Carbamylated monomeric allergoid for respiratory allergy: the advantages of LAIS®

E. Compalati

-Allergy & Respiratory Disease sec Clinic
University of Genoa. Italy

-Lofarma Spa, Milan. Italy
Medical Scientific Department
WHO position paper 1998

- SIT is indicated for *inhalants* and *venom* allergy
- SIT is positioned as the only treatment able to modify the natural course of allergy

Risk/benefit

Other routes
SLIT...from the literature

- No fatal reactions ever reported
- No difference in the incidence between children and adults
- Most reaction mild and localized in the oral mucosa or gastrointestinal tract (incidence ≈40-75%)
- Very few systemic serious reactions reported (0.26%)

Cox LS et al. JACI 2006
Radulovic S et al. Allergy 2011
Ibañez MD et al. Pediatr Allergy Immunol 2007
Anaphylaxis to SLIT

<table>
<thead>
<tr>
<th>Report</th>
<th>Age- sex</th>
<th>Allergen</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antico 2006 - Italy</td>
<td>36 y-woman</td>
<td>Latex</td>
<td>ALK-Abellò</td>
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<tr>
<td>Dunsky 2006 - USA</td>
<td>31 y-woman</td>
<td>Mix</td>
<td>Greer</td>
</tr>
<tr>
<td>Eifan 2007 - Turkey</td>
<td>11 y-girl</td>
<td>Mites, 5 grass</td>
<td>Stallergenes</td>
</tr>
<tr>
<td>Blazowski 2008 - Poland</td>
<td>16 y-girl</td>
<td>Mites</td>
<td>Stallergenes</td>
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<tr>
<td>Rodriguez- Perez 2008-Mexico</td>
<td>27 y-woman</td>
<td>Mix</td>
<td>unknown</td>
</tr>
<tr>
<td>Rodriguez- Perez 2008-Mexico</td>
<td>7 y-girl</td>
<td>Mites, Tree</td>
<td>unknown</td>
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<tr>
<td>Rodriguez- Perez 2008-Mexico</td>
<td>11 y-boy</td>
<td>Mites</td>
<td>unknown</td>
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<tr>
<td>De Groot 2009 - Netherland</td>
<td>13 y-boy</td>
<td>Grass</td>
<td>ALK-Abellò</td>
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<tr>
<td>De Groot 2009 - Netherland</td>
<td>27 y-woman</td>
<td>Grass</td>
<td>ALK-Abellò</td>
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<tr>
<td>Buyukozturk 2010 - Turkey</td>
<td>adult</td>
<td>Latex</td>
<td>ALK-Abellò</td>
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<tr>
<td>Buyukozturk 2010 - Turkey</td>
<td>adult</td>
<td>Latex</td>
<td>ALK-Abellò</td>
</tr>
</tbody>
</table>

1/100 millions administrations
Immunotherapy: adverse events

Natural exposition

Immunotherapy

Re-exposure

Immediate Mediator Release

Late Phase Inflammation

Toxic Proteins Leukotrienes

IL-3

IL-6

Eosinophil

Mediators

IL-4

IL-5

IL-13

Basophil
LAIS ®

from ALLERGEN...to ALLERGOID
Lais® is a modified allergen with a specific reaction with potassium-cianate

LYSINE:

H
\text{H}_2\text{N} - \text{C} - \text{C} \quad \text{O} \quad \text{OH}
\quad \text{(CH}_2\text{)}_3
\quad \text{H} - \text{C} - \text{NH}_2
\quad \text{H}

\text{HOMOCITRULLINE:}

H
\text{H} - \text{C} - \text{N} - \text{C} \quad \text{O} \quad \text{NH}_2
\quad \text{H}

+ KCNO

\text{“carbamylation”}
Consequences of chemical modification

1. **PRESERVATION**
   - of molecular sizes
     - monomericity-

2. **Dramatic REDUCTION**
   - of specific IgE linking
     - reduced allergenicity-

3. **NO**
   - alteration of T-epitopes
     - preserved immunogenicity-

4. **RESISTENCE**
   - to enzymatic degradation
     - high bioavailability-
polymeric >1000 kda

monomeric ~40 kda
Consequences of chemical modification

1. **PRESERVATION**
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   - alteration of T-epitopes
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   - to enzymatic degradation
   - high bioavailability
NATIVE ALLERGEN

LYSINE:

