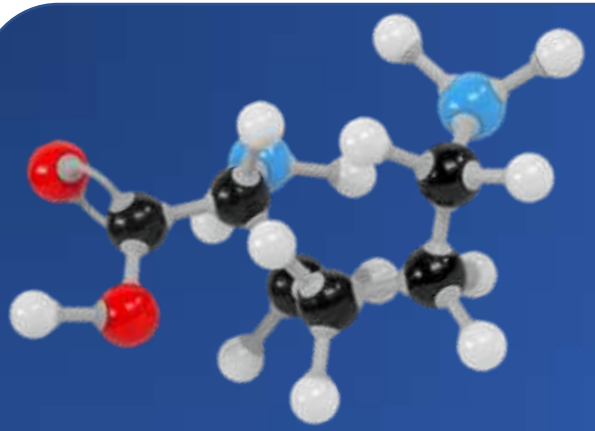

Lais ®

Monomeric Allergoids

Innovations in Allergen Immunotherapy

Moscow, Marriott Hotel

February 28th, 2019

Dr. Enrico Compalati

Medical Department

Lofarma **Milan, Italy**

Lofarma

*Lofarma S.p.A. is in the field of Allergies: several decades of activity, since its foundation back in **1945**, have made Lofarma one of the innovative reference point in allergy care*

Innovative Allergy Care

Allergy Immunotherapies
Allergy Diagnostics
Prevention:

- **Allergy**
- **Middle Ear Dysfunctions**
- **Swimmer's ear**
- **Food supplement**

