

Face to Face on LAIS®

Mechanism of action and clinical experiences

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Allergy & Respiratory Disease Clinic
University of Genoa. Italy



Frequently Asked Questions

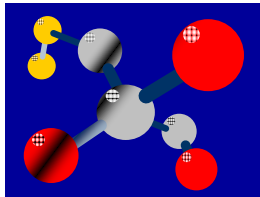
- Why using an allergoid?
- Does Lais[®] contain all relevant allergens?
- Which patients are candidate to Lais[®]?
- Special precautions?
- Which is the better intake modality?
- Suggested administration schedule?
- Maintenance posology?
- How to manage the rare side effects?
- How long treating patients?

What is LAIS®

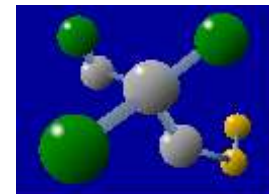
- the only existing allergoid for SLIT



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



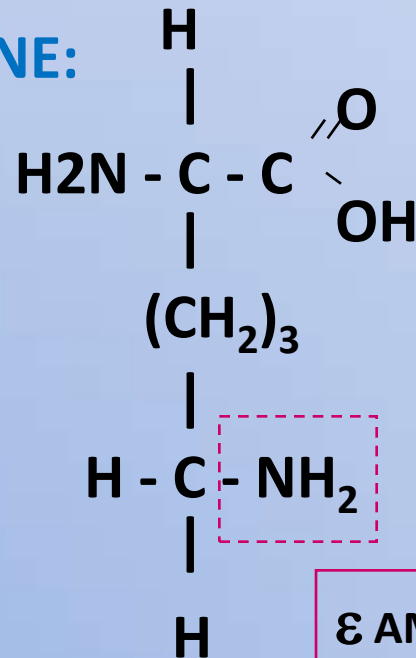
Native allergen extract



Chemically modified allergen extract

“Carbamylation”

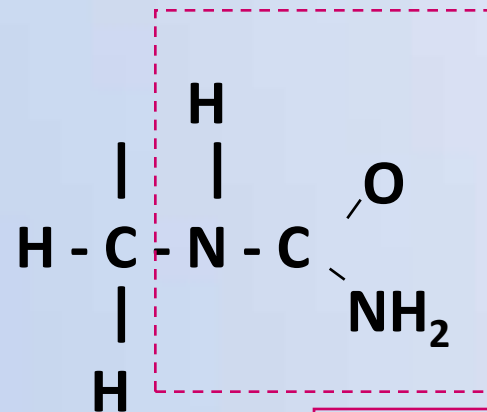
LYSINE:



ε AMINIC
GROUP

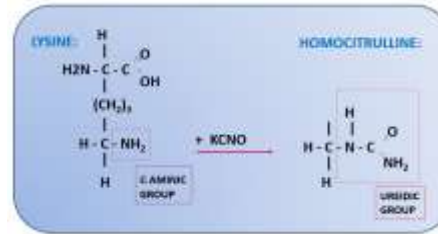


HOMOCITRULLINE:

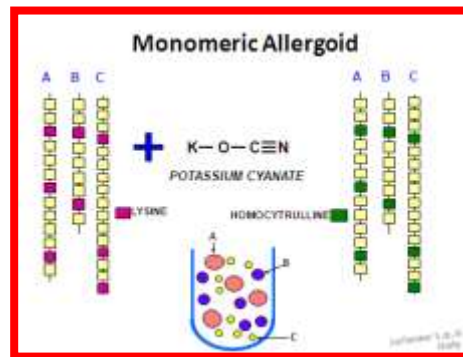


UREIDIC
GROUP

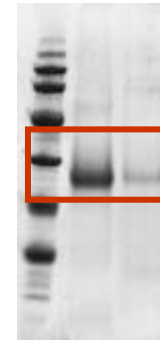
Carbamylated MONOMERIC allergoid



 monomeric ~40 kda



Der p 1
N M



available

Why using an allergoid ?

allergen



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

Passalacqua G. et al. Curr Drug Saf 2007

Ibañez MD et al. Pediatr Allergy Immunol 2007



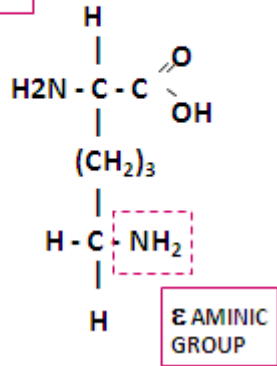
Sublingual Immunotherapy: World Allergy Organization Position Paper 2013 Update

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:



IgE-binding

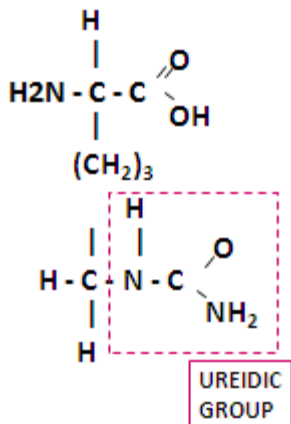
Allergen – Antibody



Side effects

MODIFIED ALLERGEN

HOMOCITRULLINE:



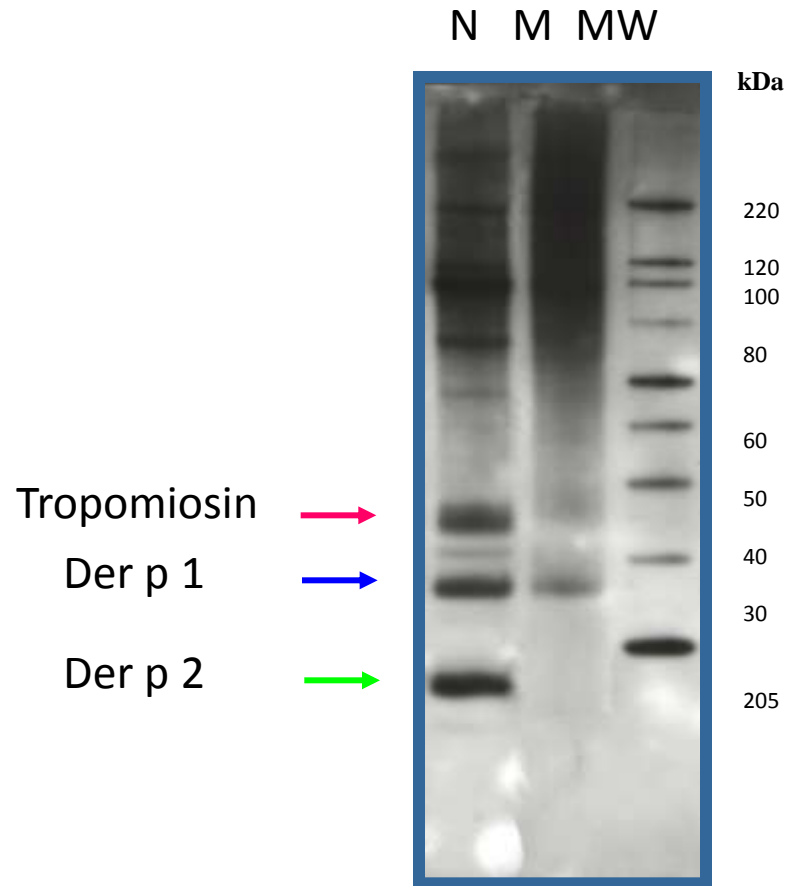
Low IgE-binding

Allergoid - Antibody



Low allergenicity
Very few side effects

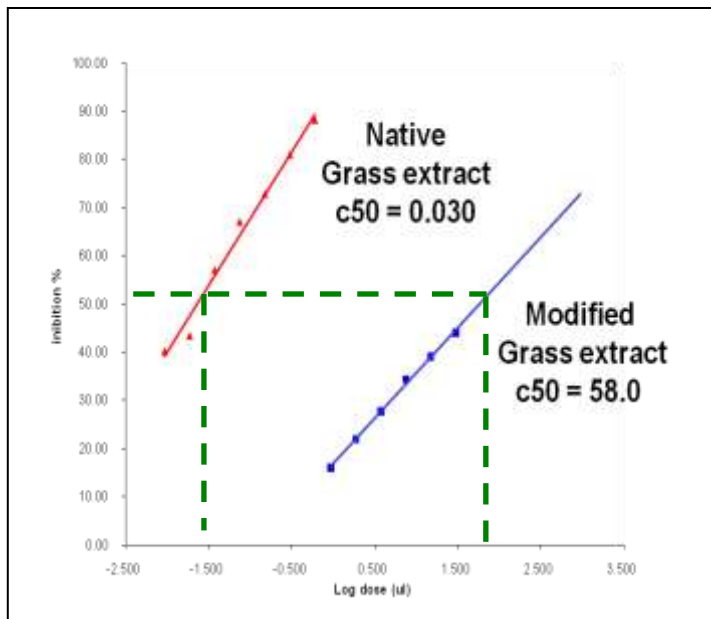
Immunoblotting profile of mite Native (N) and modified (M) extract



REDUCED REACTIVITY with IgE

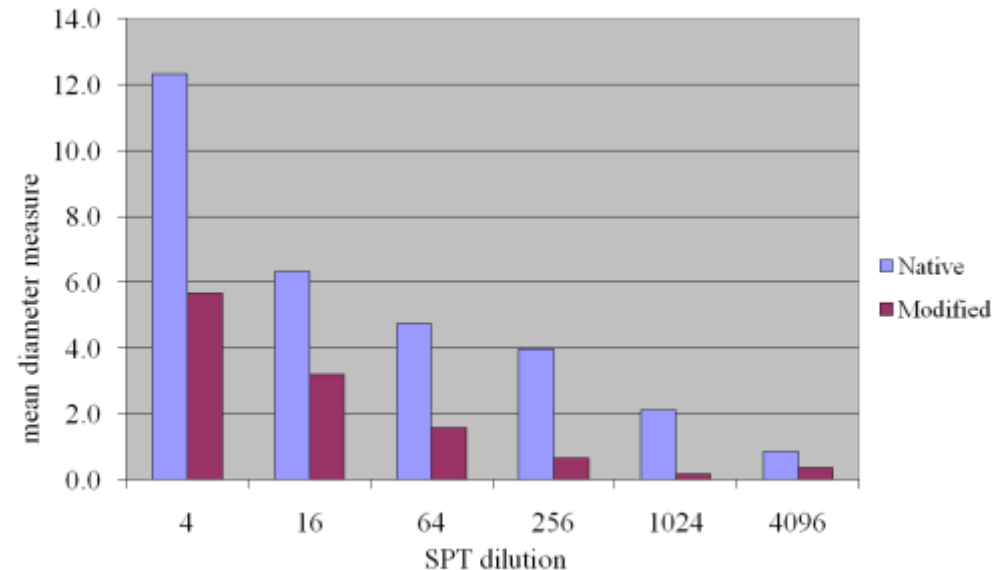
demonstrated in-vitro

(comparison between native and modified grass extract by EAST-inhibition)



demonstrated in-vivo

(comparison between native and modified grass extract by SPT)



Does the chemical modification
impair the vaccine content
of allergens ?



