[22] 2008</td>
<td>Milk</td>
<td>OIT</td>
<td>No</td>
<td>30 (5–17)</td>
<td>1 y</td>
<td>11 (36)</td>
<td>3 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>Skripak et al.,[23] 2008</td>
<td>Milk</td>
<td>OIT</td>
<td>Yes</td>
<td>13 (6–17)</td>
<td>5–6 mo</td>
<td>12 (92)</td>
<td>1 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Clark et al.,[24] 2009</td>
<td>Peanut</td>
<td>OIT</td>
<td>No</td>
<td>4 (9–13)</td>
<td>6–7 mo</td>
<td>4 (100)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Jones et al.,[25] 2009</td>
<td>Peanut</td>
<td>OIT</td>
<td>No</td>
<td>39 (1.1–9.4)</td>
<td>36 mo</td>
<td>29 (74)</td>
<td>10 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>Blumchen et al.,[26] 2010</td>
<td>Peanut</td>
<td>OIT</td>
<td>No</td>
<td>23 (3–14)</td>
<td>9 mo</td>
<td>14 (61)</td>
<td>9 (39)</td>
<td>NA</td>
</tr>
<tr>
<td>Pajno et al.,[27] 2010</td>
<td>Milk</td>
<td>OIT</td>
<td>Yes</td>
<td>15 (4–13)</td>
<td>4–5 mo</td>
<td>10 (67)</td>
<td>5 (3.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Martorell et al.,[28] 2011</td>
<td>Milk</td>
<td>OIT</td>
<td>No</td>
<td>30 (2–3)</td>
<td>12 mo</td>
<td>27 (90)</td>
<td>2 (0.07)</td>
<td>NA</td>
</tr>
<tr>
<td>Garcia Rodriguez et al.,[29] 2011</td>
<td>Egg</td>
<td>OIT</td>
<td>No</td>
<td>23 (5–17)</td>
<td>3 mo</td>
<td>20 (86.9)</td>
<td>1 (0.04)</td>
<td>NA</td>
</tr>
<tr>
<td>Anagnostou et al.,[30] 2011</td>
<td>Peanut</td>
<td>OIT</td>
<td>No</td>
<td>22 (6–18)</td>
<td>2–9 mo</td>
<td>19 (86.4)</td>
<td>1 (0.05)</td>
<td>NA</td>
</tr>
<tr>
<td>Burks et al.,[31] 2012</td>
<td>Egg</td>
<td>OIT</td>
<td>Yes</td>
<td>40 (5–11)</td>
<td>22 mo</td>
<td>30 (75)</td>
<td>6 (15)</td>
<td>11 (28) – off 4–6 wk</td>
</tr>
<tr>
<td>Enrique et al.,[32] 2005</td>
<td>Hazelnut</td>
<td>SLIT</td>
<td>Yes</td>
<td>12 (19–53)</td>
<td>5 mo</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>De Boissieu and Dupont,[33] 2006</td>
<td>Milk</td>
<td>SLIT</td>
<td>No</td>
<td>8 (6–17)</td>
<td>6 mo</td>
<td>7 (87)</td>
<td>1 (13)</td>
<td>NA</td>
</tr>
<tr>
<td>Fernandez-Rivas et al.,[34] 2009</td>
<td>Peach</td>
<td>SLIT</td>
<td>Yes</td>
<td>37 (18–65)</td>
<td>6 mo</td>
<td>33 (89)</td>
<td>4 (11)</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al.,[35] 2011</td>
<td>Peanut</td>
<td>SLIT</td>
<td>Yes</td>
<td>11 (1.6–10.5)</td>
<td>12 mo</td>
<td>11 (100)</td>
<td></td>
<td>NA</td>
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<tr>
<td>Keet et al.,[36] 2012</td>
<td>Milk</td>
<td>OIT/SLIT</td>
<td>No</td>
<td>30 (6–17)</td>
<td>60 wk</td>
<td>28 (93)</td>
<td>2 (7)</td>
<td>9 (30) – off 6 wk</td>
</tr>
</tbody>
</table>

*a Success rate is defined as number of subjects who successfully finished treatment and were able to include the targeted food into the diet or finished treatment and underwent post-treatment food challenge.