Milano, Italy

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COMMON ALLERGIC SYMPTOMS

Coughing

Ear Discomfort

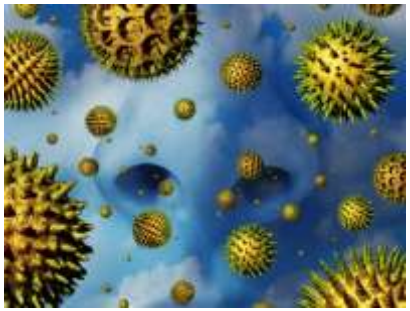
Dry Eatchy Skin

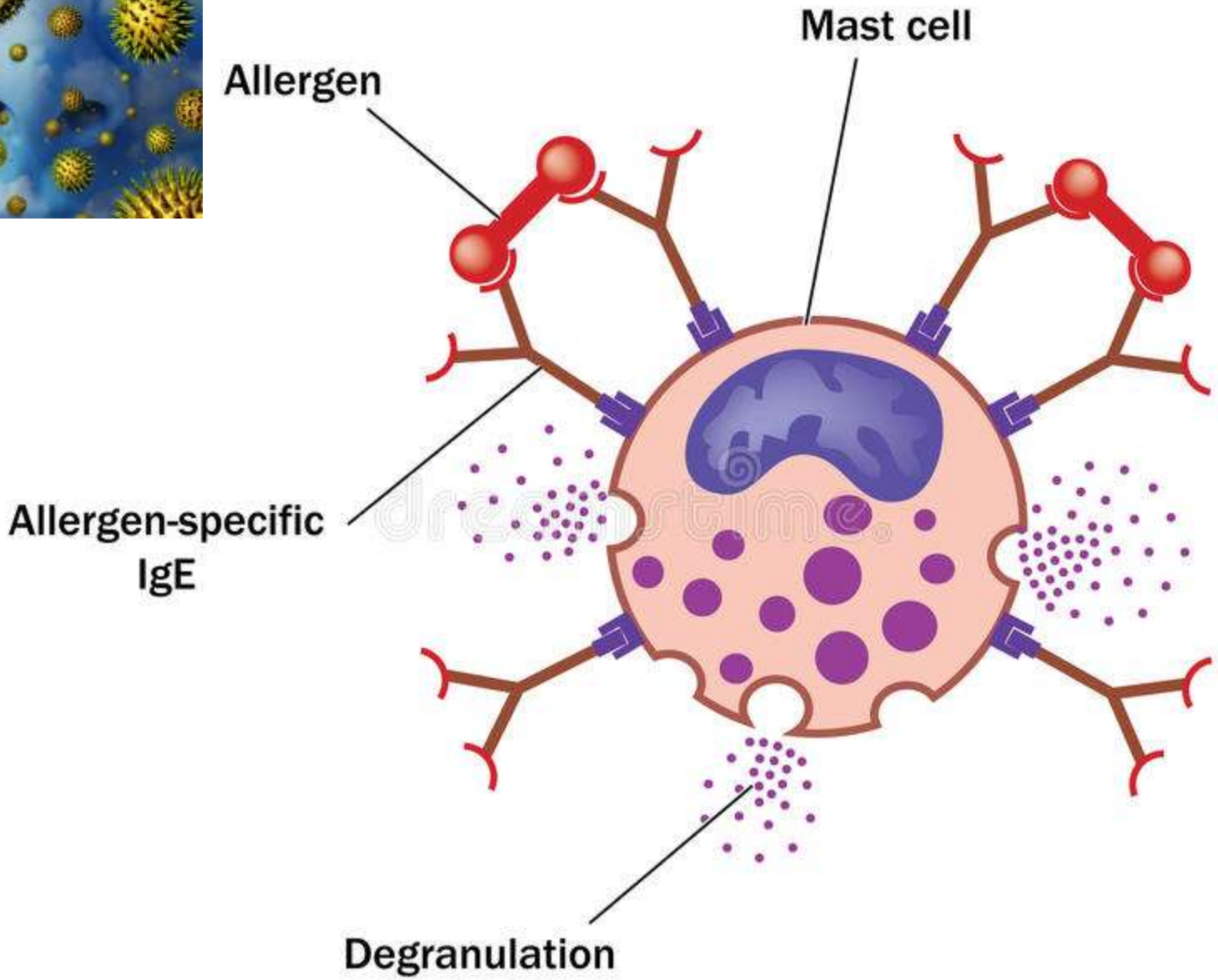
Blocked or Runy Nose

watery or eatchy eyes
with red ness

Sneezing

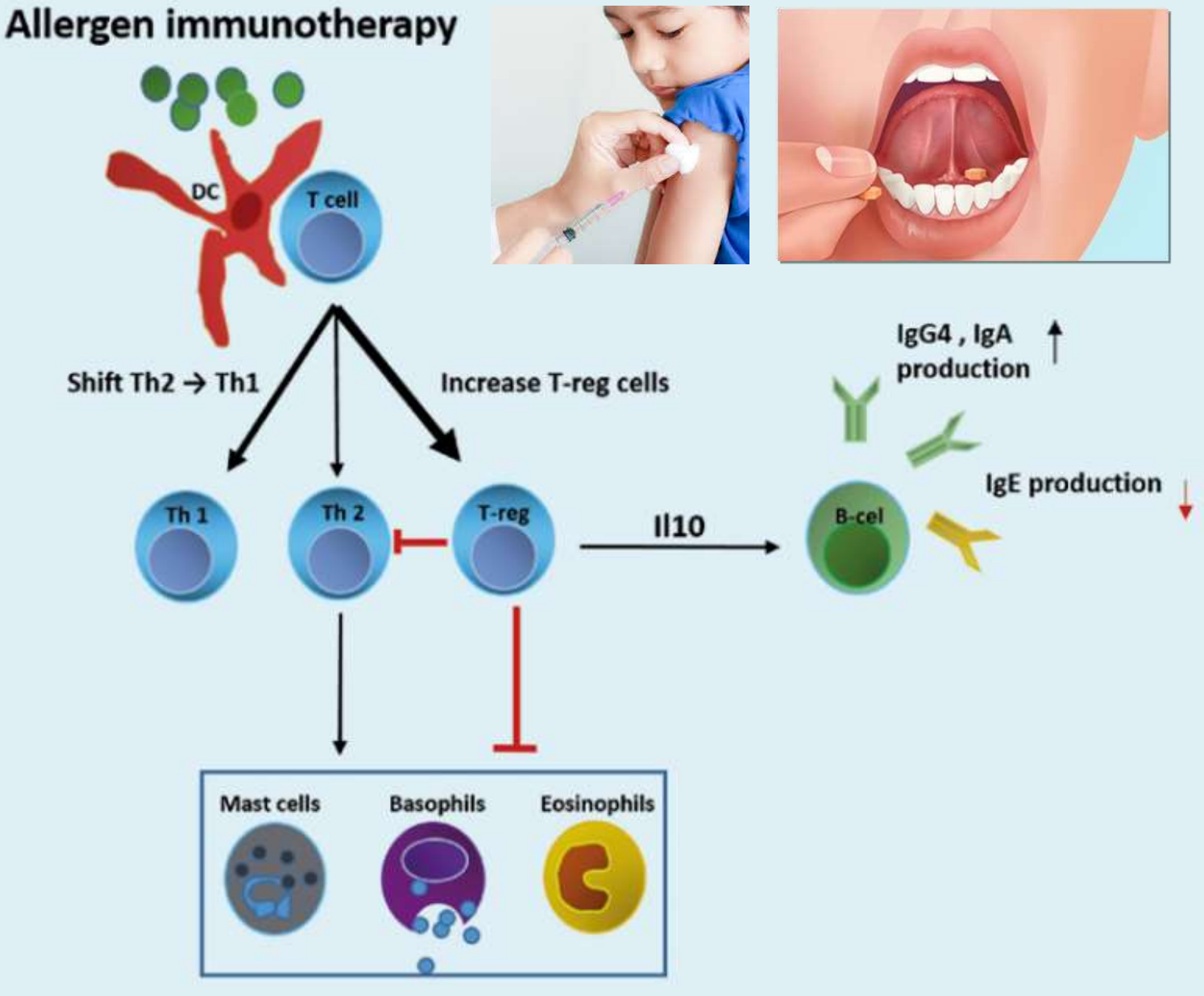
Breathing Problem




Mast cell
Allergen
Allergen-specific IgE
Degranulation

A I T : Allergen Immuno Therapy

Pathways and mechanism of actions



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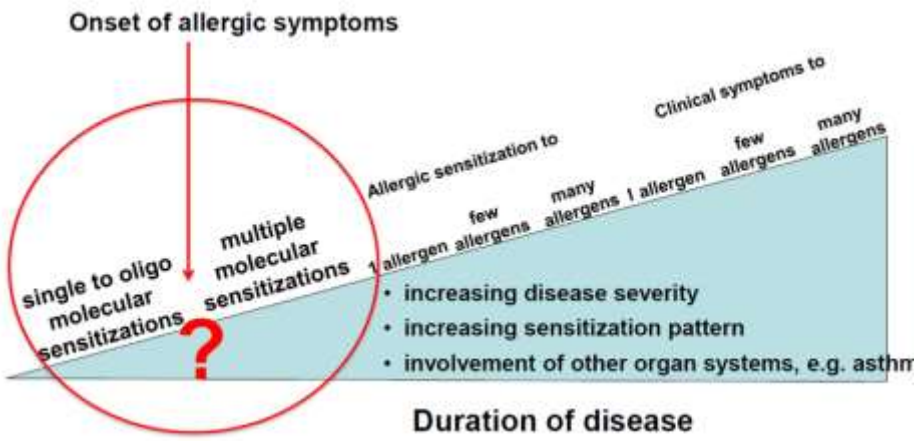


WHO Position Paper 1998

- **AIT is the <u>only one</u> causal treatment of allergy**
- **AIT is able to <u>modify the natural course of allergy</u>**

Rostrum

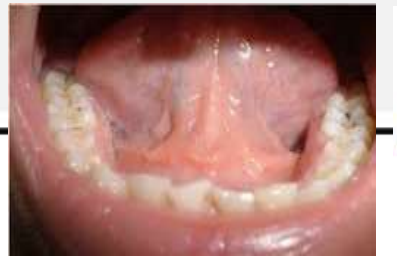
Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

Giovanni Passalacqua, MD,[a] Carlos E. Baena-Cagnani, MD,[b] Jean Bousquet, MD,[c] Giorgio Walter Canonica, MD,[a] Thomas B. Casale, MD,[d] Linda Cox, MD,[e] Stephen R. Durham, MD,[f] Desiréé Larenas-Linnemann, MD,[g] Dennis Ledford, MD,[h] Ruby Pawankar, MD,[i] Paul Potter, MD,[j] Nelson Rosario, MD,[k] Dana Wallace, MD,[l] and Richard F. Lockey, MD[h] *Genoa, Italy, Cordoba, Argentina, Montpellier, France, Omaha, Neb, Ft Lauderdale and Tampa, Fla, London, United Kingdom, Mexico City, Mexico, Tokyo, Japan, Groote Schuur, South Africa, Curitiba, Brazil, and Arlington Heights, Ill*

TABLE II. Grading system for SLIT local AEs (see Table III for the Medical Dictionary for Regulatory Activities codes)

Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	• Not troublesome AND • No symptomatic treatment required AND • No discontinuation of SLIT because of local side effects	• Troublesome OR • Requires symptomatic treatment AND • No discontinuation of SLIT because of local side effects	• Grade 2 AND • SLIT discontinued because of local side effects	The treatment is discontinued but there is no subjective and/or objective description of the severity from the patient/ physician

Each local AE can be early (<30 min) or delayed.



Clinical Commentary Review

Local Side Effects of Sublingual and Oral Immunotherapy

Giovanni Passalacqua, MD[a], Anna Nowak-Węgrzyn, MD[b], and Giorgio Walter Canonica, MD[a] *Genoa, Italy; and New York, NY*