Allergen identification and characterisation of lysine modification in monomeric allergoids

Waschl, CC¹; Steiner, M¹; Mistrello, G²; Briza, P¹;
Ferreira-Briza, F¹; Himly, M¹

¹Molecular Biology, Paris Lodron University of Salzburg, Salzburg, Austria; ²Lofarma spa, Research and Development, Milan, Austria

Mass spectrometry
+ liquid chromatography



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



Phleum pratense,
Holcus lanatus and Poa pratense



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

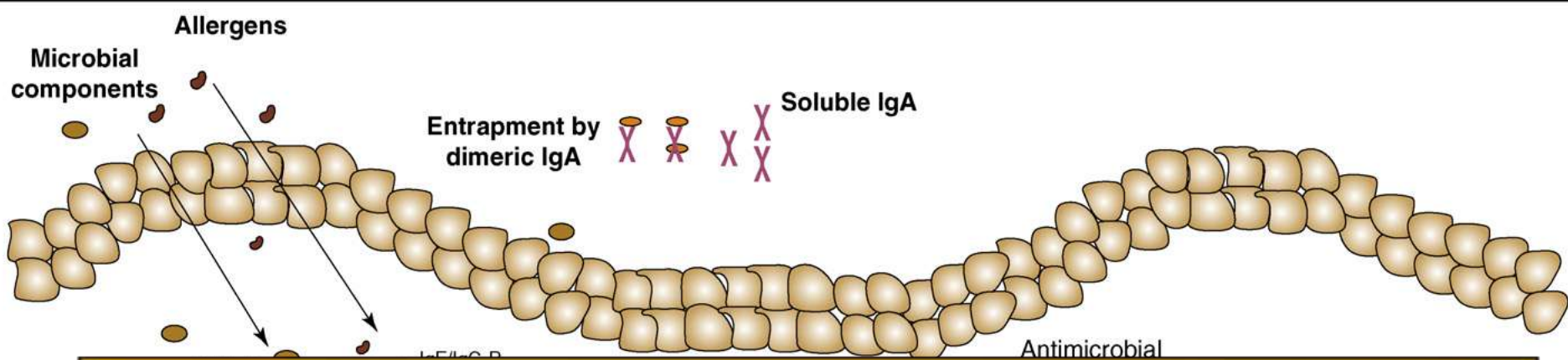


mix mite



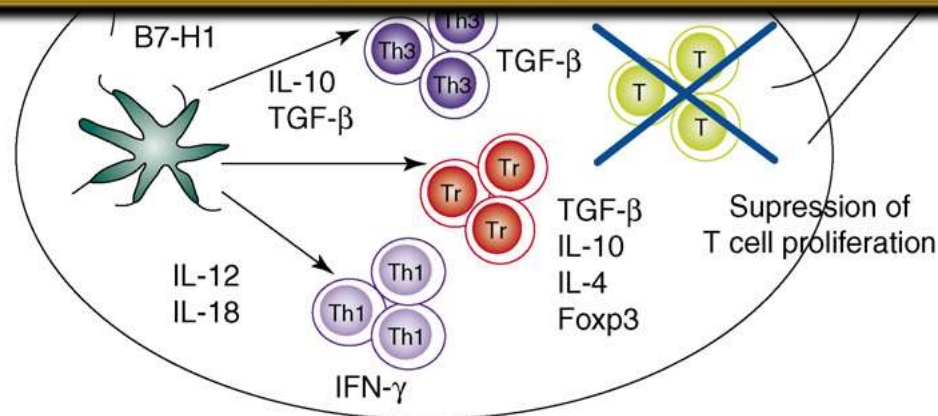
Der f 1-2-3-7-10-11-14-18
Der p 1-2-3-7-9-10-11

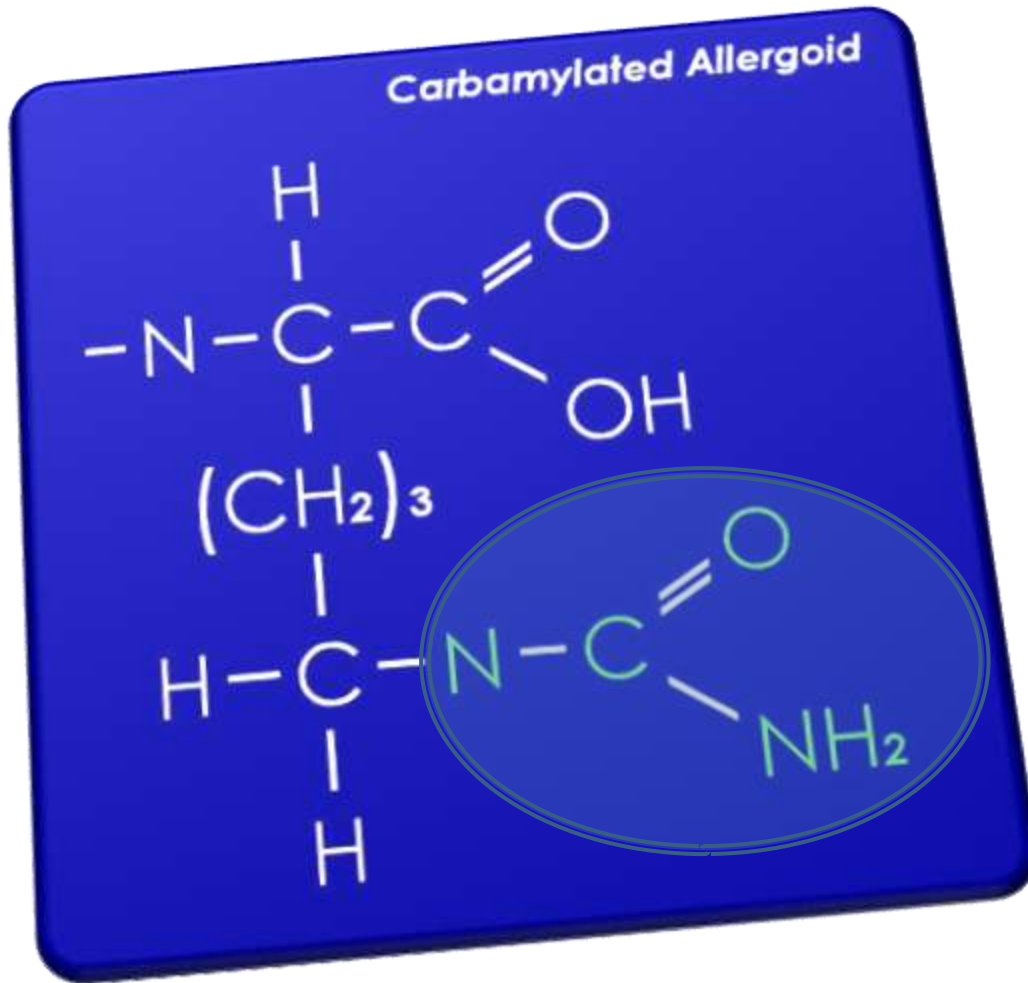
Detected allergens after modification



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





**Dramatic reduction
of specific IgE linking**



**Reduced
allergenic activity**

**Increased
Safety**

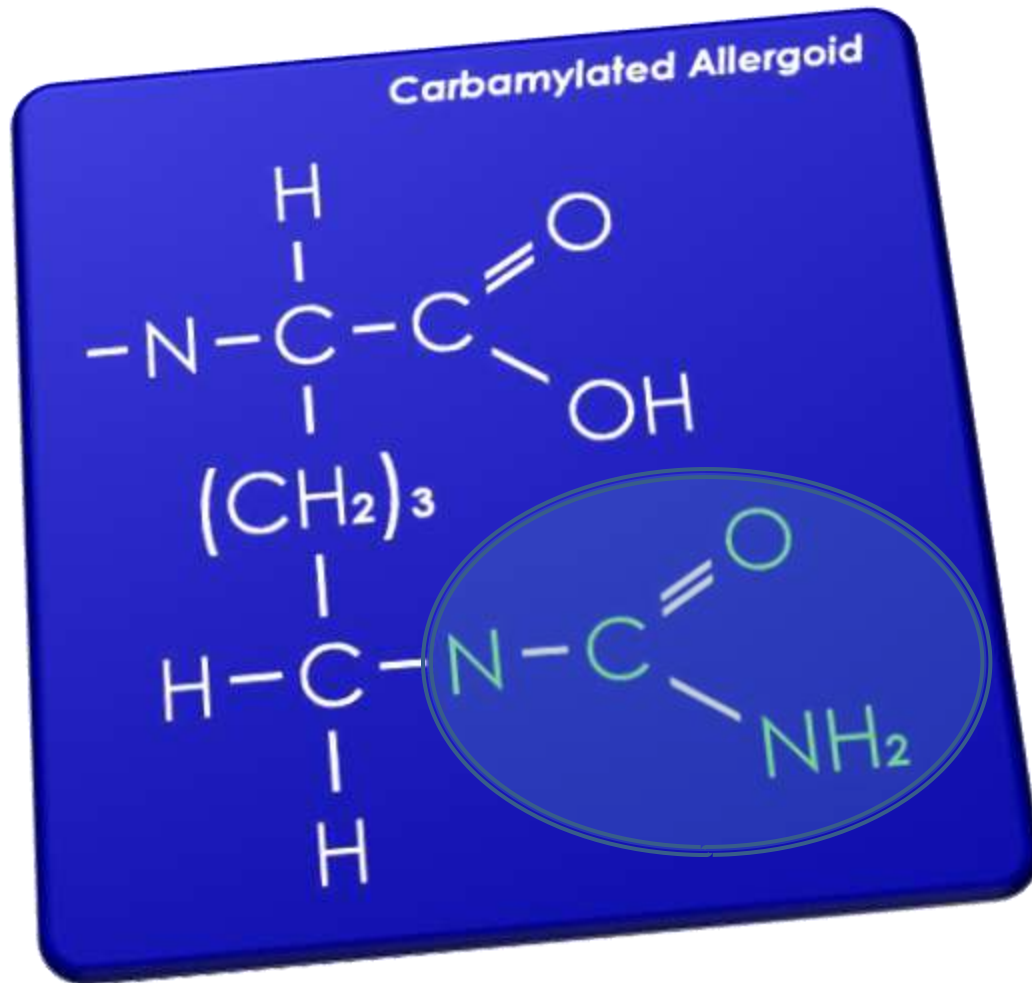
Safety of SLIT with monomeric allergoid LAIS® in adults: multicenter post-marketing surveillance study



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

SIDE EFFECT	EPISODES	% OF PATIENTS	GRADE	TIME OF ONSET
Conjunctivitis	1	0.5	Moderate	45 min
G.I. complaints	3	1.5	Mild	30-120 min
Rhinitis	7	3.5	Mild	< 60 min
Urticaria	3	1.5	2 mild 1 moderate	> 30, <60 min
Oral itching	3	1.5	Mild	< 30 min
Angioedema	0	-	-	-
Asthma	0	-	-	-
Anaphylaxis	0	-	-	-
TOTAL	17	7.5	15 mild 2 moderate	-

