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

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-Allergy & Respiratory Diseasesec 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 \(\approx 40\text{-}75\%\))
- 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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Rodriguez- Perez 2008-Mexico</td>
<td>11 y-boy</td>
<td>Mites</td>
<td>unknown</td>
</tr>
<tr>
<td>De Groot 2009 - Netherland</td>
<td>13 y-boy</td>
<td>Grass</td>
<td>ALK-Abellò</td>
</tr>
<tr>
<td>De Groot 2009 - Netherland</td>
<td>27 y-woman</td>
<td>Grass</td>
<td>ALK-Abellò</td>
</tr>
<tr>
<td>Buyukozturk 2010 - Turkey</td>
<td>adult</td>
<td>Latex</td>
<td>ALK-Abellò</td>
</tr>
<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
LAIS ®
from ALLERGEN...to ALLERGOID
Lais® is a modified allergen with a specific reaction with potassium-cianate

LYSINE:

\[
\begin{align*}
&\text{H2N - C - C - OH} \\
&(\text{CH}_2)_3 \\
&\text{H - C - NH}_2 \\
&\text{H}
\end{align*}
\]

HOMOCITRULLIN:

\[
\begin{align*}
&\text{H - C - N - C - OH} \\
&\text{NH}_2
\end{align*}
\]

\[+ \text{KCNO}\]

“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**
   - 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
NATIVE ALLERGEN

LYSINE:

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

ε AMINIC GROUP

IgE-binding

Allergen – Antibody

Side effects
MODIFIED ALLERGEN - LAIS®

HOMOCITRULLINE:

\[
\begin{align*}
&\text{H} \\
&\quad \text{H2N} - \text{C} - \text{C}^{\text{(CH}_2\text{)}_3} \text{OH} \\
&\quad \text{H} - \text{C} - \text{N} - \text{C}^{\text{NH}_2} \\
&\text{H}
\end{align*}
\]

URALIDIC GROUP

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%)

Safety and tolerability of ultra-rush regimen and high dose

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**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>
</tr>
<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.

Gammeri. Allergologia et Immunopathologia 2005

---

**Demographic characteristics of subjects**

<table>
<thead>
<tr>
<th></th>
<th>Asthma intermittent/mild persistent</th>
<th>Rhinitis intermittent/persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children (n = 10)</td>
<td>Adults (n = 31)</td>
</tr>
<tr>
<td></td>
<td>Children (n = 18)</td>
<td>Adults (n = 46)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/1</td>
<td>17/14</td>
</tr>
<tr>
<td></td>
<td>11/17</td>
<td>13/22</td>
</tr>
<tr>
<td>Age (± SDI)</td>
<td>12 ± 0</td>
<td>34.1 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>13.1 ± 2.1</td>
<td>35.07 ± 11.1</td>
</tr>
<tr>
<td>HDM positive</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Parietaria positive</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Grass positive</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD unless otherwise indicated.
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 ALLERGOIDS

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

IL-10 increase

<table>
<thead>
<tr>
<th>Days</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>**</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>*</td>
<td>-</td>
</tr>
</tbody>
</table>

enrollment

Run in
15 days
1st blood sampling
2nd blood sampling

2nd blood sampling

Der p1 induced IL-10 increase (%)
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.

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

### Systematic Review

**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

*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
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

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

Passalacqua. Lancet 1998
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
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>450</td>
<td>750</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>1200</td>
</tr>
<tr>
<td>3</td>
<td>750</td>
<td>900</td>
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<tr>
<td>4</td>
<td>1200</td>
<td>1800</td>
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<td>5</td>
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<td>12</td>
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<tr>
<td>Mean</td>
<td>848</td>
<td>1188</td>
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<tr>
<td>SD</td>
<td>381</td>
<td>454</td>
</tr>
<tr>
<td>P (t test)</td>
<td>.01</td>
<td></td>
</tr>
</tbody>
</table>
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
Prevention asthma & new sensitizations

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.


After 36 months treatment
Carbamylated monomeric allergoid has:

1) SAFETY ✔

2) EFFICACY ✔

3) PREVENTIVE EFFECTS ✔
Consequences of chemical modification

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

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

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

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

**LYSINE:**

\[
\begin{align*}
\text{H} & \quad \text{(CH}_2\text{)}_3 \\
\text{H}_2\text{N} & \quad \text{C} & \quad \text{C} & \quad \text{O} \\
\text{OH} & \quad \text{H} & \quad \text{C} & \quad \text{NH}_2 \\
\text{H} & \quad \text{NH}_2
\end{align*}
\]

**E AMINIC GROUP**

**Reduced bioavailability**
**High doses needed**

Enzymatic degradation

**MODIFIED ALLERGEN - LAIS®**

**HOMOCITRULLINE:**

\[
\begin{align*}
\text{H} & \quad \text{(CH}_2\text{)}_3 \\
\text{H}_2\text{N} & \quad \text{C} & \quad \text{C} & \quad \text{O} \\
\text{OH} & \quad \text{H} & \quad \text{C} & \quad \text{N} & \quad \text{C} & \quad \text{NH}_2 \\
\text{H} & \quad \text{NH}_2
\end{align*}
\]

**UREIDIC GROUP**

**NO Enzymatic degradation**

**High bioavailability**
**Efficient dose**

**PROTEIN**

**PROTEASES**
Increased biodistribution

Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers.

Bagnasco M, Passalacqua G, Villa G, Augeri C, Flamigni G, Borini E, Falagiani P, Mistrello G, Canonica GW, Mariani G. Allergy and Clinical Immunology, Department of Internal Medicine, Genoa, Italy.

Lais®: Systemic effects:

- Serum
- PBMC
- Peyer’s patches
- CD4+CD25+ T reg
- IgE
- IL4
Monomeric allergoid: oral ingestion provides clinical effects

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

Absorption:

Oromucosal
Enteric
Oromucosal + enteric

Marogna et al. EAACI 2013
Biologically active dose
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