TABLE I. Local AEs in the "large trials" with SLIT

Author (year)	Patients enrolled	Age range (y)	Allergen (preparation)	Duration	% patients with local AE in the active groups
Dahl (2006)[27]	634	18-65	Grass (tablet)	8 mo	Oral itching, 46%; Mouth edema, 18%; Throat itching, 9%
Durham (2006)[28]	855	18-65	Grass, 3 doses (tablet)	6 mo	75%-90%, not detailed
Didier (2007)[29]	628	18-45	Grass, 3 doses (tablet)	6 mo	Oral itching, 19.7%-25.8%; Mouth edema, 3.2%-6.3%; Throat itching, 9%-14.4%; Tongue edema, 3.2%-5.6%
Ott (2008)[30]	211	8-65	Grass (solution)	4 mo*	69%, not detailed. Most AE defined as local
Wahn (2009)[31]	278	5-17	Grass (solution)	5 mo	Oral itching, 32%; Mouth edema, 13%; Throat itching, 8%
Bufe (2009)[32]	253	5-16	Grass (solution)	6 mo	Oral itching, 33%; Swollen lips, 7%; Throat itching, 10%
Blaiss (2011)[33]	345	5-17	Grass (tablet)	6 mo	70% overall. Mainly oral itching, oral edema, throat itching, oral swelling. Not detailed
Nelson (2011)[34]	439	18-63	Grass (solution)	6 mo	83% overall. Oral itching, 35%; Mouth edema, 8%; Throat itching, 30%; swollen tongue, 5%
Wahn (2012)[35]	207	4-12	Grass (solution)	6 mo	Oral itching, 72%; Throat itching, 11%
Cox (2012)[36]	473	18-65	Grass (tablet)	6 mo	82%. Mostly oropharyngeal pruritus
DeBot (2012)[37]	257	6-18	Mite (solution)	2 y	Oral-pharyngeal irritation/swelling, 11%; gastrointestinal complaints, 85%
Nolte (2013)[38]	565	18-50	Ragweed, 2 doses (tablet)	1 y	Oral itching, 19%; Mouth/tongue edema, 15%; Throat itching, 26%; pharyngeal edema, 4.2%
Creticos (2013)[39]	784	18-50	Ragweed, 3 doses (tablet)	1 y	Oral/tongue itching, 15%; Mouth edema, 8%; Throat itching, 13%
Bergmann (2014)[40]	509	18-50	Mite, 2 doses (tablet)	1 y + follow-up	Oral/tongue itching 40%; Mouth/tongue edema 35%; Throat itching 33%; Pharyngeal edema 5%
Creticos (2014)[41]	429	18-55	Ragweed (solution)	8 mo	Oral/tongue itching 4%; Mouth edema 6%; Diarrhea/dyspepsia 4%
Mosbech (2014)[42]	604	14-65	Mite, 3 doses (tablet)	1 y	Oral/tongue itching, 2%-19%; Mouth edema, 4%-8%; Throat, itching 3%-7%
Maloney (2014)[43]	1501	5-65	Grass (tablet)	8 mo	Oral/tongue itching, 18%; Mouth edema, 13%; Throat itching, 23%
Wang (2014)[44]	484	14-50	Mite (solution)	1 y	Abdominal pain, swollen tongue, oral pruritus, cheilitis, and mouth edema, all mild and more frequent in the active group (no detail)
Okamoto (2015)[45]	532	12-64	Cedar (solution)	18 mo	Mouth edema, 3.8%; stomatitis and throat irritation, 1.9%; oral itching, 1.1%

*Three seasons, coseasonal regimen.

35-90% of patients in a clinical trial have local reactions

J Allergy Clin Immunol Pract 2017;5:13-21

Efficacy and safety of sublingual immunotherapy for allergic rhinitis in pediatric patients: A meta-analysis of randomized controlled trials

Bohai Feng, M.D., Jueting Wu, M.D., Bobei Chen, M.D., Haijie Bangliang Li, M.D., and Si Chen, M.D.

Table 2 Reported AEs in the patients in the active and placebo groups included in the safety evaluation

Organ Class	AEs	SLIT, no. (%) (n = 1167)	Placebo, no. (%) (n = 1025)
Oral	Oral pruritus	273 (23.4)	47 (4.6)
	Labial swelling	25 (2.1)	3 (0.3)
	Edema mouth	36 (2.8)	1 (0.1)
Nose	Aggravating rhinitis	164 (14.1)	124 (12.1)
	Nasal symptoms	123 (10.5)	122 (11.9)
Gastrointestinal	Gastrointestinal symptoms	199 (17.1)	155 (15.1)
	Stomach symptoms	30 (2.3)	4 (0.4)
Pharygeal	Pharygeal edema	16 (1.4)	3 (0.3)
	Pharyngolaryngeal pain	14 (1.2)	4 (0.4)
	Throat irritation	102 (8.1)	32 (3.1)
Others	Aggravating asthma	23 (1.8)	2 (0.2)
	Conjunctivitis symptoms	168 (14.4)	169 (16.5)
	Ear pruritus	20 (1.7)	2 (0.2)
	Local skin allergic reaction	183 (15.7)	174 (17.0)
	Headaches	10 (0.9)	7 (0.7)
	Upper respiratory tract infection	197 (16.9)	184 (18.0)

AE = Adverse event.

26 studies

American Journal of Rhinology & Allergy, 31(1), 27–35.

Patient Adherence

In the overall population, 374 patients (12.8%), of whom 191 received SLIT, discontinued treatment. Treatment discontinuation was due to AEs in 65 patients (2.5%), lack of compliance in 95 patients (3.6%), loss to follow up in 35 patients (1.0%), poor efficacy in 13 patients (0.5%), and incomplete data in 38 patients (1.4%). One trial did not provide data regarding discontinuation.

American Journal of Rhinology & Allergy, 31(1), 27–35.

SLIT
and eosinophilic esophagitis

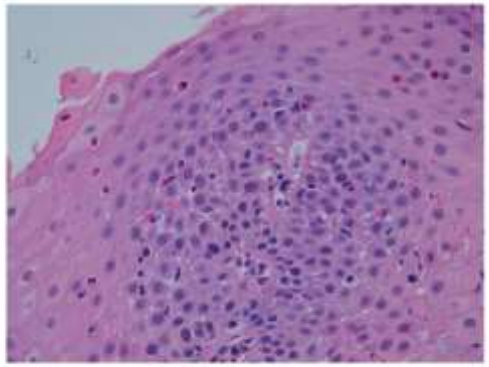


FIG 1. Biopsy specimen of the middle esophagus. The figure shows an inflammatory infiltration of the esophageal epithelium with numerous eosinophils.