Percentage of Adverse Events : **<7.5%**



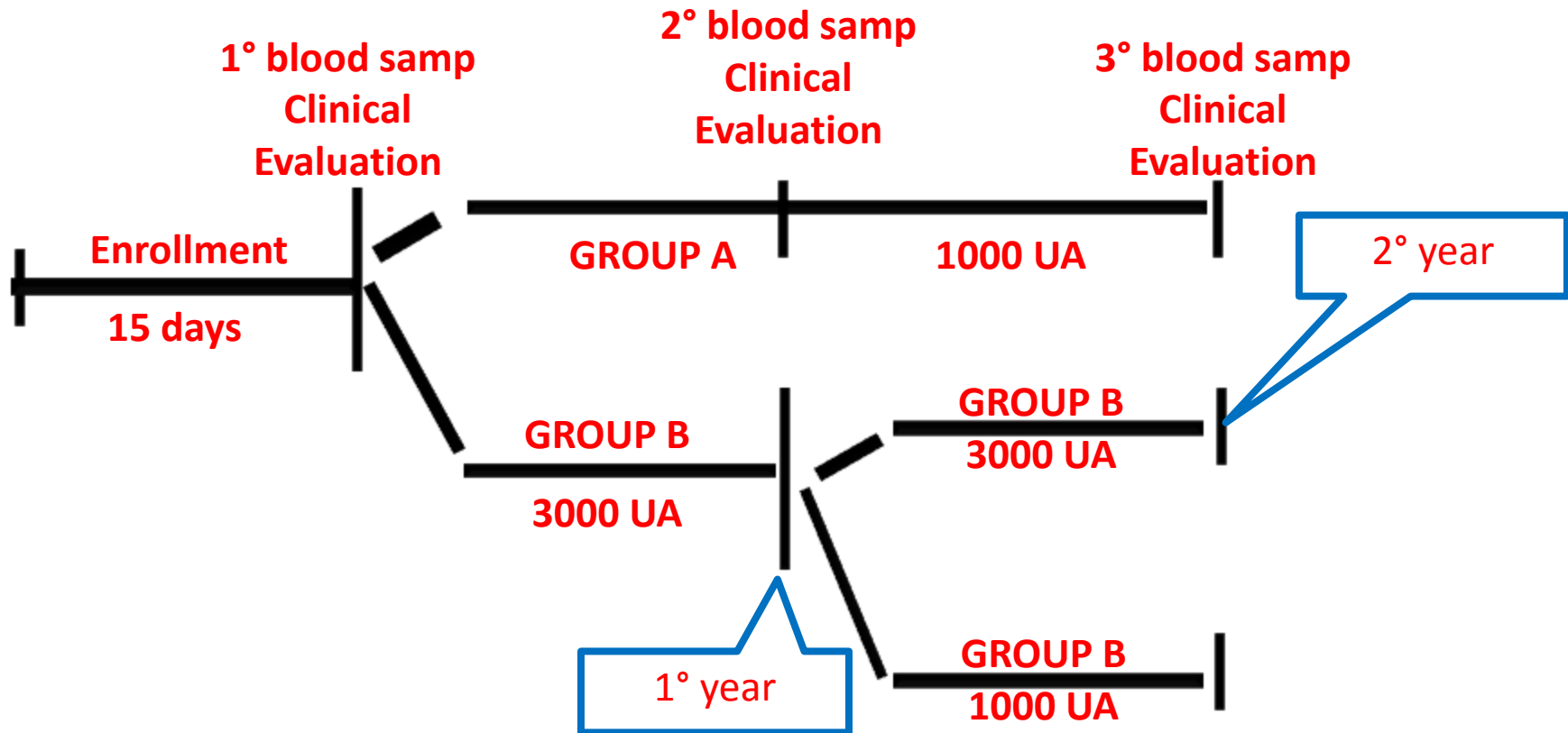
**Increase
of specific IgG linking**



**Increased
immunogenic activity**

**Enhanced effective
dose**

Comparison between two different SLIT doses with carbamylated allergoid



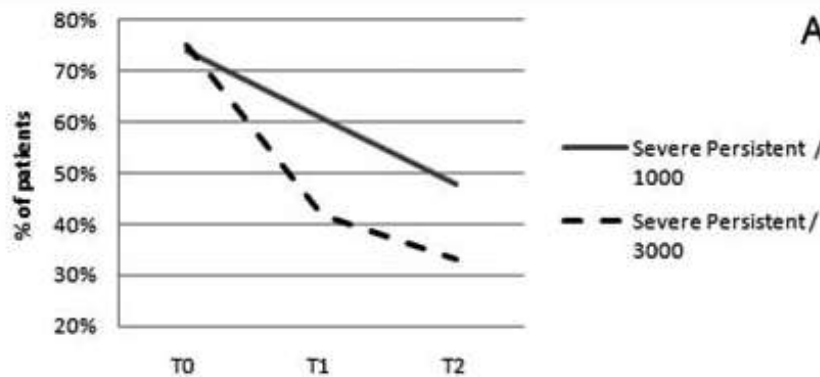
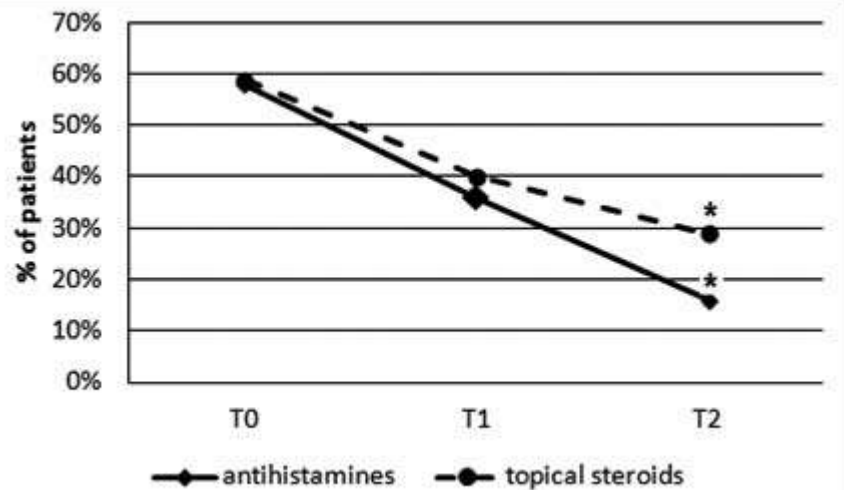
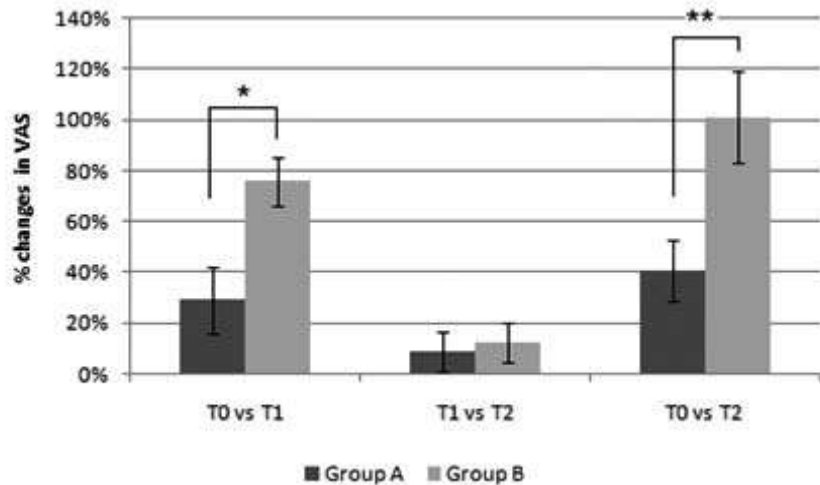
I° YEAR

- 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

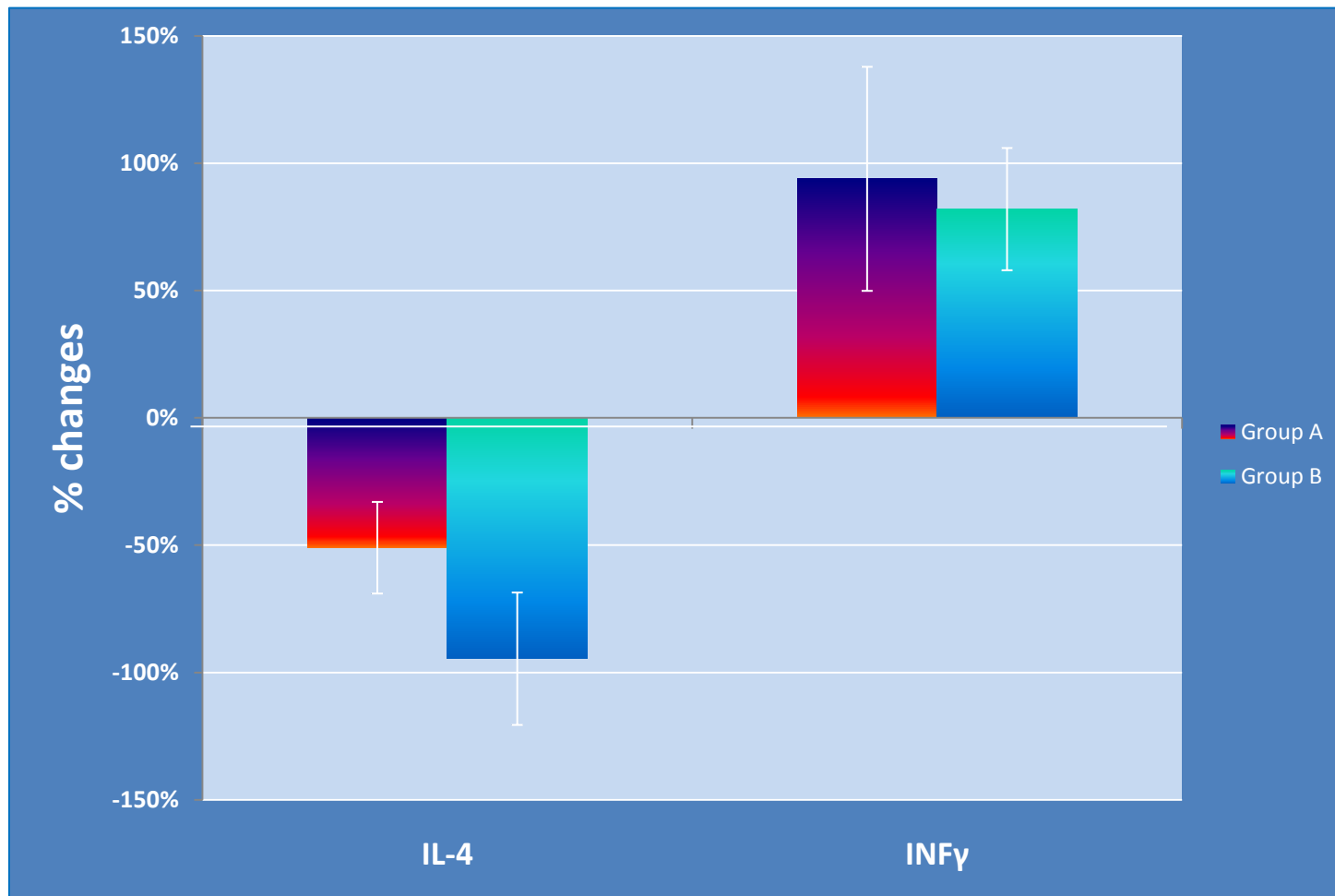


1° year: clinical evaluations

Di Gioacchino et al, 2012



Comparison between two different SLIT doses with carbamylated allergoid



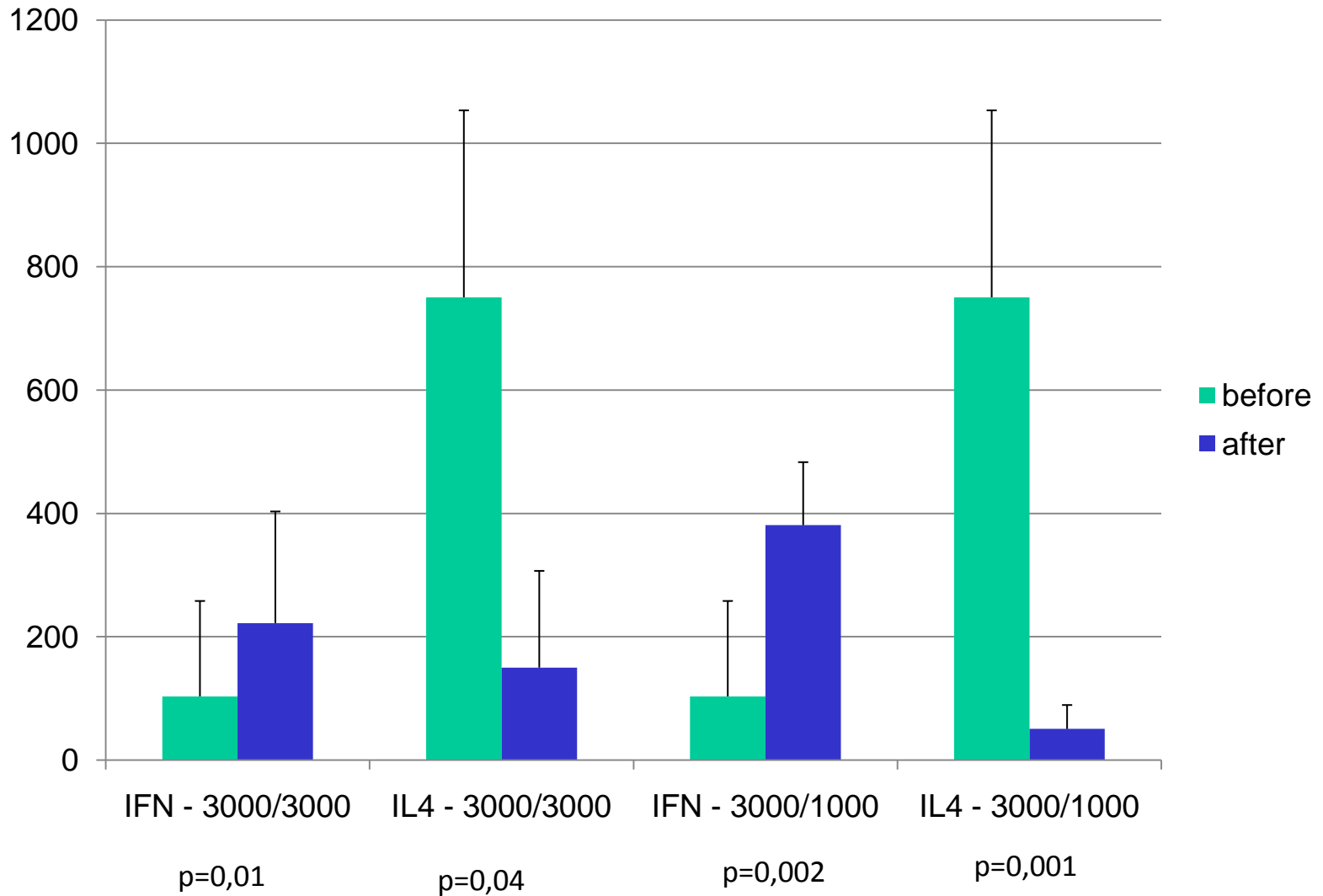
After one year, no significant differences in cytokine release by PBMCs were found between the group treated with High versus low doses