NA = not applicable; OIT = oral immunotherapy; SLIT = sublingual immunotherapy.
# My experience

## 1st DAY
Intervals: 1 hour

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>HOUR</th>
<th>REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml dilution 1/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 ml 1/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 ml 1/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 ml 1/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,6 ml 1/10</td>
<td></td>
<td></td>
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</tbody>
</table>

## 2nd DAY
Intervals: 1 hour

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>HOUR</th>
<th>REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,6 ml 1/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,2 ml 1/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 ml 1/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 ml 1/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,5 ml pure milk</td>
<td></td>
<td></td>
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</tbody>
</table>
Milk without dilution. Increasing by weeks

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>DAY</th>
<th>REACTION IN HOSPITAL</th>
<th>REACTION AT HOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SOTI with milk in our hospital

40 childds (2010-2014)

- Age: 6-14 y
- Medium IgE casein: 45 UI/ml (4->100)
- Weeks for SOTI: medium 10,5 w. (intervals 9- 15)
- CAREFOUL WITH PATIENTS WITH HIGH RISK OF ANAPHYLAXIS

Number of patients with total tolerance to milk: 35
Quantity: 240 ml but with individual increases if the patient want to drink o eat foods with milk.

5 patient only got 100 ml of tolerance and actually maintance this dosage

Adverse reactions:
- abdominal pain (5)
- eosinophilic esophagitis (1)
- ANAPHYLAXIS (10): treatments with Adrenaline via IM
Omalizumab: high risk of anaphylaxis

Human and monoclonal antibody
It binds to circulating IgE despite Their specificity
It builds small complex biologically inert of Omalizumab:IgE
Don´t activate the complement way
Decreases the IgE levels, depending of the doses

Inhibits the delivery of hisyamine and others precharged mediators

It cause the down regulation of the high affinity receptors

• Results:

**Placebo**: 735 mg
913 mg in the group given 150 mg of TNX-901.
1650 mg in the group given 300 mg of TNX-901
2627 mg in the group given 450 mg of TNX-901

P<0.001 for the comparison of the 450-mg dose with placebo, and P<0.001 for trend with increasing dose

**TNX-901 was well tolerated**
Objective: evaluate the efficacy of Omalizumab in food allergy

Method: retrospective analysis to test the effectiveness of Omalizumab in 22 patients with persistent asthma and IgE mediated food allergy. Were analyzed: Juniper quality of life measurements and Investigator Global Assessment scores.

Results: 13 women and 9 men, age: 28 años (14-66).

All the patients with Prick test positive to foods. And all of them get a significative improvement of the clinical symptoms when they were reexposure with the food

Conclusiones: Omalizumab could be effective as treatment in patients with food allergy IgE mediated
• Omalizumab in peanut-allergic patients reduces free anti-IgE peanut and Skin Prick test to peanut

• Not all the patients respond similar to Omalizumab.

• **Hypotesis**: the decrease of free IgE and Prick test after the treatment with 12 weeks of Omalizumab can be predicted to happen to make the oral provocation.

• **Method**: 5 patients of 5-25 years. Prick test: >8mm, Cap: >15 KU/ml. IgE free and Prick test when free IgE less of 15 KU/ml.