Case Rep Gastroenterol. 2013 Sep 3;7(3):363-8. doi: 10.1159/000355161. eCollection 2013.

Induction of eosinophilic esophagitis by sublingual pollen immunotherapy.

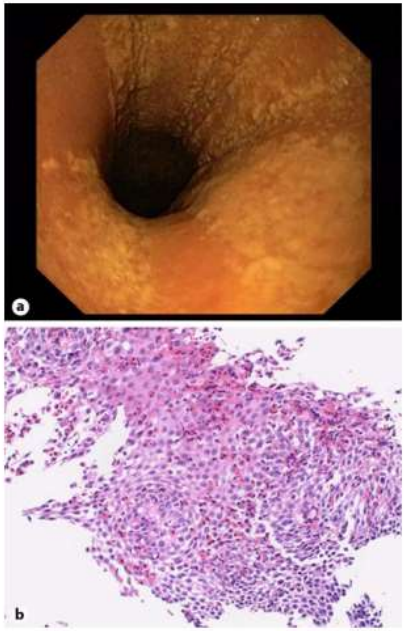
Miehlke S[1], Alpan O, Schröder S, Straumann A.

Author information

TREES

Abstract

Sublingual immunotherapy (SLIT) is increasingly investigated and utilized for the treatment of food and pollen allergies. Previous case reports suggested that eosinophilic esophagitis (EoE) might develop as a long-term complication in children after completion of oral immunotherapy. Here, we describe a 44-year-old female with a medical history of pollinosis who for the first time in her life developed complete manifestation of EoE (peak eosinophils 164/high power field) 4 weeks after initiation of SLIT using specific soluble allergens (hazelnut, birch, alder) according to previous specific serum IgE testing. After discontinuation of SLIT, EoE resolved completely within 4 weeks without any other medical intervention. During a follow-up of 12 months the patient remained free of any esophageal symptoms. This is the first case report demonstrating a close and therefore likely causative association between pollen SLIT and EoE in an adult patient.



J Allergy Clin Immunol. 2014 May;133(5):1482-4. doi: 10.1016/j.jaci.2014.01.030. Epub 2014 Mar 15.

Esophageal hypereosinophilia induced by grass sublingual immunotherapy.

Antico A[1], Fante R[2].

GRASS

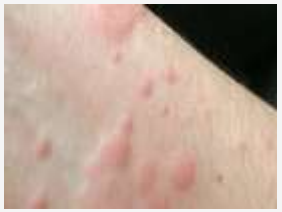
Ann Allergy Asthma Immunol. 2016 Jun;116(6):583-4. doi: 10.1016/j.anai.2016.03.017. Epub 2016 Apr 6.

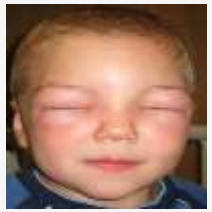
Eosinophilic esophagitis after desensitization to dust mites with sublingual immunotherapy.

Béné J[1], Ley D[2], Roboubi R[3], Gottrand F[2], Gautier S[4].

MITES

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
*Symptom(s)/sign(s) of 1 organ system present** **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth† **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	*Symptom(s)/sign(s) of more than 1 organ system present* **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV_1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV_1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death





AAAAI-ACAAI-EAACI-WAO grading system 2010 SYSTEMIC REACTIONS

Clinical Commentary Review

Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States

Tolly G. Epstein, MD, MS[a], Christopher Calabria, MD[b], Linda S. Cox, MD[c], and Sten Dreborg, MD[d] *Cincinnati, Ohio; San Antonio, Tx; Ft. Lauderdale, Fla; and Uppsala, Sweden*

SLIT Local Reaction and Systemic Allergic Reaction Emergency Plan

Patient name: _____ Age: _____
Allergies: _____
_____
Additional health problems: _____
_____
Concurrent medications: _____
_____

FOR MILD TO MODERATE LOCAL REACTION

MOUTH: bothersome itching, and/or mild swelling of lips and/or tongue
THROAT: bothersome itching, irritation, and/or mild tightness
EAR: bothersome itching
GASTROINTESTINAL: mild abdominal pain, nausea, and/or cramps

ACTION→ Use antihistamine: _____ mg or mL

FOR SEVERE LOCAL REACTION*

MOUTH/THROAT: swelling that causes hoarseness and/or throat closing

OR FOR SYSTEMIC REACTION*

SKIN: hives all over body and/or redness all over body
LUNG: shortness of breath, cough, and/or wheezing
HEART: weak pulse, dizziness, and/or passing out
GASTROINTESTINAL: severe abdominal pain, vomiting, diarrhea, and/or cramping

*You may only have a few symptoms. Symptoms can be life-threatening.