1° v/s 2° year: clinical evaluations

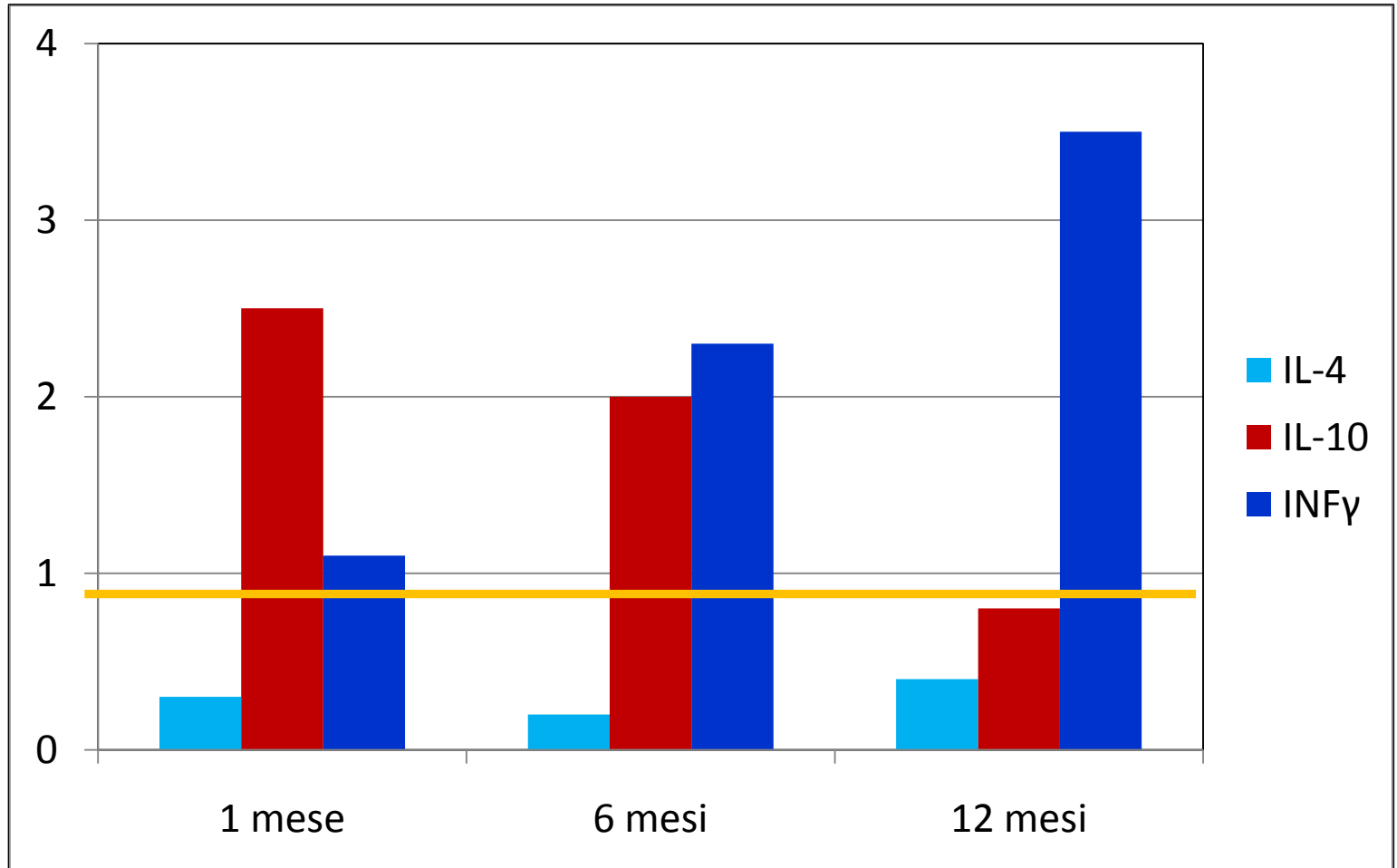
No significant differences between the two groups (B-high/B-low doses), considering:

- VAS
- Drugs as needed
- Changes in severity of the disease (ARIA)
- Side effects

Baseline v/s 2° year: Immunological parameters



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®?**



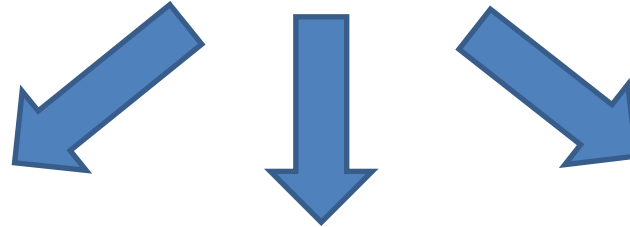
LAIS[®] Indications

- **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



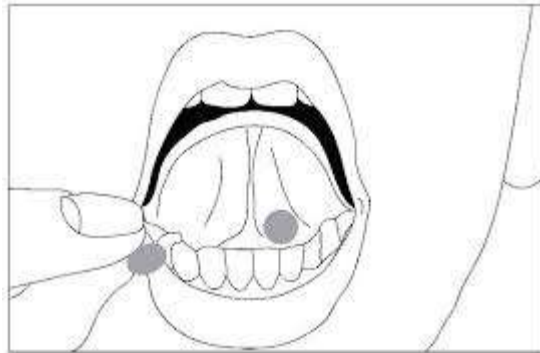
Consider alternative drugs or benefits/risk ratio