• **Results**: Decrease of free IgE from 119,4 KU/ml. to 6 KU/ml. 1 patient negative the Prick tests after 4 weeks of treatment with Omalizumab, oral provocation negative.
Treatment with Omalizumab in **childs with anafylactics reactions** to cow´s milk proteins

**Objective:**
- To evaluate the tolerance to cow´s milk allergy, after 16 weeks of treatment, 1 year and 2 years with Omalizumab

**Material and methods:**
- Is an observational study
- Childs with more than 5 years, anaphylactics with cow´s milk protein, prick test positive, specific IgE positive.
Material and Methods

- At 16 weeks, 1 year and 2 years of treatment with Omalizumab, each 2-4 weeks, depending the dosage

- We did:
  - 1. Oral provocation,
  - 2. Prick test,
  - 3. Specific IgE to cow’s milk

- Oral provocation: lips contact with 1 drop of milk, each 30 minutes: 1 ml, 2´5ml, 5ml, 10ml, 20 ml, 50ml y 100 ml.

- Place: Pediatric Hospital Day
## Características de los pacientes

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>10 childs</th>
<th>4 boys</th>
<th>6 girls</th>
<th>Asthma</th>
<th>10 childs</th>
<th>100%</th>
<th>Anaphylaxis</th>
<th>10 childs</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>medium</td>
<td>8,7 years</td>
<td>Range</td>
<td>5 y – 15y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE</td>
<td>medium</td>
<td>1321 Ul/ml</td>
<td>Range</td>
<td>150-2500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>medium</td>
<td>37Kg</td>
<td>Range</td>
<td>20-57Kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE level</td>
<td>medium</td>
<td>75 KU/ml</td>
<td>Range</td>
<td>7-100 KU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prick test</td>
<td>medium</td>
<td>7 x 5mm</td>
<td>Range</td>
<td>4x5 - 14x14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab dosage</td>
<td></td>
<td></td>
<td>Range</td>
<td>75mg/4s 300mg/2s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results oral provocation with 1 year / 2 years

- Neither child presented reaction with 1 year and with 2 years of treatment

- Oral provocation: 1 ml, 2.5 ml, 5 ml, 10 ml, 20 ml, 50 ml y 100 ml.
Prick Test

CAP to casein

Quantity of milk tolerated
No adverse effects during treatment with Omalizumab

- Headache: 0 casos
- Urticaria: 0 casos
- Local reactions: 0 casos

Conclusions:
Omalizumab is sure and efficacy in childs with anaphylaxis to cow´s milk protein allergy
**Objective**

- To evaluate the security and tolerability of Omalizumab to do the desensitization to many foods with a sura and fast method.

**Methods**

- Multiallergic patients to food, OIT 5 o more allergens in the same time + omalizumab (rush OIT). The reactions in their home were recorded daily.
Omalizumab was stopped at 16 weeks, 8 weeks before and 8 weeks OIT+ Omalizumab

### Table 1
Rush mOIT initial escalation day schedule

<table>
<thead>
<tr>
<th>Dose in mg of protein</th>
<th>Dosing interval in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>150</td>
<td>30</td>
</tr>
<tr>
<td>300</td>
<td>30</td>
</tr>
<tr>
<td>625</td>
<td>30</td>
</tr>
<tr>
<td>1250</td>
<td>120</td>
</tr>
</tbody>
</table>

### Table 2
Rush mOIT dose escalation schedule

<table>
<thead>
<tr>
<th>Dose of protein (mg)</th>
<th>Interval in weeks</th>
<th>% of increase from previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>2350 mg</td>
<td>2</td>
<td>88%</td>
</tr>
<tr>
<td>4000 mg</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>5800 mg</td>
<td>2</td>
<td>45%</td>
</tr>
<tr>
<td>7600 mg</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>9400 mg</td>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>11200 mg</td>
<td>2</td>
<td>20%</td>
</tr>
<tr>
<td>14000 mg</td>
<td>2</td>
<td>25%</td>
</tr>
</tbody>
</table>
Conclusions:
- OIT+Omalizumab many foods
- Sure
- Efficacy
- Specialist and training personal
- Place: quiet and with equipment
**Allergen Peptide**