ACTION→ Inject epinephrine in thigh using (circle one):

Adrenaclick (0.3 mg) Adrenaclick (0.15 mg)
EpiPen (0.3 mg) EpiPen Jr. (0.15 mg)

- Call 911 (before calling contact)

Emergency contact #1: home_____ work_____ cell_____
Emergency contact #2: home_____ work_____ cell_____
Emergency contact #3: home_____ work_____ cell_____

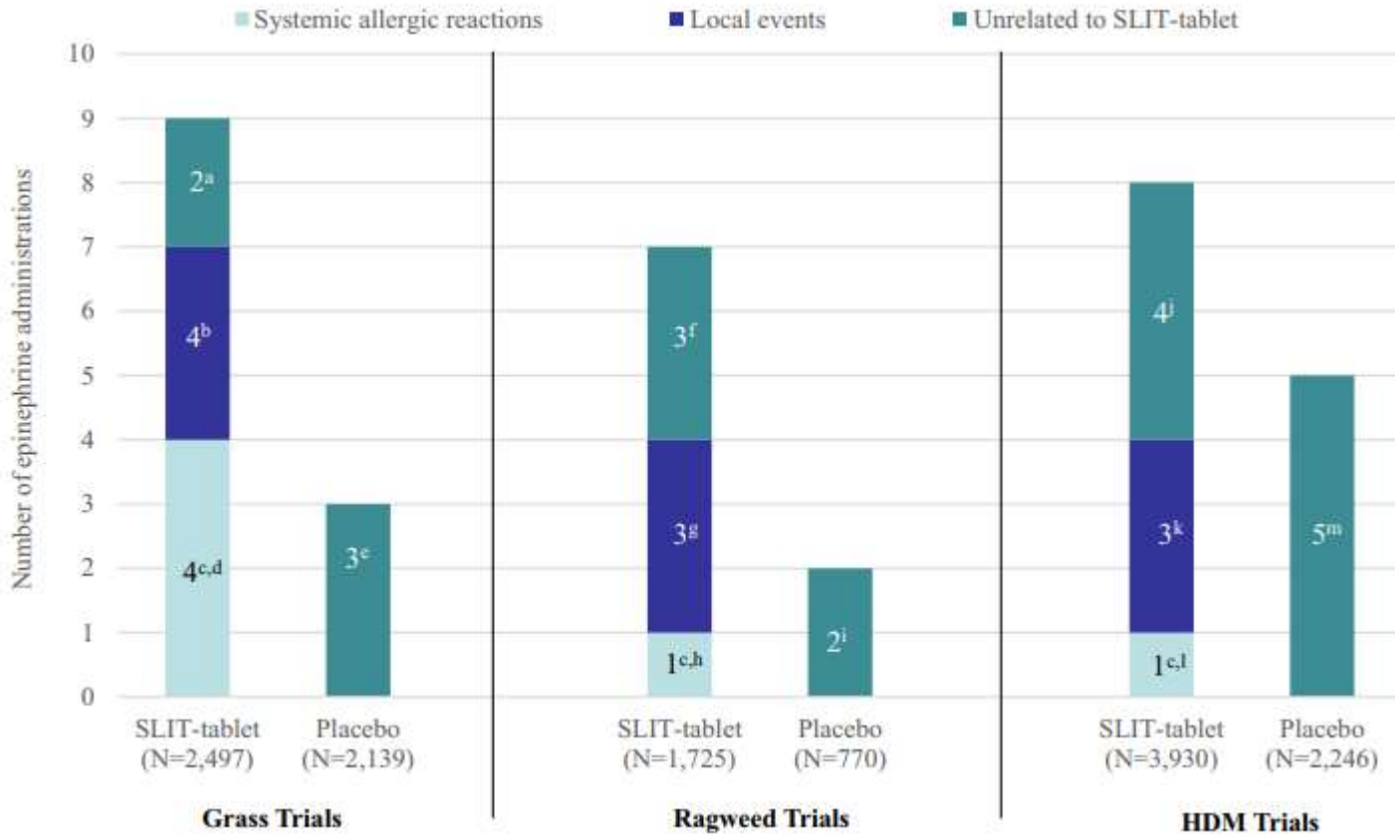
Comments_____
Doctor's Signature/Date/Phone Number _____

All 3 approved tablets were accompanied by FDA product information boxed warnings, which stipulate that physicians/ health care professionals should "prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use." To the authors' knowledge, this requirement is unique to the US licensed sublingual tablets.

Original Article

Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets

Hendrik Nolte, MD, PhD[a], Thomas B. Casale, MD[b], Richard F. Lockey, MD[b], Bodil Svanholm Fogh, MSc[c], Amarjot Kaur, PhD[a], Susan Lu, PharmD[a], and Harold S. Nelson, MD[d] *Kenilworth, NJ; Tampa, Fla; Hørsholm, Denmark; and Denver, Colo*



Epinephrine administrations in SLIT-tablet trials: 1.8 per 100,000 tablet doses.

