Face to Face on LAIS®
Mechanism of action and clinical experiences

Mario di Gioacchino
Dept. of Medicine and Ageing Science
University of Chieti, Italy

Enrico Compalati
Allergy & Respiratory Disease Clinic
University of Genoa, Italy
Frequently Asked Questions

- Why using an allergoid?
- Does Lais® contain all relevant allergens?
- Which patients are candidate to Lais®?
- Special precautions?
- Which is the better intake modality?
- Suggested administration schedule?
- Maintenance posology?
- How to manage the rare side effects?
- How long treating patients?
What is LAIS®

- the only existing allergoid for SLIT

- a chemically modified extract resulting in a substitution of ε-aminogroups of allergen lysine residues
“Carbamylation”

LYSINE: 

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

\[\varepsilon\text{ AMINIC GROUP}\]

HOMOCITRULLINE: 

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

\[\text{UREIDIC GROUP}\]

\[+ \text{ KCNO} \]
Carbamylated MONOMERIC allergoid

monomeric ~40 kDa
Why using an allergoid?
SLIT safety

SLIT with traditional native-allergen extracts

- Very few systemic serious reactions reported (0.26%)
- Most reaction mild and localized in the oral mucosa or gastrointestinal tract (incidence ≈40-75%)
- Eleven cases of anaphylaxes described

Cox LS et al. JACI 2006
Radulovic S et al. Allergy 2011
Ibañez MD et al. Pediatr Allergy Immunol 2007
Sublingual Immunotherapy: World Allergy Organization Position Paper 2013 Update

Chapter 12. ADHERENCE

➢ Tolerability plays a pivotal role

➢ Adverse events: 1/4 of all dropouts in clinical trials even more in real-life setting

➢ Severity, persistence of local reactions may increase the risk of treatment discontinuation
**NATIVE ALLERGEN**

**LYSINE:**

\[
\text{H}_2\text{N} - \text{C} - \text{C} \quad \text{O}
\]

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

\[
\text{H} - \text{C} - \text{NH}_2
\]

\[
\text{H}
\]

\[
\text{E AMINIC GROUP}
\]

**MODIFIED ALLERGEN**

**HOMOCITRULLINE:**

\[
\text{H}_2\text{N} - \text{C} - \text{C} \quad \text{O}
\]

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

\[
\text{H} - \text{C} - \text{N} - \text{C} \quad \text{NH}_2
\]

\[
\text{H}
\]

\[
\text{UREIDIC GROUP}
\]

**Allergen – Antibody**

**IgE-binding**

**Side effects**

**Allergoid – Antibody**

**Low IgE-binding**

**Low allergenicity**

**Very few side effects**
Immunoblotting profile of mite
Native (N) and modified (M) extract

Tropomiosin
Der p 1
Der p 2
REDUCED REACTIVITY with IgE

*demonstrated in-vitro* (comparison between native and modified grass extract by EAST-inhibition)

*demonstrated in-vivo* (comparison between native and modified grass extract by SPT)

Mistrello et al. Allergy. 1996 Jan;51(1):8-15
Does the chemical modification impair the vaccine content of allergens?
Mass spectrometry + liquid chromatography

Most lysine residues of the modified extracts were determined to be carbamylated.

Phleum partense, Holcus lanatus and Poa pratense

 Detected allergens after modification

Phl p1-2-4-5-6-7-11-12-13
Hol l1-5
Poa p1-5

mix mite

Der f 1-2-3-7-10-11-14-18
Der p 1-2-3-7-9-10-11
The link between an allergen and IgE or IgG receptors on DC can induce different effects:

- IgE > induction of inflammation/tolerance
- IgG > preferential induction of tolerance
Reduced allergenic activity

Dramatic reduction of specific IgE linking

Increased Safety
Safety of SLIT with monomeric allergoid LAIS® in adults: multicenter post-marketing surveillance study