H2N - C - C \text{O} \text{OH}

\text{(CH}_2\text{)}_3

H - C - \text{NH}_2

\varepsilon \text{ AMINIC GROUP}

IgE-binding

Allergen – Antibody

Side effects
MODIFIED ALLERGEN - LAIS®

HOMOCITRULLLINE:

H - C - C
\(\text{OH}\)
\((\text{CH}_2)_3\)

\(\text{H2N - C - C - O}\)

UREIDIC GROUP

\(\text{H - C - N - C - NH}_2\)

NO IgE-binding

Allergen - Antibody

No Side effects
**REDUCED REACTIVITY** with IgE of LAIS demonstrated *in-vitro* (comparison between native and modified grass extract by EAST-inhibition)
REDUCED REACTIVITY with IgE of LAIS demonstrated in-vivo

(comparison between native and modified grass extract by SPT)
Tolerability from literature

SLIT with Traditional allergens

Incidence of side effects:
- Local: 40-70%
- Systemic: <5%

SLIT with LAIS®

Incidence of side effects:
- Local: sporadic
- Systemic: sporadic

No serious events ever reported
Safety of SLIT with monomeric allergoid LAIS® in adults: multicenter post-marketing surveillance study

C.Lombardi et al. 2001

198 patients
32800 doses
Follow-up: 3 years
Pollen, mites LAIS®

Percentage of Adverse Events: <7.5%
(17 episodes – 15 mild, 2 moderate)
Safety of SLIT with a monomeric carbamylated allergoid in very young children

F. Agostinis et al. 2005

33 children
Follow-up: 2 years
Mite (19), grass (17) LAIS®
Aqueous LAIS® drops - Oral intake
Parents’s diary card for 22.2 months follow-up

Adverse events: 5% of patients
(0.071 per 1000 doses)

Age range: 1.5 - 3.5 y
1 case of stomach upset in 105 patients (0.9%)

Table I

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Dose of monomeric allergoid in orosoluble tablets (AU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
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<tr>
<td>10</td>
<td>600</td>
</tr>
<tr>
<td>15</td>
<td>1,000</td>
</tr>
<tr>
<td>20</td>
<td>2,000</td>
</tr>
</tbody>
</table>

AU: allergenic units.

Data are expressed as mean ± SD unless otherwise indicated.

Gammeri. Allergologia et Immunopathologia 2005

Safety and tolerability of ultra-rush regimen and high dose
Carbamylated monomeric allergoid has:

1) SAFETY 🟢
Consequences of chemical modification

1. **PRESERVATION** of molecular sizes
   - monomericity -

2. Dramatic **REDUCTION** of specific IgE linking
   - reduced allergenicity -

3. **NO** alteration of T-epitopes
   - preserved immunogenicity -

4. **RESISTENCE** to enzymatic degradation
   - high bioavailability -
The WAO SLIT position paper 2009

1) increased IL-10 cytokine

2) reduced lymphocytes proliferative capacity after specific stimulation

3) No early IgE peak
EARLY CYTOKINE MODULATION AFTER THE RAPID INDUCTION PHASE OF SUBLINGUAL IMMUNOTHERAPY WITH MITE MONOMERIC ALLERGOLDS

M. DI GIOACCHINO, A. PERRONE, C. PETRARCA, F. DI CLAUDIO, G. MISTRELLO¹, P. FALAGIANI¹, V. DADORANTE², N. Verna, M. BRAGA³, E. BALLONE⁴ and E. CAVALUCCI

IL-10 increase

98 days

16 days

enrollment

Run in
15 days

Group A

1st blood sampling

2nd blood sampling

16 days

Group B

2nd blood sampling

98 days

Der p1 induced IL-10 increase (%)

Before

After

All

Group A

Group B

* * *
F. Agostinis¹, C. Foglia¹, M.E. Bruno², P. Falagiani²

Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen

¹Pediatric Division, Ospedali Riuniti, Bergamo; ²Scientific Direction, Lofarma S.p.A., Milano

- prospective, open-label, randomized study
- 1000 AU five times a week **without any** up-dosing Vs pharmacotherapy
- pre/co-seasonally for 12 weeks/year for 2 consecutive years.
- 40 allergic children (16 with rhinitis and 24 with rhinitis and asthma)
- range 4-16 years

**no systemic, no local adverse events**
Carbamylated monomeric allergoid: doses & schedule

Grass: Holcus lanatus, Phleum pratense, Poa pratensis
Pellitory: Parietaria judaica, Parietaria officinalis
Ragweed: Ambrosia artemisiifolia
Olive: Olea europea
Birch: Alnus incana, Betula pendula
Mugwort: Artemisia vulgaris
Cat: Felis domesticus
Mites: Dermatophagoides p, Der f