- **DZ1**
- **Hochdosis**
- **Allergen**

**THn** → **Treg** → **IL-10** → **B\(_{\gamma_1}\)** → **IgG\(_4\)**

**IL-12** → **TH1** → **IFN-γ** → **B\(_{\gamma_1}\)** → **IgG\(_1\)**

**TGF-β** → **B\(_{\alpha}\)** → **IgA**

**B\(_{\alpha}\)**: IgA-produzierende B-Zelle

**B\(_{\gamma}\)**: IgG-produzierende B-Zelle

**DZ** = Dendritische Zelle (Antigen präsentierende Zelle)

**IFN** = Interferon

**IgA** = Immunglobulin A

**IgG** = Immunglobulin G

**IL** = Interleukin

**TGF** = Transformierender Wachstumsfaktor

**TH** = T-Helferzelle

**THn** = naive T-Helferzelle

**Treg** = T-Regulatorzelle
Antigen

Dendritic Cell

1. Suppression of mast cells, basophils and eosinophils

2. Suppression of effector T cells

3. Suppression of tissue inflammation

4. Suppression of mucus production

5. Suppression of inflammatory DCs
   Induction of tolerogenic DCs

6. Suppression of IgE
   Induction of IgG4

Changes in the immunology

- iT$_{\text{reg}}$ and nT$_{\text{reg}}$ inhibiting response Th2
- IgA$_1$ and IgA$_2$ induce production of IL-10 by Mo/Mφ
- IL-10 favors great production towards IgG$_4$
- IgG$_4$, IgA$_1$ e IgA$_2$ compete for the Ag with the IgE:
  - Less sensibilization
  - Less presentation provide of Ag
  - Less activation of mast cells and basophils
6 patients

1st day: diluted milk 1/100: 1 ml-2ml-4ml-6ml-8ml-16 ml.
Intervals: 1 hour between them

2nd day: diluted milk 1/100: 16 ml-32 ml and after dilution 1/10: 6-12-24 ml. Intervals: 1 h

3rd day: diluted milk 1/10: 24-48 ml and after pure milk: 8-16-32 ml. Intervals: 1 h

4th day: 32-64-100 ml pure milk. Intervals: 2 h

5th day: 100-200 ml pure milk. Intervals: 2 h
The general experience is less

• Some studies excluded anaphilactic patients (Buchanan)

• Patriarca: beaten egg

• Staden: lyophilized egg

• Itoh: severe allergy and cluster protocol

• My hospital: we used commercial egg with capsules containing ovomucoide protein increasing the concentration at each feeding
Ingredients: Dried egg white

Dosage 1º: 7 capsules with 4 mg
Dosage 2º: 7 capsules with 20 mg
Dosage 3º: 7 capsules with 50 mg
Dosage 4º: 7 capsules with 100 mg
Dosage 5º: 7 capsules with 225 mg
Dosage 6º: 7 capsules with 450 mg
Dosage 7º: 7 packet with 900 mg
Dosage 8º: 7 packet with 1800 mg
Dosage 9º: 1 packet with 3600 mg

3 days after the final packet the patient is subject a double-blind placebo control trial with a omelette and after with a mixture of milk and raw clear.

During the next year the patient must eat, at least, one egg each 2-3 days (3 eggs/week)
SOTI with egg in our hospital

10 childs (2013-2014)

- Age: 6-10 y
- Medium IgE ovomucid: 35 UI/ml (4->100)
- Weeks for SOTI: medium 10 w. (9-12)

Number of patients with total tolerance to egg: 9

1 patient only got 225 mg of tolerance and desertion by anaphylaxis

**Adverse reactions:**
- abdominal pain (2)
- **ANAPHYLAXIS (1):** treatment with Adrenaline via IM
SPECIFIC ORAL TOLERANCE INDUCTION WITH OTHER FOODS

Patriarca: inductions with many foods: fish, apple, cereals, peanut, kiwi, lettuce...