TABLE E2. Grass SLIT-tablet-related systemic allergic reactions treated with epinephrine in grass trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Anaphylactic reaction	Swelling of lips, oral itch, and dysphagia	Moderate	1	Epinephrine, cetirizine	No	Yes
Drug hypersensitivity	Chest discomfort, dysphagia, dysphonia, oral pharyngeal itch, swelling and irritation, rash	Mild	1	Epinephrine, loratadine, prednisone	No	Yes
Anaphylactic reaction	Oral itch, sneezing, rhinorrhea, and throat irritation	Mild	1	Epinephrine, loratadine	No	No
Hypersensitivity	Lip swelling, dysphagia, and intermittent cough	Moderate	1	Epinephrine	No	Yes

TABLE E3. Ragweed SLIT-tablet-related systemic allergic reactions treated with epinephrine in ragweed trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Anaphylactic reaction	Oral symptoms, throat swelling, dyspnea, nausea, light-headedness	Severe	6	Epinephrine, diphenhydramine, prednisone, ranitidine	Yes	Yes

TABLE E4. SQ-HDM SLIT-tablet-related systemic allergic reactions treated with epinephrine in HDM trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Hypersensitivity	Itchy palms, facial flushing, dyspnea, presyncope, throat swelling	Moderate	1	Epinephrine, desloratadine, pseudoephedrine	No	Yes

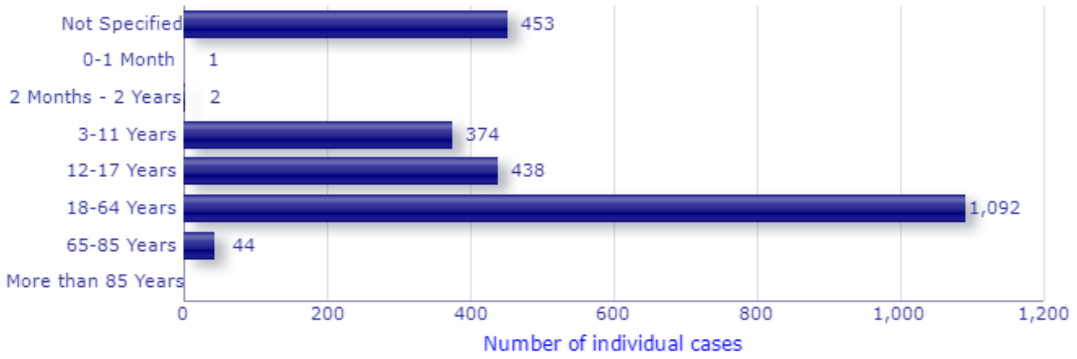
6 SRs with use of Epinephrine

EudraVigilance - European database of suspected adverse drug reaction reports

- In the past 5 years, the EMA has documented 45 reports of suspected anaphylactic reactions following SLIT with timothy grass pollens in its databases, 9 of which were life-threatening

Number of individual cases by Age Group

Age Group	Cases	%
Not Specified	453	18.8%
0-1 Month	1	0.0%
2 Months - 2 Years	2	0.1%
3-11 Years	374	15.6%
12-17 Years	438	18.2%
18-64 Years	1,092	45.4%
65-85 Years	44	1.8%
More than 85 Years	0	
Total	**2,404**	**100.0%**



KEY Message

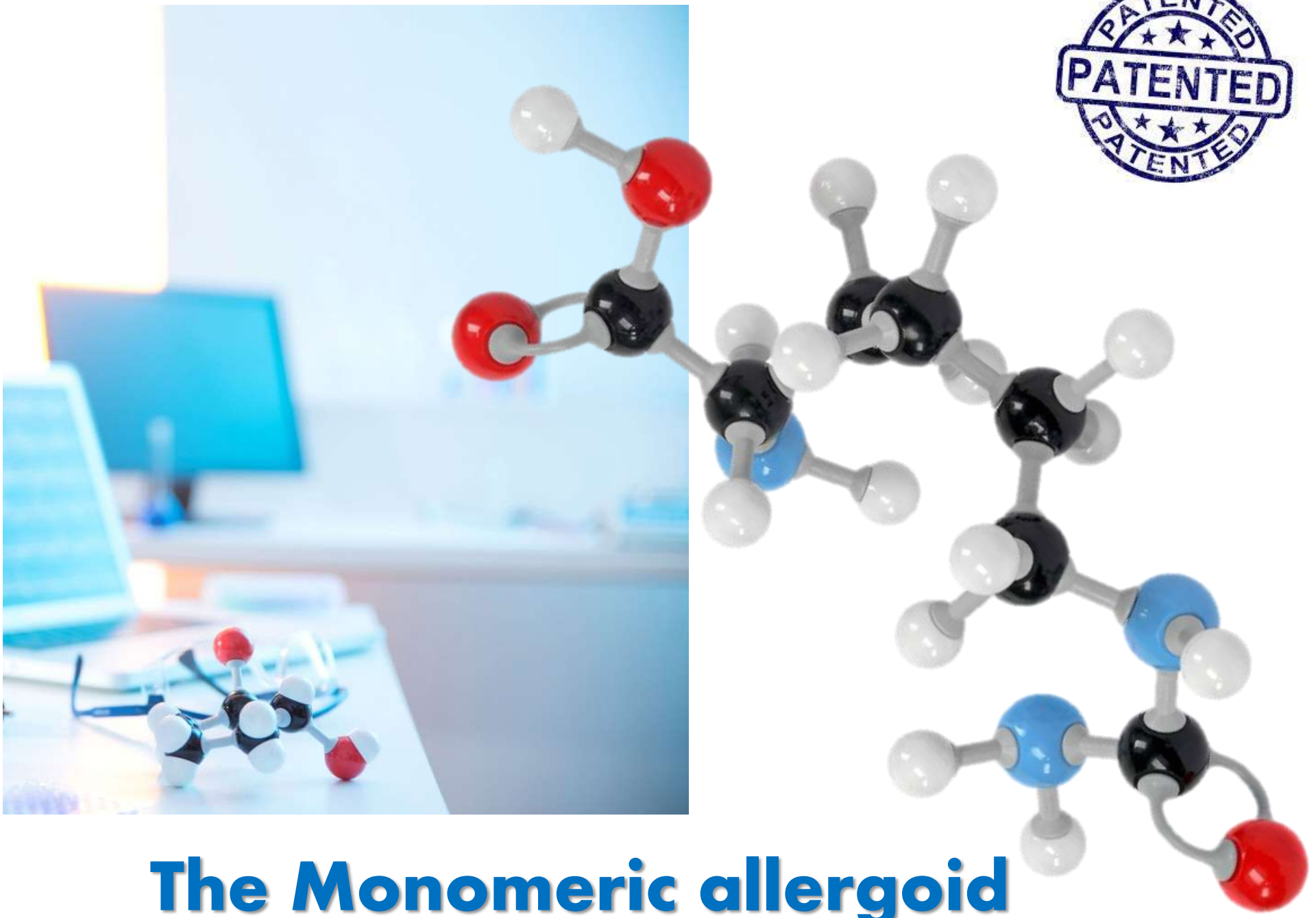
- Local side effects of SLIT are common and contribute to treatment course discontinuation
- Systemic reactions may occur during an Allergen Immunotherapy course
- Anaplylaxis is rare with SLIT, but a number of cases are reported in literature and international pharmacovigilance databases.
- Epinephrine is prescribed in some countries together with native allergen SLIT