Dosages
300-1,000 Allergenic Units (AU)/tablet.
Double-blind, placebo-controlled randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allergen</th>
<th>Group</th>
<th>Duration</th>
<th>Results</th>
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<tr>
<td>Passalacqua 1998</td>
<td>Mites</td>
<td>adults</td>
<td>2 years</td>
<td>↓ symptoms/EOS/ICAM1</td>
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<tr>
<td>Caffarelli 2000</td>
<td>Grass</td>
<td>kids</td>
<td>1 season</td>
<td>↓ symptoms/drugs</td>
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<tr>
<td>Passalacqua 2006</td>
<td>Mites</td>
<td>adults</td>
<td>3 years</td>
<td>↓ symptoms/drugs</td>
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<tr>
<td>Palma-Carlos 2006</td>
<td>Grass</td>
<td>adults</td>
<td>2 years</td>
<td>↓ symptoms/drugs</td>
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<tr>
<td>Ariano 1998</td>
<td>Pellitory</td>
<td>adults</td>
<td>2 years</td>
<td>↓ symptoms/drugs</td>
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<tr>
<td>Mezei 1996</td>
<td>Ragweed</td>
<td>adults+kids</td>
<td>1 season</td>
<td>↓ symptoms/drugs</td>
</tr>
<tr>
<td>Bordignon 1994</td>
<td>Grass</td>
<td>adults</td>
<td>1+2 years</td>
<td>↓ symptoms/drugs</td>
</tr>
<tr>
<td>Cavagni 1996</td>
<td>Grass</td>
<td>kids</td>
<td>1+1 years</td>
<td>↓ symptoms/drugs</td>
</tr>
</tbody>
</table>

**Grass Vs placebo:**
- Difference: -34% in symptoms reduction
- Difference: -48% in medication use reduction

**Mites Vs placebo:**
- Difference: -22% in symptoms reduction
- Difference: -24% in medication use reduction

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Carbamylated monomeric allergoids as a therapeutic option for sublingual immunotherapy of dust mite- and grass pollen–induced allergic rhinoconjunctivitis: a systematic review of published trials with a meta-analysis of treatment using Lais® tablets

R. Mosges, B. Ritter, G. Kayoko, and S. Allekotte
The WAO SLIT position paper 2009

Double-blind randomized placebo-controlled trial (DB PC RCT) with TABLET

Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis

Giovanni Passalacqua, Monica Albano, Laura Fregonese, Annamaria Riccio, Caterina Pronzato, Giuseppe Sandro Mela, Giorgio Walter Canonica
Conjunctival provocation Test

Passalacqua. Lancet 1998

2 tablet 1000AU x 2 / week
Monosensitized patients
2 years of study
Original article

Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial

C. Caffarelli
Pediatric Department, Parma

DB PC RCT with tablets *in children*

44 subjects with asthma/rhinitis/conjunctivitis

Pre-seasonal grass pollen tablet (3 months)
Symptoms + medications

Caffarelli. Allergy 2000
Controlled Study of Preseasonal Immunotherapy with Grass Pollen Extract in Tablets: Effect on Bronchial Hyperreactivity

Table 2. PD20 (µg) at the MCh test in the two groups at baseline and after 3 years

<table>
<thead>
<tr>
<th>Patients</th>
<th>IT group</th>
<th>Controls</th>
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<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>1</td>
<td>450</td>
<td>750</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
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<td>3</td>
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<td>19</td>
<td>1200</td>
<td>1500</td>
</tr>
<tr>
<td>20</td>
<td>750</td>
<td>950</td>
</tr>
</tbody>
</table>

Mean: 848 1188 800 958
SD: 381 454 368 488

P (t test): .01 NS

Lombardi et al. JIACI 1999
Carbamylated monomeric allergoid has:

1) SAFETY ✓

2) EFFICACY ✓
Long lasting effect


Long-Lasting Effects of Sublingual Immunotherapy for House Dust Mites in Allergic Rhinitis with Bronchial Hyperreactivity: A Long-Term (13-Year) Retrospective Study in Real Life

Maurizio Marogna, Marco Bruno, Alessandro Massolo, Paolo Falagiani

4 years 7-8 years
Sublingual immunotherapy in the context of a clinical practice improvement program in the allergological setting: results of a long-term observational study.