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>EPISODES</th>
<th>% OF PATIENTS</th>
<th>GRADE</th>
<th>TIME OF ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>1</td>
<td>0.5</td>
<td>Moderate</td>
<td>45 min</td>
</tr>
<tr>
<td>G.I. complaints</td>
<td>3</td>
<td>1.5</td>
<td>Mild</td>
<td>30-120 min</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7</td>
<td>3.5</td>
<td>Mild</td>
<td>&lt; 60 min</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3</td>
<td>1.5</td>
<td>2 mild, 1 moderate</td>
<td>&gt; 30, &lt;60 min</td>
</tr>
<tr>
<td>Oral itching</td>
<td>3</td>
<td>1.5</td>
<td>Mild</td>
<td>&lt; 30 min</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>17</strong></td>
<td><strong>7.5</strong></td>
<td><strong>15 mild, 2 moderate</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

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

Percentage of Adverse Events: <7.5%

Increased immunogenic activity

Enhanced effective dose

Increase of specific IgG linking

Increased immunogenic activity
Comparison between two different SLIT doses with carbamylated allergoid

I° YEAR
- Group A: 20 patients
- Group B: 50 patients

II° YEAR
- Group C: 25 patients of Group B
- Group D: 25 patients of Group B
Comparison between two different SLIT doses with carbamylated allergoid

1° year: clinical evaluations

Di Gioacchino et al, 2012
Comparison between two different SLIT doses with carbamylated allergoid

After one year, no significant differences in cytokine release by PBMCs were found between the group treated with High versus low doses.
No significant differences between the two groups (B-high/B-low doses), considering:

- VAS
- Drugs as needed
- Changes in severity of the disease (ARIA)
- Side effects
Baseline v/s 2° year: Immunological parameters

- IFN - 3000/3000: p=0.01
- IL4 - 3000/3000: p=0.04
- IFN - 3000/1000: p=0.002
- IL4 - 3000/1000: p=0.001

(before and after comparison)
Immune system modulation during SIT

Modified from:
Barbara Bohle, et al. JACI, 2007
M. Di Gioacchino, et al IJIP, 2010
Which patient is candidate to LAIS®?
LAIS® Indications

- **Grass extract**
  (Phleum pratense 33%, Holcus lanatus 33%, Poa Pratensis 33%)
- **Mites extract**
  (Dermatophagoides pteronissinus 50%, Dermatophagoides farinae 50%)

Asthma  Rhino-conjunctivitis
LAIS® contraindications

- lactose intolerance,
- severe systemic diseases,
- autoimmunity
- immunodeficiency,
- chronic inflammatory diseases,
- heart failure,
- neoplasia,
- viral infection,
- severe uncontrolled asthma
Special precautions

Do not started in pregnancy, but do not interrupt within

Concomitant acute illnesses (fever, flu..): interrupt up to recovery
Special precautions

Anti-infective vaccinations:
Interrupt 1 week before, restart 2 weeks after

Consider alternative drugs or benefits/risk ratio
Intake modalities

• **Sublingual-swallow** modality
  keep under the tongue for a couple of minutes on an empty stomach

• Avoid alcoholics and strong physical exercise
Swallowing
Persistence of radioactivity in the mouth

Der p 2 purified (2 hours)

Der p 2 allergoid (2 hours)


Par j 1 allergoid
Biologically active dose
Plasma kinetics of Par j 1: comparison of different preparations given sublingually (Bagnasco, Clin Exp All 2001)

Plasma kinetics of Lais allergoid tablets could be higher than the native allergen in tablets and solution.
Allergen immune response and GALT

MONOMERIC ALLERGOID INTRAGASTRIC ADMINISTRATION INDUCES LOCAL AND SYSTEMIC TOLERGENIC RESPONSE INVOLVING IL-10-PRODUCING CD4+CD25+ T REGULATORY CELLS IN MICE

C. PETRARCA1, F. LAZZARIN1, T. PANNELLINI2, M. IEZZI2, M. BRAGA3, G. MISTRELLO4, P. FALAGIANI4, L. DI GIampaolo1 and M. Di GIOACCHINO1,5


Exposure of the allergen exclusively to the GALT induces a tolerogenic response

OVA – PP – TCD4+25+IL10+

Parietaria - Spleen TCD4+25+IL10+

spontaneous and PAR-j1 driven release of IL4

not sensitized sensitized sensitized and treated

not sensitized sensitized sensitized and treated

spontaneous PAR-induced
Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-γ- and interleukin-10-production