Intake modalities

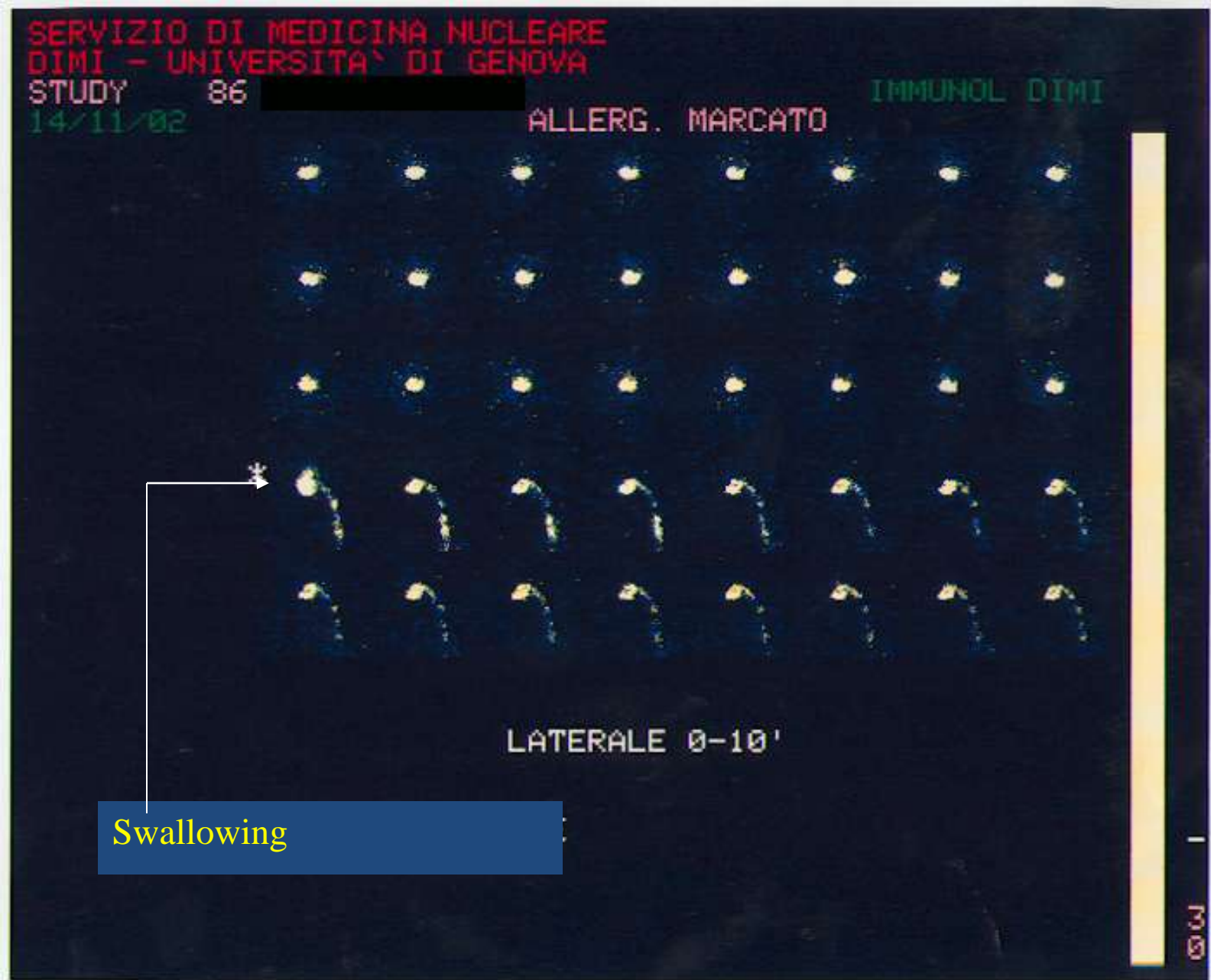
- Sublingual-swallow modality

keep under the tongue for a couple of minutes
on an empty stomach

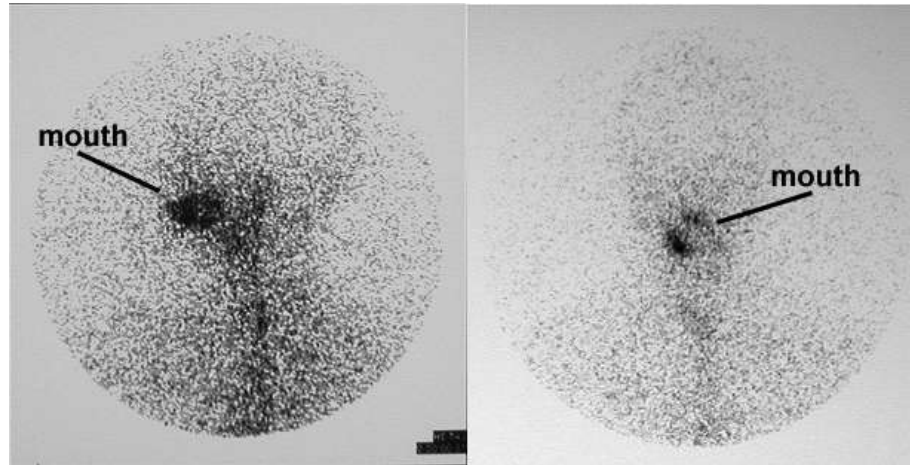


- Avoid alcoholics and strong physical exercise

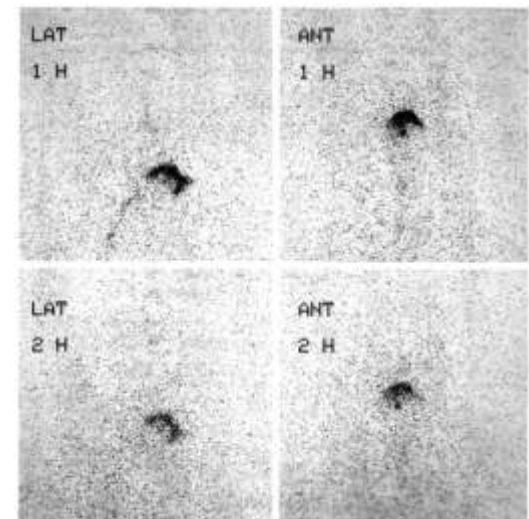




Persistence of radioactivity in the mouth

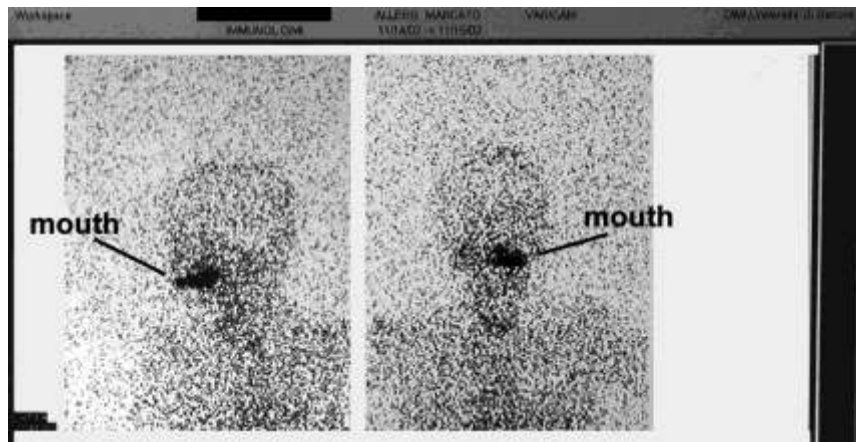


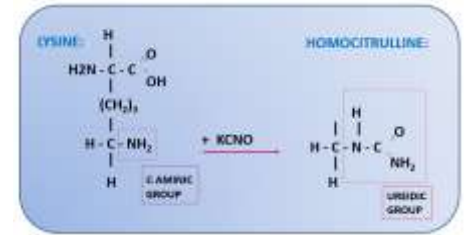
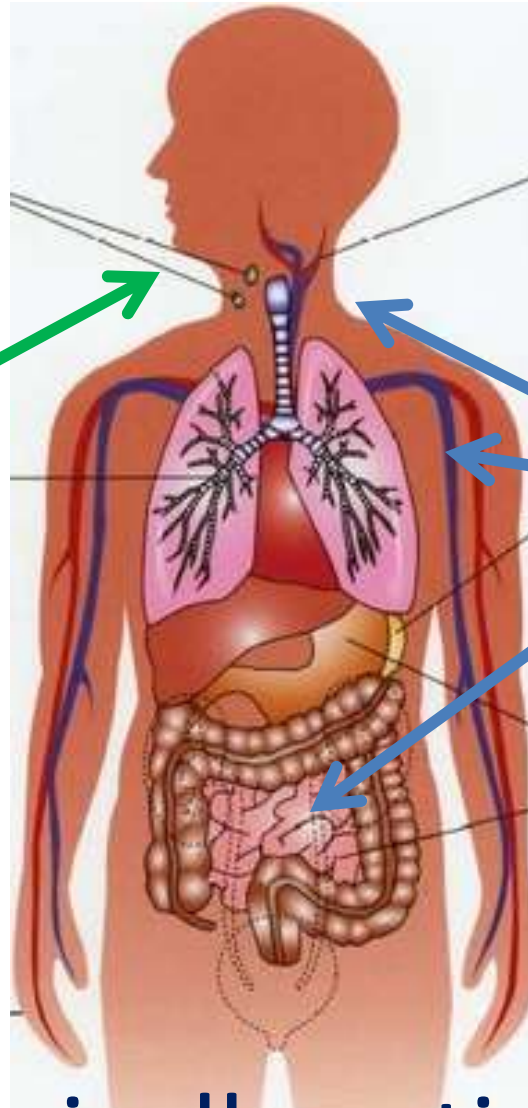
Der p 2 purified
(2 hours)



Der p 2
allergoid
(2 hours)

Par j 1 allergoid





Biologically active dose

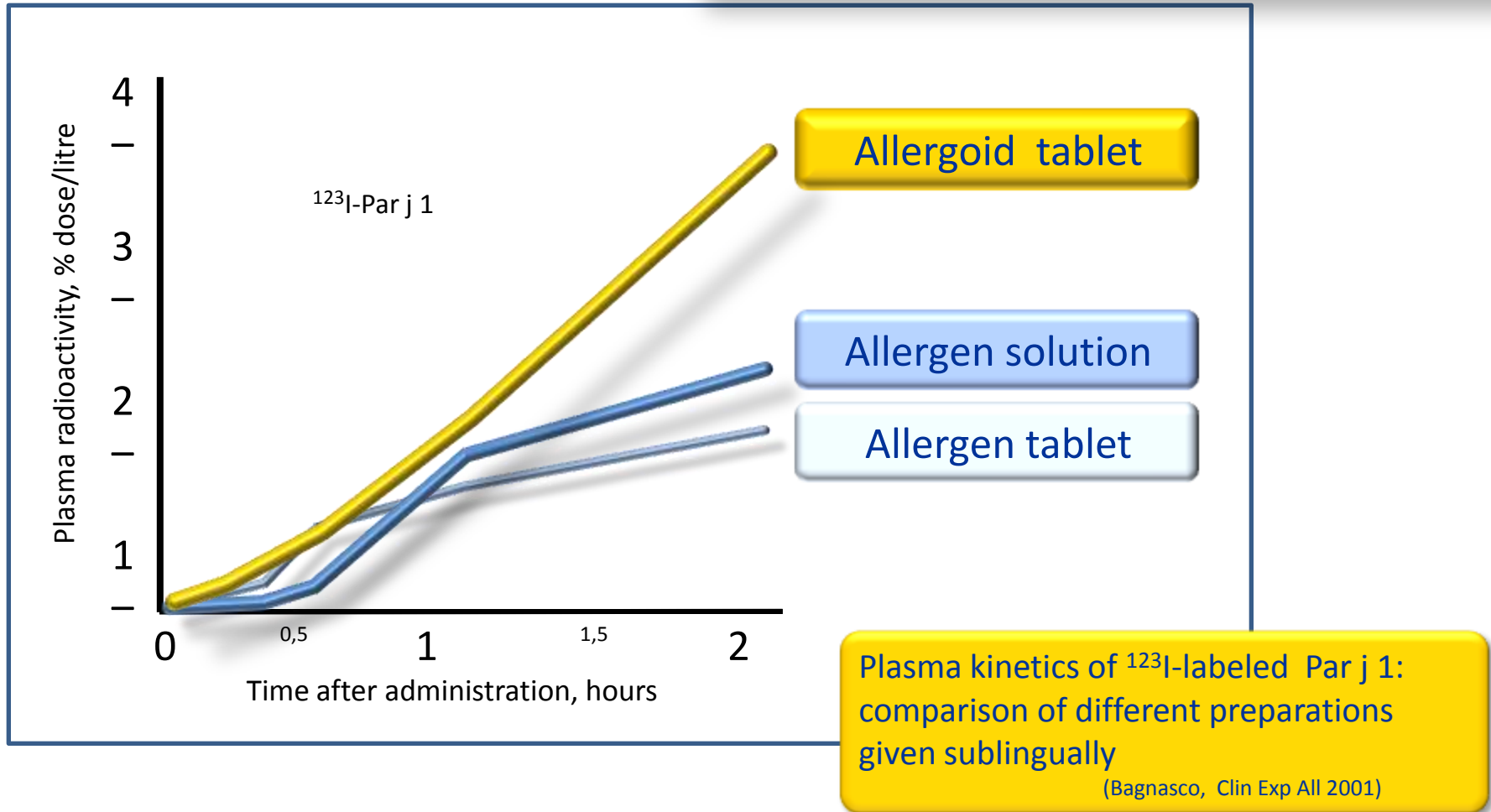
Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers.

Bagnasco M, Passalacqua G, Villa G, Augeri C, Flamigni G, Borini E, Falagiani P, Mistrello G, Canonica GW, Altrineti V, Pesce G, Caputo M, Mistrello G, Falagiani P, Canonica GW, Passalacqua G. Allergy and Clinical Immunology, Department of Internal Medicine, Genoa, Italy.
Comment in: *Clin Exp Allergy*. 2001 Jan;31(1):8-10.

Int Arch Allergy Immunol. 2005 Nov;138(3):197-202. Epub 2005 Oct 3.

Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers.

Bagnasco M, Altrineti V, Pesce G, Caputo M, Mistrello G, Falagiani P, Canonica GW, Passalacqua G. Medical and Radiometabolic Therapy, University of Genoa, Genoa, Italy.



Plasma kinetics of Lais allergoid tablets could be higher than the native allergen in tablets and solution

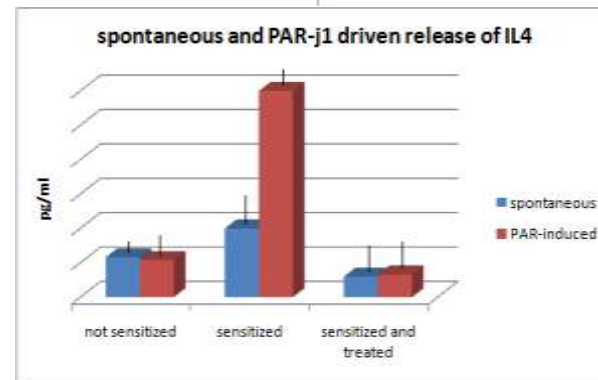
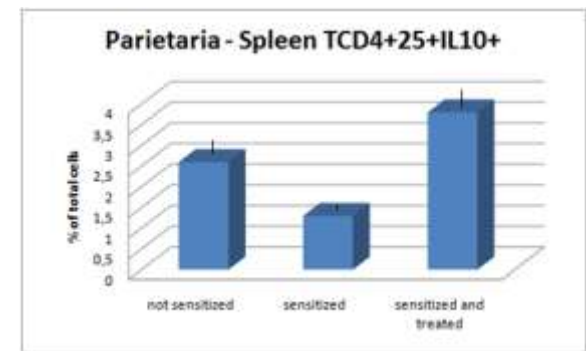
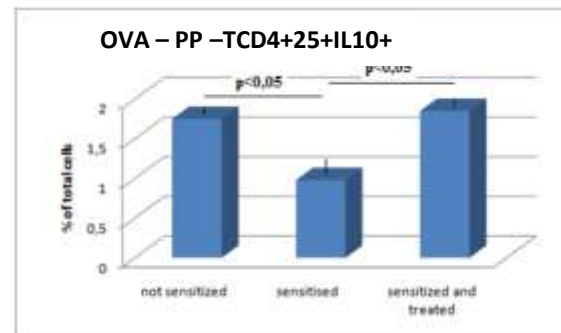
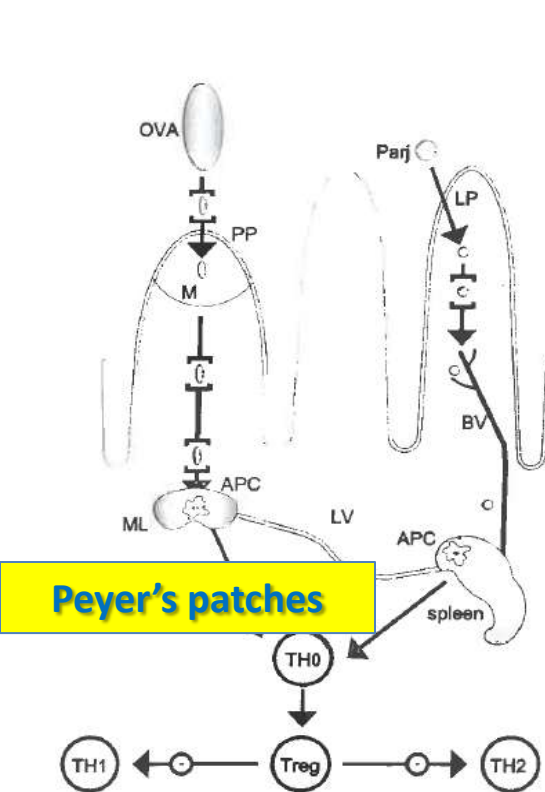
Allergen immune response and GALT

MONOMERIC ALLERGOID INTRAGAESTRIC ADMINISTRATION INDUCES LOCAL AND SYSTEMIC TOLEROGENIC 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 GIOACCHINO^{1,5}

Int J Immunopathol Pharmacol. 2010; 23 (4): 1021-1031.