Marogna M, Massolo A.


<table>
<thead>
<tr>
<th>From</th>
<th>to</th>
<th>SLIT n</th>
<th>%</th>
<th>CONTROL n</th>
<th>%</th>
<th>X²</th>
<th>df</th>
<th>p value (two tailed)</th>
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<tr>
<td>RHINITIS</td>
<td>N</td>
<td>48</td>
<td>100.0</td>
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<td></td>
<td>H</td>
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<td>0.0</td>
<td>14</td>
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<td>12.000</td>
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<tr>
<td></td>
<td>A</td>
<td>0</td>
<td>0.0</td>
<td>17</td>
<td>26.6</td>
<td>15.132</td>
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<td></td>
<td>Sub-total</td>
<td>48</td>
<td>100</td>
<td>64</td>
<td>100</td>
<td>-</td>
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<tr>
<td>HYPER-REACTIVITY</td>
<td>N</td>
<td>19</td>
<td>86.4</td>
<td>23</td>
<td>45.1</td>
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<td>H</td>
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<td>9.1</td>
<td>18</td>
<td>35.3</td>
<td>5.305</td>
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<td>10</td>
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<td>1</td>
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<tr>
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<td>22</td>
<td>100</td>
<td>51</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>ASTHMA</td>
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<td>28</td>
<td>77.8</td>
<td>19</td>
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<td>16.284</td>
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<td>12</td>
<td>21.8</td>
<td>1.721</td>
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<td></td>
<td>Sub-total</td>
<td>36</td>
<td>100</td>
<td>55</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

After 36 months treatment

**The Allergic March**

- Rhinitis
- Food Allergy
- Asthma
- Eczema

Typical Age of Onset

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>n</th>
<th>New sensitisations</th>
<th>%</th>
<th>X²</th>
<th>df</th>
<th>p value (two tailed)</th>
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</thead>
<tbody>
<tr>
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<td>106</td>
<td>3</td>
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<td>47.021</td>
<td>2</td>
<td>p &lt; 0.001</td>
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<tr>
<td>CONTROL</td>
<td>170</td>
<td>64</td>
<td>37.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Carbamylated monomeric allergoid has:

1) SAFETY ✓
2) EFFICACY ✓
3) PREVENTIVE EFFECTS ✓
Consequences of chemical modification

1. **PRESERVATION**
   - of molecular sizes
   - monomericity

2. Dramatic **REDUCTION**
   - of specific IgE linking
   - reduced allergenicity

3. **NO**
   - alteration of T-epitopes
   - preserved immunogenicity

4. **RESISTENCE**
   - to enzymatic degradation
   - high bioavailability

**Chemical Structure**

-Dramatic REDUCTION of specific IgE linking - reduced allergenicity.
- NO alteration of T-epitopes - preserved immunogenicity.
- RESISTENCE to enzymatic degradation - high bioavailability.
NATIVE ALLERGEN

LYSINE:

H₂N - C - C - O
| (CH₂)₃
| H - C - NH₂
| H

utive degradation

Reduced bioavailability
High doses needed

MODIFIED ALLERGEN - LAIS®

HOMOCITRULLINE:

H₂N - C - C - O
| (CH₂)₃
| H - C - N - C - NH₂
| H

NO Enzymatic degradation

High bioavailability
Efficient dose
Increased biodistribution
Lais®: Systemic effects:

- Serum
- PBMC
- Peyer’s patches

IgE
IL4

CD4+CD25+ T reg
Monomeric allergoid: oral ingestion provides clinical effects

Absorption:
- Oromucosal
- Enteric
- Oromucosal + enteric

Prospective randomized open controlled study
HDM – monomeric allergoid (1000 AU tw/w)
87 adults with AR±AA
September–February assessment

Marogna et al. EAACI 2013
Carbamylated monomeric allergoid has:

1) SAFETY  ✓
2) EFFICACY  ✓
3) PREVENTIVE EFFECTS  ✓
4) EFFICIENCY  ✓
EFFECTIVENESS IN REAL LIFE

SAFETY

EFFICACY/ PREVENTION

EFFICIENCY

...to center the target
SUMMARY:
Carbamylated monomeric allergoid (Lais ®)

1. preserved molecular size = sublingual
2. reduced allergenic activity = well tolerated
3. retained immunological activity = effective
4. High bioavailability = high efficient dose

Milan, Italy