1) increased **IL-10** cytokine

2) reduced lymphocytes proliferative capacity after specific stimulation

3) No early IgE peak

---

**Group 1**: Lais

**Group 2**: untreated controls

Before After 6 months
EARLY CYTOKINE MODULATION AFTER THE RAPID INDUCTION PHASE OF
SUBLINGUAL IMMUNOTHERAPY WITH MITE MONOMERIC ALLERGÖIDS

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

1st blood sampling

2nd blood sampling

Group A

Group B

2nd blood sampling

98 days

Graph showing IL-10 increase with time points at 98 days and 16 days.
Which is the suggested administration schedule?
## Delivery schedules

### Traditional build-up scheme:

<table>
<thead>
<tr>
<th>day</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 st</td>
<td>1 tablet 300 AU</td>
</tr>
<tr>
<td>2 nd</td>
<td>2 tablets 300 AU</td>
</tr>
<tr>
<td>3 rd</td>
<td>3 tablets 300 AU</td>
</tr>
<tr>
<td>4 th</td>
<td>4 tablets 300 AU</td>
</tr>
<tr>
<td>maintenance</td>
<td>1 tablet 1000 AU</td>
</tr>
</tbody>
</table>

### No build-up scheme:

<table>
<thead>
<tr>
<th>day</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 st</td>
<td>1 tablet 1000 AU</td>
</tr>
</tbody>
</table>
1 case of stomach upset in 105 patients (0.9%)

Safety and tolerability of ultra-rush regimen and high dose

Gammeri. Allergologia et Immunopathologia 2005
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
A double-blind, randomised, controlled dose-finding study of carbamylated monomeric allergoid tablets in patients suffering from grass pollen-induced allergic rhinoconjunctivitis

R Mösges, C Rohdenburg, A Eichel, G Zadoyan, E Compalati, K Hosseini, W Lehmacher, P Schmalz

- Multi-centre phase II study
- Double-blind, randomized
- Four different daily doses were applied pre-seasonally
- for 12 weeks
- 158 patients allergic to grass
- NO up-dosing

<table>
<thead>
<tr>
<th>daily dose (UA)</th>
<th>TEAE(s)/patient</th>
<th>number of patients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>0</td>
<td>27 (75%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>600</td>
<td>0</td>
<td>37 (86.0%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5 (11.6%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>1,000</td>
<td>0</td>
<td>34 (87.2%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>2,000</td>
<td>0</td>
<td>30 (81.1%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (8.1%)</td>
</tr>
</tbody>
</table>
How to manage side effects?
How to manage side effects

**LOCAL**

- oral itching-swelling
- stomach-ache
- nausea-vomiting

**SYSTEMIC**

- urticaria/angioedema
- rhinitis
- asthma

- anaphylaxis

---

**LOCAL**

- Rare. Usually self-resolving. If persist, reduce the dose.

**SYSTEMIC**

- Very rare. Give symptomatic treatment and reduce the dose. If persist, stop SLIT.

- NEVER reported
Home maintenance treatment?
Maintenance administration regimen

**Traditional:**

- **Perennial allergy treatment:** 1 tablet at 1000 AU/day 2 times per week.
- **Seasonal allergy treatment:** 1 tablet at 1000 AU/day 5 times per week.

**Optional:** modulated and adapted to the disease course or individualized according to doctor’s strategy.

- **All year**
- **2 months before pollen peak + 3 months during**
Supporting data from the literature...
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

Double-blind randomized placebo-controlled trial with TABLET

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

Symptoms level in two consecutive years

Passalacqua. Lancet 1998
Original article
Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites
Supporting data from the literature...
44 subjects with asthma/rhinitis/conjunctivitis
Age: 4-14 years (mean 8.5y)

Pre-seasonal (3 months before grass pollen season)
1000 AU tablet x3 /weekly
Symptoms + medications

Caffarelli. Allergy 2000
Efficacy and safety of sublingual immunotherapy with grass monomeric allergoid: comparison between two different treatment regimens