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

ORIGINAL PAPER

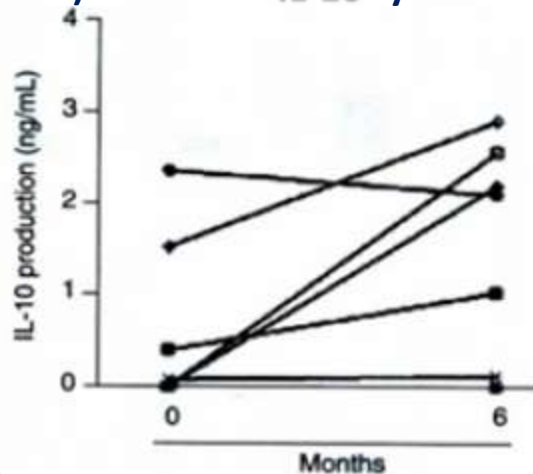
Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon- γ - and interleukin-10-production

L. Cosmi¹*, V. Santarlasci¹*, R. Angeli², F. Liotta², L. Maggi², F. Frosali², O. Rossi², P. Falagiani¹, G. Riva¹, S. Romagnani², F. Annunziato² and E. Maggi²*

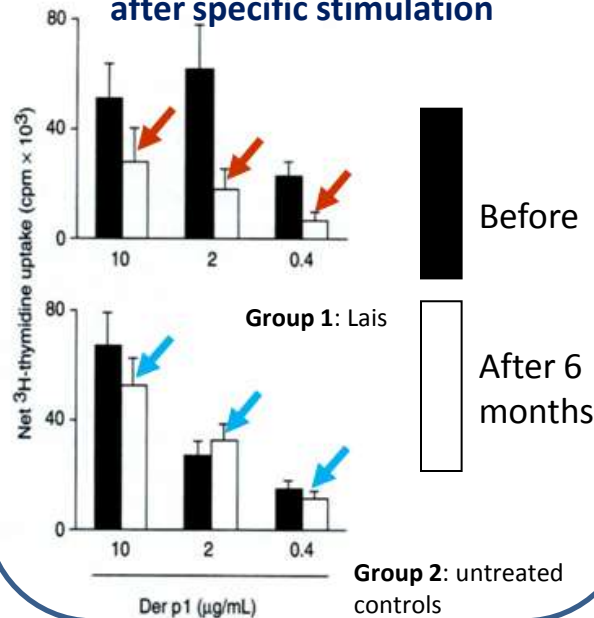
*Center of Research, Transfer, High Education 'DENOnthe', University of Florence, Firenze and ²Lofarma Allergeni, SpA, Milano, Italy



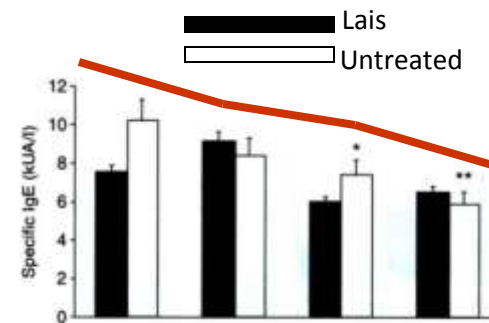
1) increased IL-10 cytokine



2) reduced lymphocytes proliferative capacity after specific stimulation

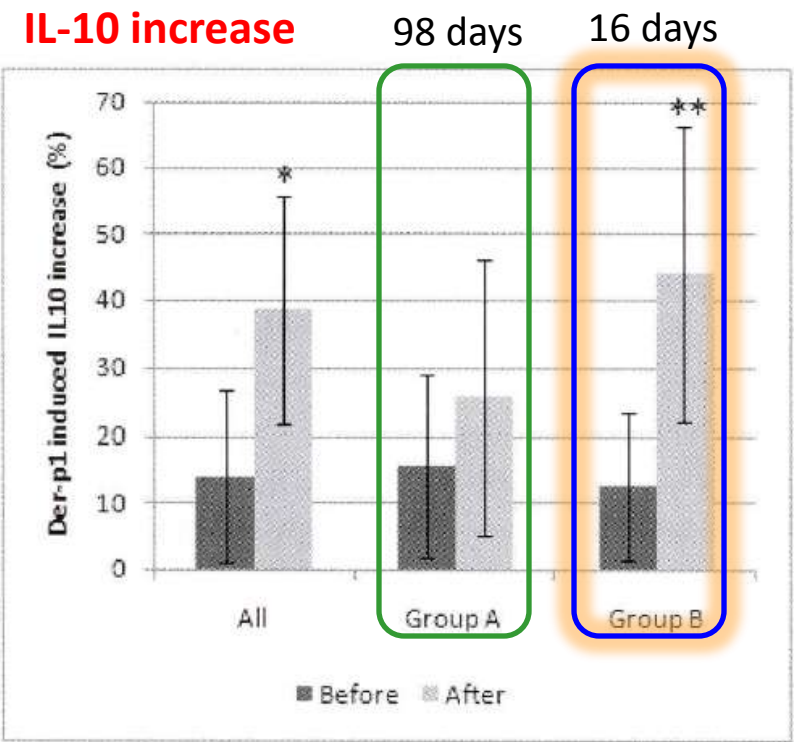
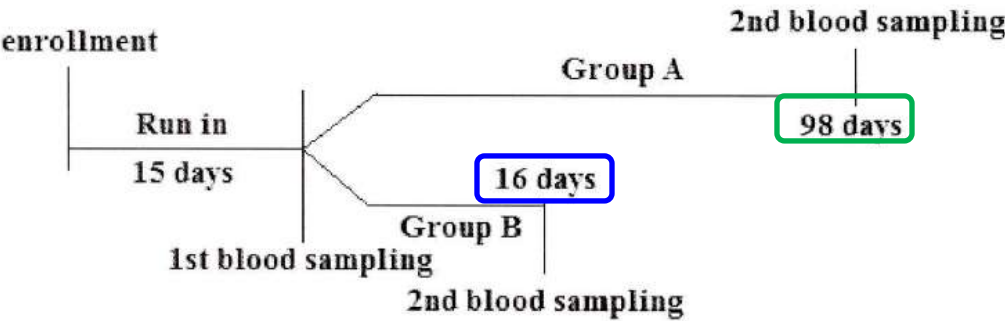


3) No early IgE peak



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



Which is the suggested
administration schedule?



Delivery schedules



Traditional build-up scheme:

day	dose	
1 st	1 tablet	300 AU
2 nd	2 tablets	300 AU
3 rd	3 tablets	300 AU
4 th	4 tablets	300 AU
maintenance	1 tablet	1000 AU

No build-up scheme:

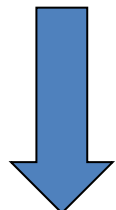
day	dose	
1 st	1 tablet	1000 AU

Table I

Immunotherapy protocol of patients treated with 4000 AU of a chemically modified allergen extract (monomeric allergoid). Tablets had to be kept under the tongue for at least two minutes before swallowing

Time (min)	Dose of monomeric allergoid in orosoluble tablets (AU)
0	100
5	300
10	600
15	1,000
20	2,000

AU: allergenic units.



Demographic characteristics of subjects

	Asthma Intermittent/mild persistent		Rhinitis Intermittent/persistent	
	Children (n = 10)	Adults (n = 31)	Children (n = 18)	Adults (n = 46)
Sex, M/F	9/1	17/14	11/7	12/34
Age (\pm SD)	12 \pm 0	34.1 \pm 7.8	13.1 \pm 2.1	35.07 \pm 11.1
HDM positive	3	23	8	22
Parietaria positive	2	7	5	20
Grass positive	5	1	5	4

Data are expressed as mean \pm SD unless otherwise indicated.

Gammeri. Allergologia et Immunopathologia 2005

1 case of stomach upset in 105 patients (0.9%)

**Safety and tolerability
of ultra-rush regimen and high dose**

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

¹ Pediatric Division, Ospedali Riuniti, Bergamo; ² Scientific 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



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

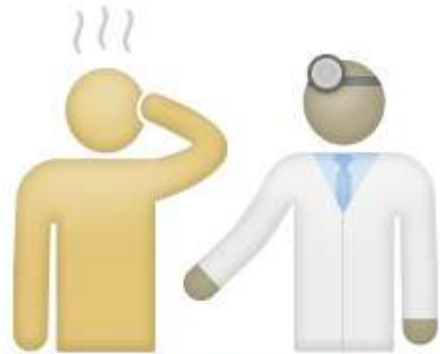
R Mösges, C Rohdenburg, A Eichel, G Zadoyan, E Compalati, K Hosseini, W Lehmacher, P Schmalz



- 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

daily dose (UA)	TEAE(s)/patient	number of patients (percentage)
300	0	27 (75%)
	1	5 (13.9%)
	2	3 (8.3%)
	3	1 (2.8%)
600	0	37 (86.0%)
	1	5 (11.6%)
	2	1 (2.3%)
1,000	0	34 (87.2%)
	1	4 (10.3%)
	3	1 (2.6%)
2,000	0	30 (81.1%)
	1	4 (10.8%)
	2	3 (8.1%)

How to manage side effects ?



**DON'T LET SEVERE SIDE EFFECTS TAKE OVER
YOUR TREATMENT PLAN. REPORT THE SIDE
EFFECTS TO YOUR HEALTHCARE PROVIDER
IMMEDIATELY.**

How to manage side effects

LOCAL

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

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

SYSTEMIC

- urticaria/angioedema
- rhinitis
- asthma

- anaphylaxis

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

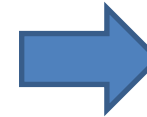
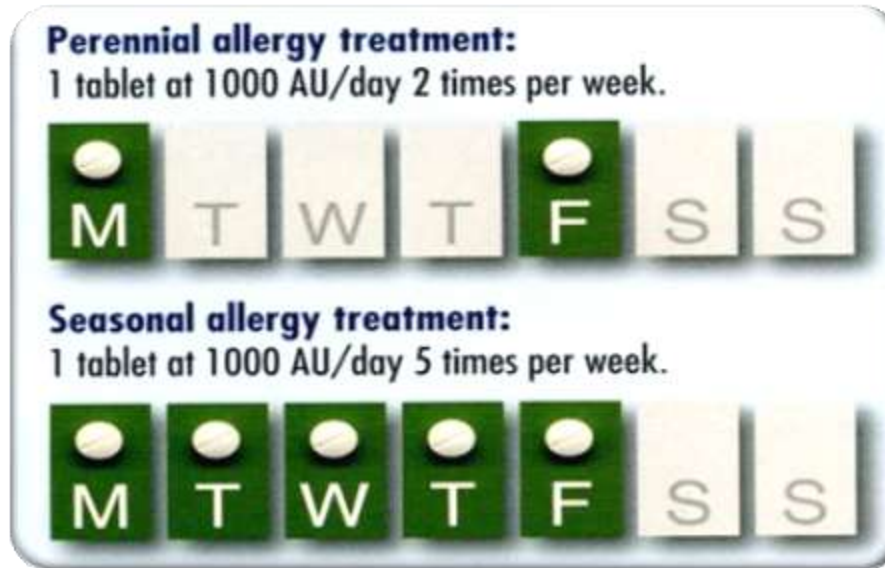
NEVER reported

Home maintenance treatment?

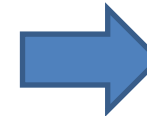


Maintenance administration regimen

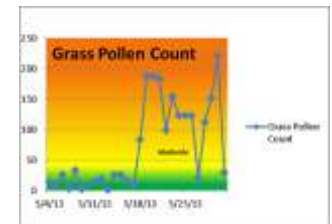
Traditional:



All year



2 months before
pollen peak +
3 months during



Optional:

modulated and adapted to the disease course or individualized according to doctor's strategy



Supporting data from the literature...