Ernesto Enríquez: sublingual with hazelnut

Ana Tabar: peach

(actually is possible administrate sublingual immunotherapy with Pru p3)

My experience: wheat (2 patient)

• 8 years tolerated in 24 weeks one year ago.
  • IgE wheat: 935 kU/ml. 6 months after end SOTI: 87,5 kU/ml
• 12 years, actually in SOTI with cereals
It is necessary to continue a medium-term control of these patients, a month, 6 months, 12 months, 2 and 3 years.

Patriarca: follow up 18 months. No clinical dates. Decreased prick test and milk serum IgE

Martorell: follow up 4 years

Meglio: follow up 4 years. No important incidence. No urgencies assistance. Continue tolerance.

My experience: follow up 2 years in milk SOTI. 1 desertion. One patient had abdominal pain and vomiting. Abundant hematological. Endoscopy was performed and the image was considered suggestive of eosinophilic esophagitis. Negative biopsy. Pending new endoscopic control and assessment. Background RGE. Eosinophilia 14-16%. Family RGE.
### Table 3. Future treatment of food allergy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Allergen</th>
<th>Efficacy</th>
<th>Study (published year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT</td>
<td>Hazelnut</td>
<td>45% of the subjects reached 20 g after 8–12 weeks of study</td>
<td>Enrique et al. [32]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2005)</td>
</tr>
<tr>
<td></td>
<td>Peanut</td>
<td>70% of 20 subjects were able to increase the threshold doses after 44 weeks of therapy</td>
<td>Fleischer et al. [33]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2013)</td>
</tr>
<tr>
<td>SLIT + OIT</td>
<td>Milk</td>
<td>70% of 20 subjects were able to pass the 8-gram oral challenge after 80 weeks of therapy</td>
<td>Keet et al. [11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2012)</td>
</tr>
<tr>
<td>OIT + omalizumab</td>
<td>Milk</td>
<td>9 of 11 subjects reached 2,000 mg, passed the oral challenge on week 24 of the study</td>
<td>Nadeau et al. [36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2012)</td>
</tr>
<tr>
<td>EPIT</td>
<td>Milk</td>
<td>90% of 10 subjects tended to increase the threshold doses at follow-up oral challenge (day 90)</td>
<td>Dupont et al. [37]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2010)</td>
</tr>
</tbody>
</table>

**SLIT:** SubLingual ImmunoTherapy  
**OIT:** Oral ImmunoTherapy  
**EPIT:** EPicutaneous ImmunoTherapy
**The safety and efficacy of sublingual and oral immunotherapy for milk allergy.**

Keet J Allergy Clin Immunol 2011

**Methods:** We randomized children with CM allergy to SLIT alone or SLIT followed by OIT. After screening double-blind, placebo-controlled food challenges and initial SLIT escalation, subjects either continued SLIT escalation to 7 mg daily or began OIT to either 1000 mg (the OITB group) or 2000 mg (the OITA group) of milk protein. They were challenged with 8 g of milk protein after 12 and 60 weeks of maintenance. If they passed the 60-week challenge, therapy was withdrawn, with challenges repeated 1 and 6 weeks later.

**Conclusion:** OIT was more efficacious for desensitization to CM than SLIT alone but was accompanied by more systemic side effects. Clinical desensitization was lost in some cases within 1 week off therapy.
FUTURE PROJECTS IN 2015

SOTI to hake

Multicenter study
What are the 14 most common allergens in Europe?

- Soybean
- Sesame seeds
- Fish
- Mustard
- Shellfish
- Seafood
- Milk
- Eggs
- Nuts
- Sulfur dioxide
- Cereals containing gluten
- Peanuts
- Celery
- Lupins
INDUCTION OF TOLERANCE IN FOOD ALLERGY IS A REASONABLY SAFE AND EFFICIENT METHOD

The benefits of SOTI method overcome difficulties

We need to increase our expertise in various protocols, guidelines, roads, use of allergen

Above all know about what we are acting

WE NEED TO KNOW MUCH
Thanks for your attention