1 Allergological Department, U.O. Medicina, Presidio Ospedaliero di Faenza (RA), Italy
2 Allergy & Respiratory Diseases Clinic. Dept. Of Internal Medicine. University of Genoa - E-mail: enrico.compalati@unige.it
3 Scientific Direction, Lofarma S.p.A., Milan, Italy
A double-blind, randomised, controlled dose-finding study of carbamylated monomeric allergoid tablets in patients suffering from grass pollen-induced allergic rhinoconjunctivitis

R Mösges, C Rohdenburg, A Eichel, G Zadoyan, E Compalati, K Hosseini, W Lehmacher, P Schmalz

- Multi-centre phase II study
- Double-blind, randomized
- Four different daily doses were applied pre-seasonally
- for 12 weeks (3 months)
- 158 patients allergic to grass
- NO up-dosing

<table>
<thead>
<tr>
<th>daily dose (UA)</th>
<th>change of threshold compared to CPT V1</th>
<th>V3 number (percentage)</th>
<th>V4 number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>worse</td>
<td>2 (5.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>18 (51.4%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>15 (42.9%)</td>
<td>19 (70.4%)</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>35 (100%)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>600</td>
<td>worse</td>
<td>2 (4.8%)</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>20 (47.6%)</td>
<td>10 (28.6%)</td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>20 (47.6%)</td>
<td>22 (62.9%)</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>42 (100%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>1,000</td>
<td>worse</td>
<td>1 (2.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>18 (46.2%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>20 (51.3%)</td>
<td>23 (76.7%)</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>39 (100%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>2,000</td>
<td>worse</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>18 (51.4%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>17 (48.6%)</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>35 (100%)</td>
<td>30 (100%)</td>
</tr>
</tbody>
</table>
### Double-blind, placebo-controlled randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allergen</th>
<th>Group</th>
<th>Duration</th>
<th>Effect</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/drugs</td>
</tr>
<tr>
<td>Passalacqua 2006</td>
<td>Mites</td>
<td>adults</td>
<td>3 years</td>
<td>↓ symptoms/drugs</td>
</tr>
<tr>
<td>Palma-Carlos 2006</td>
<td>Grass</td>
<td>adults</td>
<td>2 years</td>
<td>↓ symptoms/drugs</td>
</tr>
<tr>
<td>Ariano 1998</td>
<td>Pellitory</td>
<td>adults</td>
<td>2 years</td>
<td>↓ symptoms/drugs</td>
</tr>
<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>
<tr>
<td>SMART_5 2013</td>
<td>Grass</td>
<td>adults</td>
<td>3 months</td>
<td>↓ response to NPT</td>
</tr>
<tr>
<td>SMART_1 2013</td>
<td>Birch</td>
<td>adults</td>
<td>3 months</td>
<td>↓ response to NPT</td>
</tr>
<tr>
<td>LaisAmb11 2013</td>
<td>Ragweed</td>
<td>adults</td>
<td>3 months</td>
<td>↓ response to NPT</td>
</tr>
<tr>
<td>SMART_2 2014</td>
<td>Mites</td>
<td>adults</td>
<td>3 months</td>
<td>ongoing</td>
</tr>
<tr>
<td>SMART_8 2015</td>
<td>Mites</td>
<td>adults</td>
<td>12 months</td>
<td>-</td>
</tr>
</tbody>
</table>

**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. Koyoko, and S. Allekotte

---

**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

How long should the treatment be continued?
65 patients (18-41 y) with rhinitis and BHR caused by HDM allergy:

15 pts for 1 year
10 pts for 2 years
14 pts for 3 years
14 pts for 4 years

4 years

7-8 years
Metacholine Response 6-years after interruption of allergoid-SLIT

65 patients (18-41 y) with rhinitis and BHR caused by HDM

KEY MESSAGE

Long term treatment with AIT provides long term Protection on aspecific BHR

Take home messages

- The unique sublingual allergoid
- Reduced allergenicity, high tolerability
- Enhanced tolerogenic activity
- Efficacy and long term effects
- High manageability
- For adults & children
THANK YOU
FOR YOUR ATTENTION!