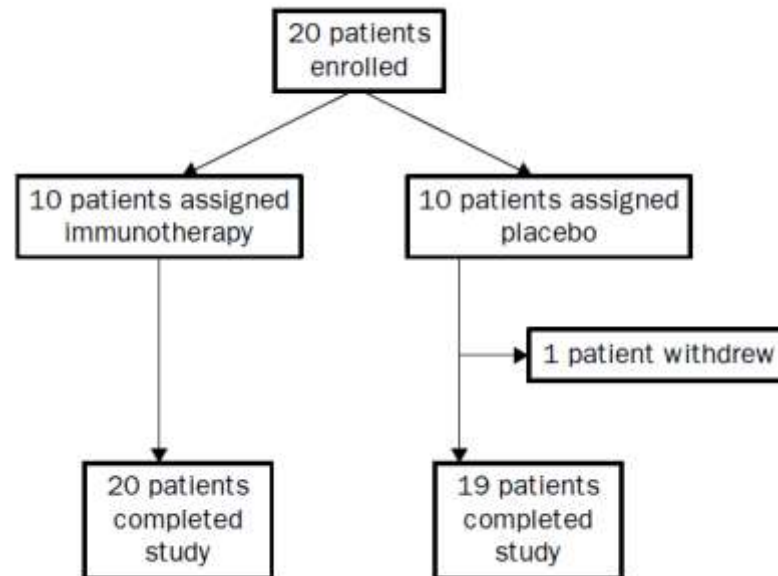
Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis

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

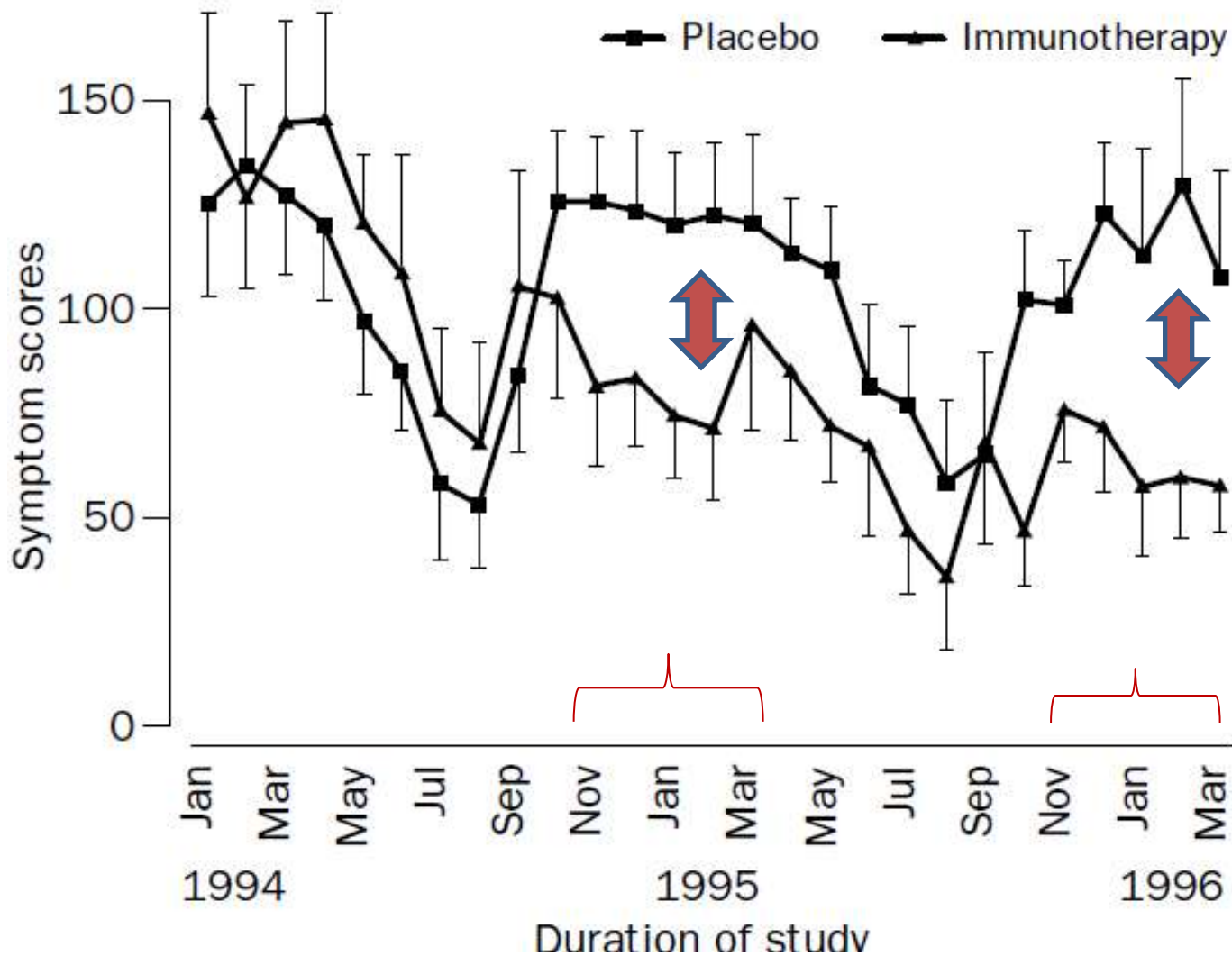


Double-blind randomized placebo-controlled trial *with TABLET*

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



Symptoms level in two consecutive years

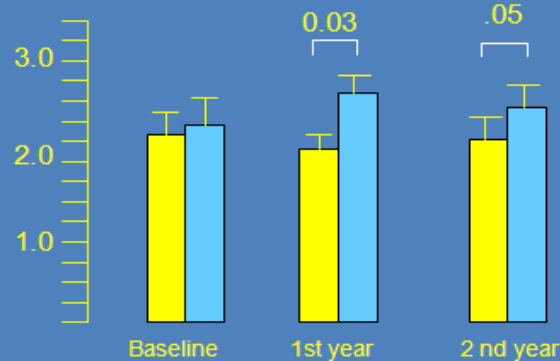




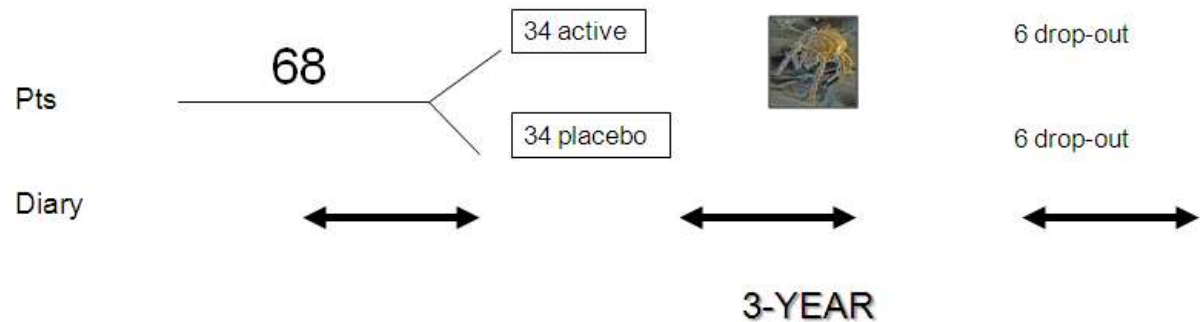
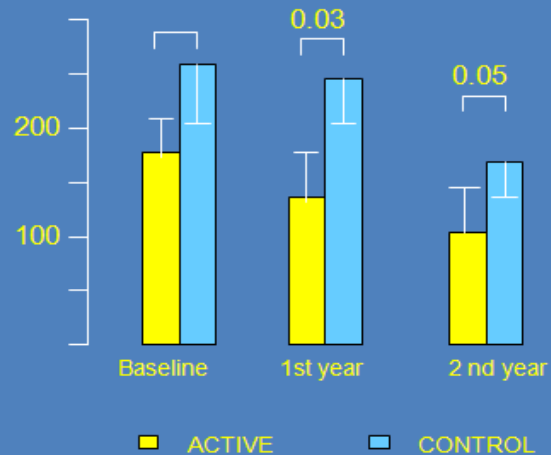
Original article

Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites

Symptom score



Medication score



1000 AU tablet x 2 /weekly

Supporting data
from the literature...

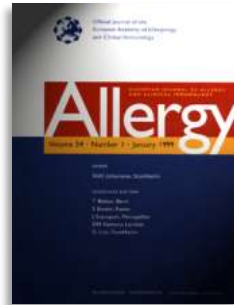


Original article

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

C. Caffarelli

Pediatric Department, Parma



Allergy. 2000;
55(12):1142-7.

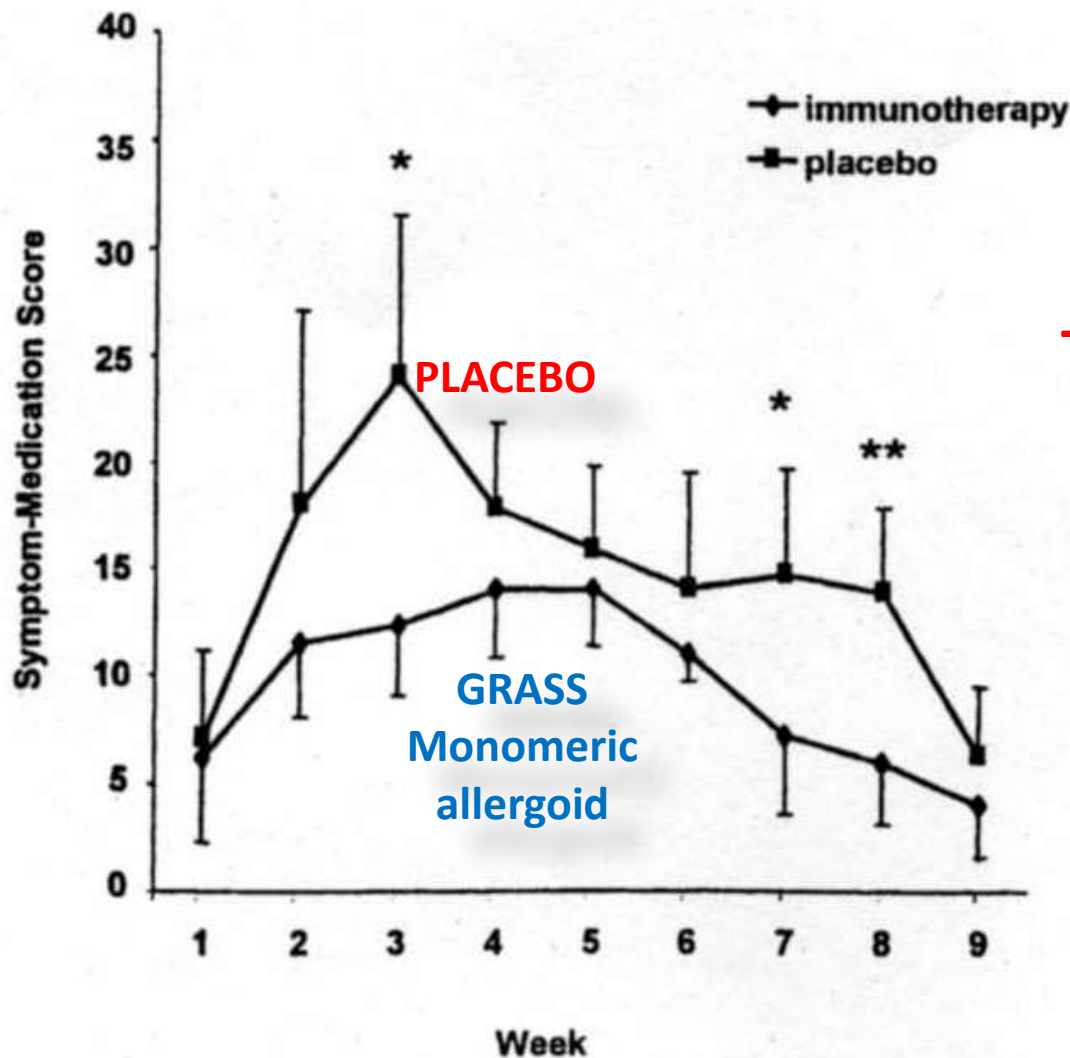


Double-blind randomized placebo-controlled trial
with TABLET in children

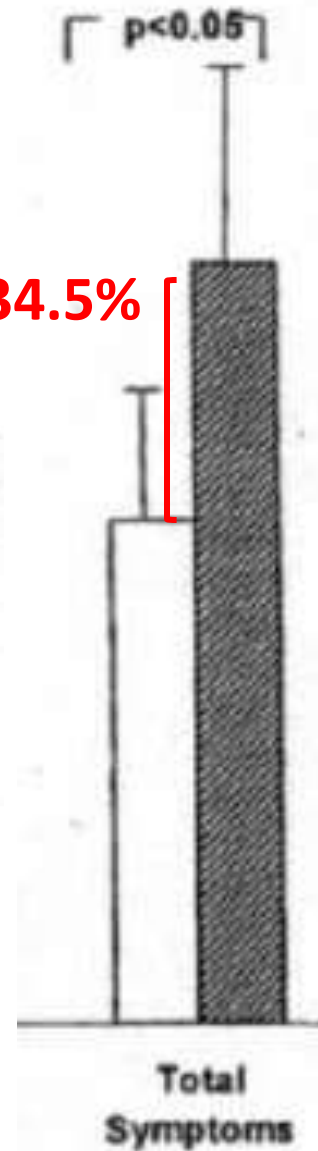
44 subjects with asthma/rhinitis/conjunctivitis
Age: 4-14 years (mean 8,5y)

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





-34.5%



Symptoms + medications

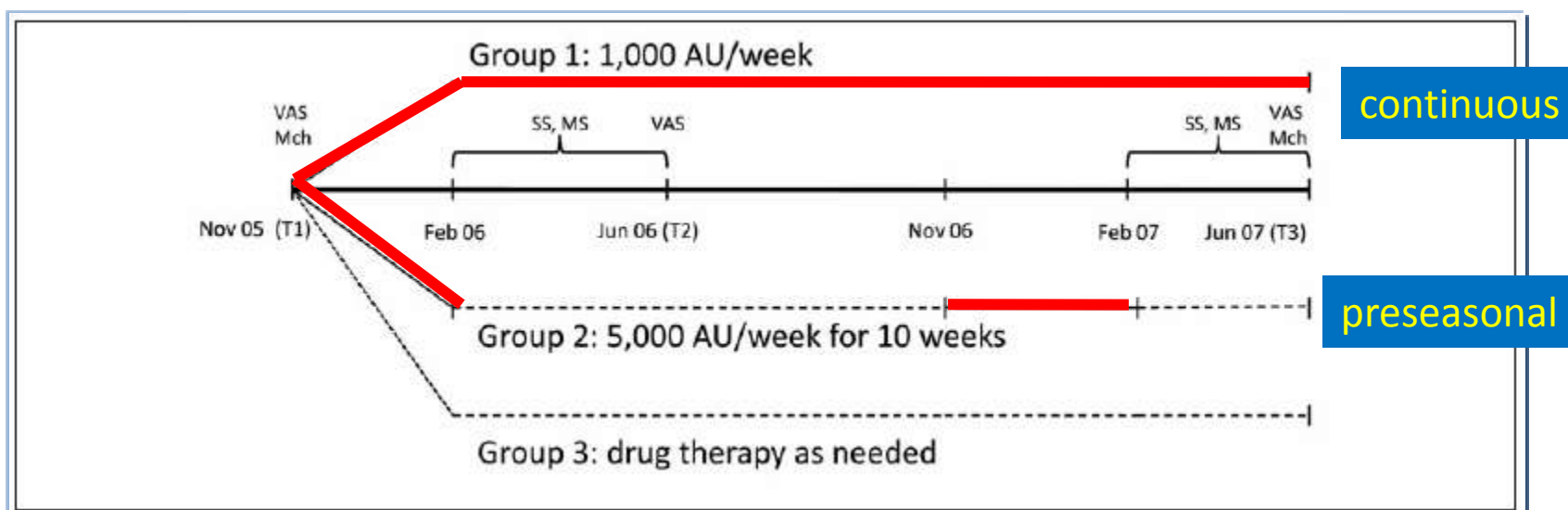
O. QUERCIA¹, M.E. BRUNO³, E. COMPALATI², P. FALAGIANI³, G. MISTRELLO³,
G.F. STEFANINI¹

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

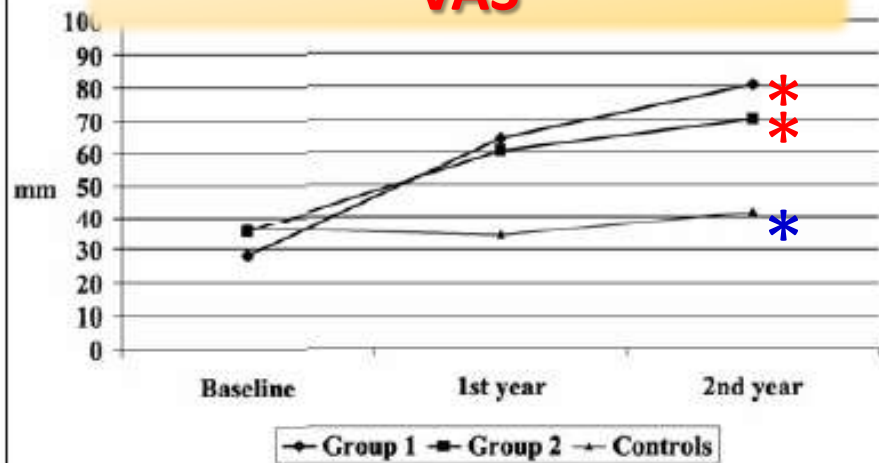
¹ Allergological Department, U.O. Medicina, Presidio Ospedaliero di Faenza (RA), Italy

² Allergy & Respiratory Diseases Clinic. Dept. Of Internal Medicine. University of Genoa - E-mail: enrico.compalati@unige.it

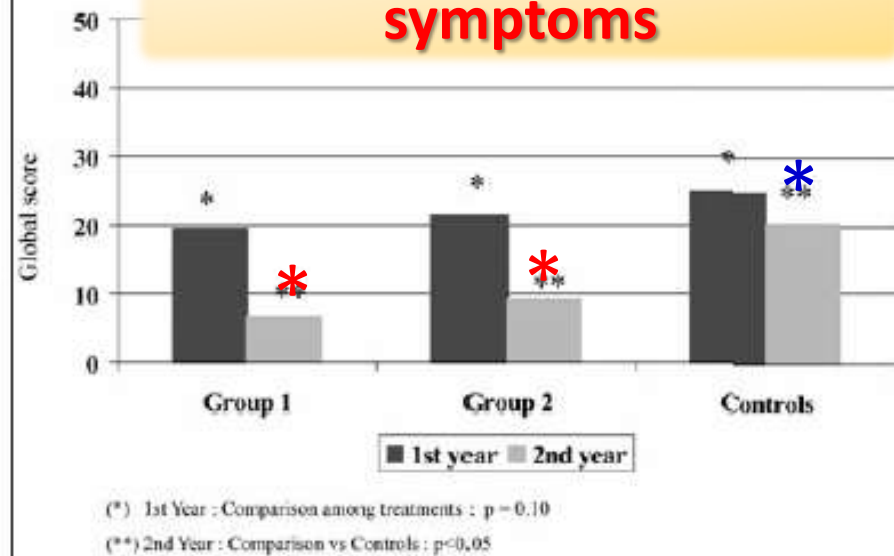
³ Scientific Direction, Lofarma S.p.A., Milan, Italy



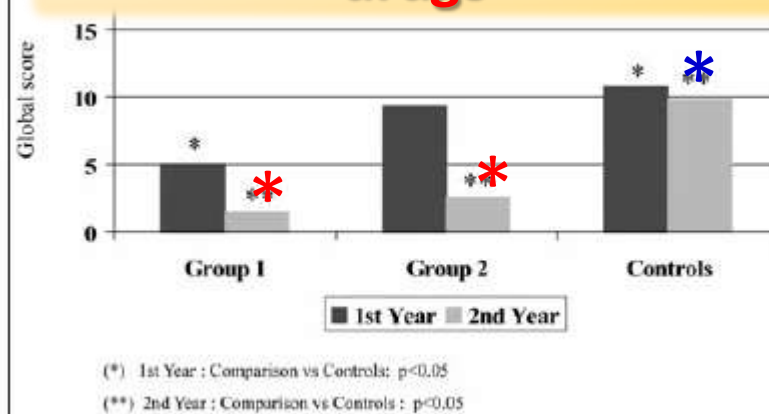
VAS



symptoms



drugs



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



1 month

3 months

- 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

daily dose (UA)	change of threshold compared to CPT V1	V3	V4
		number (percentage)	number (percentage)
300	worse	2 (5.7%)	0 (0%)
	unchanged	18 (51.4%)	8 (29.6%)
	improved	15 (42.9%)	19 (70.4%)
	total	35 (100%)	27 (100%)
600	worse	2 (4.8%)	3 (8.6%)
	unchanged	20 (47.6%)	10 (28.6%)
	improved	20 (47.6%)	22 (62.9%)
	total	42 (100%)	35 (100%)
1,000	worse	1 (2.6%)	0 (0%)
	unchanged	18 (46.2%)	7 (23.3%)
	improved	20 (51.3%)	23 (76.7%)
	total	39 (100%)	30 (100%)
2,000	worse	0 (0%)	0 (0%)
	unchanged	18 (51.4%)	10 (33.3%)
	improved	17 (48.6%)	20 (66.7%)
	total	35 (100%)	30 (100%)

Double-blind, placebo-controlled randomized studies

Passalacqua 1998	Mites	adults	2 years	↓ symptoms/EOS/ICAM1
Caffarelli 2000	Grass	kids	1 season	↓ symptoms/drugs
Passalacqua 2006	Mites	adults	3 years	↓ symptoms/drugs
Palma-Carlos 2006	Grass	adults	2 years	↓ symptoms/drugs
Ariano 1998	Pellitory	adults	2 years	↓ symptoms/drugs
Mezei 1996	Ragweed	adults+kids	1 season	↓ symptoms/drugs
Bordignon 1994	Grass	adults	1+2 years	↓ symptoms/drugs
Cavagni 1996	Grass	kids	1+1 years	↓ symptoms/drugs
SMART_5 2013	Grass	adults	3 months	↓ response to NPT
SMART_1 2013	Birch	adults	3 months	↓ response to NPT
LaisAmb11 2013	Ragweed	adults	3 months	↓ response to NPT
SMART_2 2014	Mites	adults	3 months	ongoing
SMART_8 2015	Mites	adults	12 months	-



SYSTEMATIC REVIEW

*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. Mösges, B. Ritter, G. Kayoko, 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 ?



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^a Marco Bruno^b Alessandro Massolo^c Paolo Falagiani^b

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

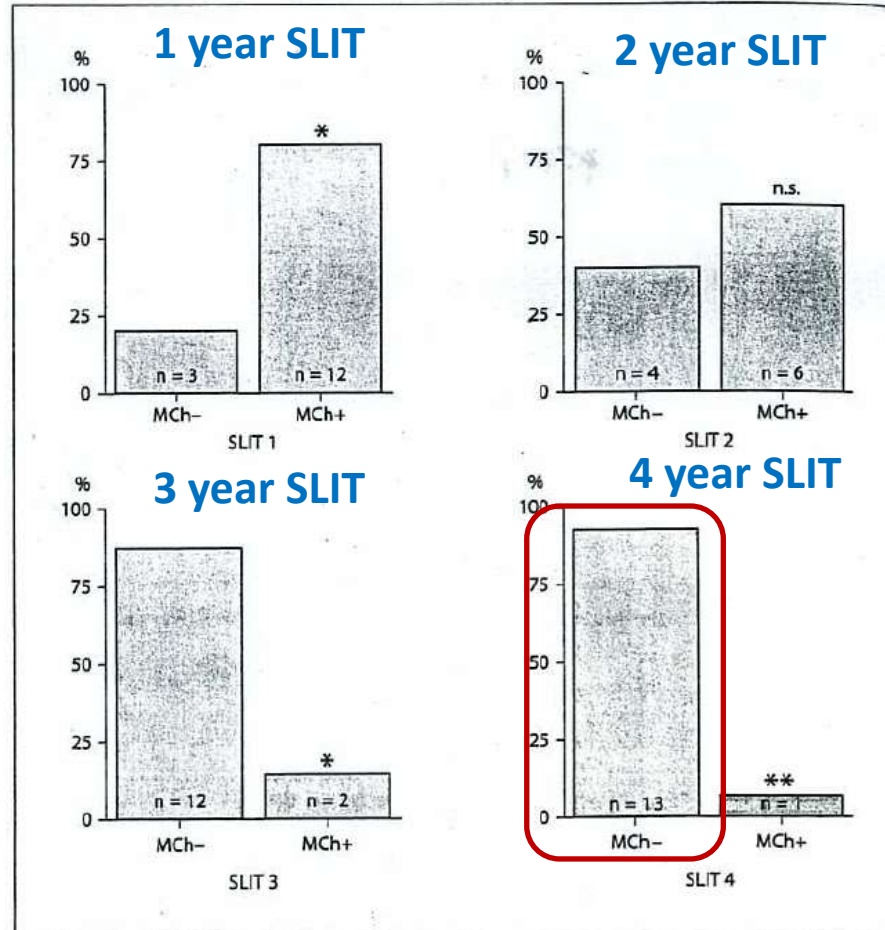


Metacholine Response 6-years after interruption of allergoid-SLIT

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!**