Why using an allergoid ?

Improving the “risk/benefit” ratio

immunogenicity
allergenicity

- enhancing immune-stimulation
- bypass IgE-linking



The Monomeric allergoid

Extracts:

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.

Dr. Falagiani
Medical Director

Dr. Mistrello
Research Director

Immunological and physicochemical characteristics of the Monomeric Allergoid

Allergy 1996: 51: 8–15
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ALLERGY
ISSN 0105–4538

Monomeric chemically modified allergens: immunologic and physicochemical characterization

Mistrello G, Brenna O, Roncarolo D, Zanoni D, Gentili M, Falagiani P. Monomeric chemically modified allergens: immunologic and physicochemical characterization.
Allergy 1996: 51: 8–15. © Munksgaard 1996.

Allergenic extracts (*Der p*, grass, and *Parietaria*) or single allergens such as *Par j* I (the major allergen of *Parietaria*) and ovalbumin (OA), a food allergen widely used in animal models, were chemically modified by reaction with potassium cyanate (KCNO), which transforms the ε-amino group of the lysine of proteinaceous allergens into ureido groups. KCNO-modified (carbamylated) allergens have low allergenic potency, as demonstrated *in vitro* (RAST inhibition) and *in vivo* (passive cutaneous anaphylaxis). When used to immunize rabbits, carbamylated allergens still induce IgG antibodies able to cross-react with native allergens (immunoblotting experiments). An interesting feature distinguishing carbamylated allergens from other chemically modified allergens is the preservation of the native monomeric dimension as demonstrated by SDS-PAGE analysis. Results are discussed from the perspective of clinical application of carbamylated allergens.

G. Mistrello[1], O. Brenna[2], D. Roncarolo[1], D. Zanoni[1], M. Gentili[1], P. Falagiani[1]

[1]Department of Research, Laboratorio Farmaceutico Lofarma, Milan; [2]Department STAAM, Faculty of Agriculture, University of Molise, via Tiberio 21, 86100 Campobasso, Italy

Key words: allergens; monomeric modified allergens; potassium cyanate; RAST inhibition.

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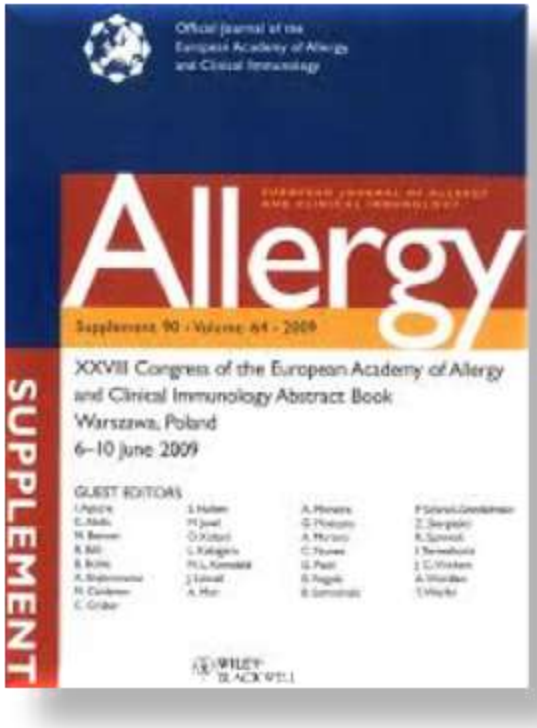
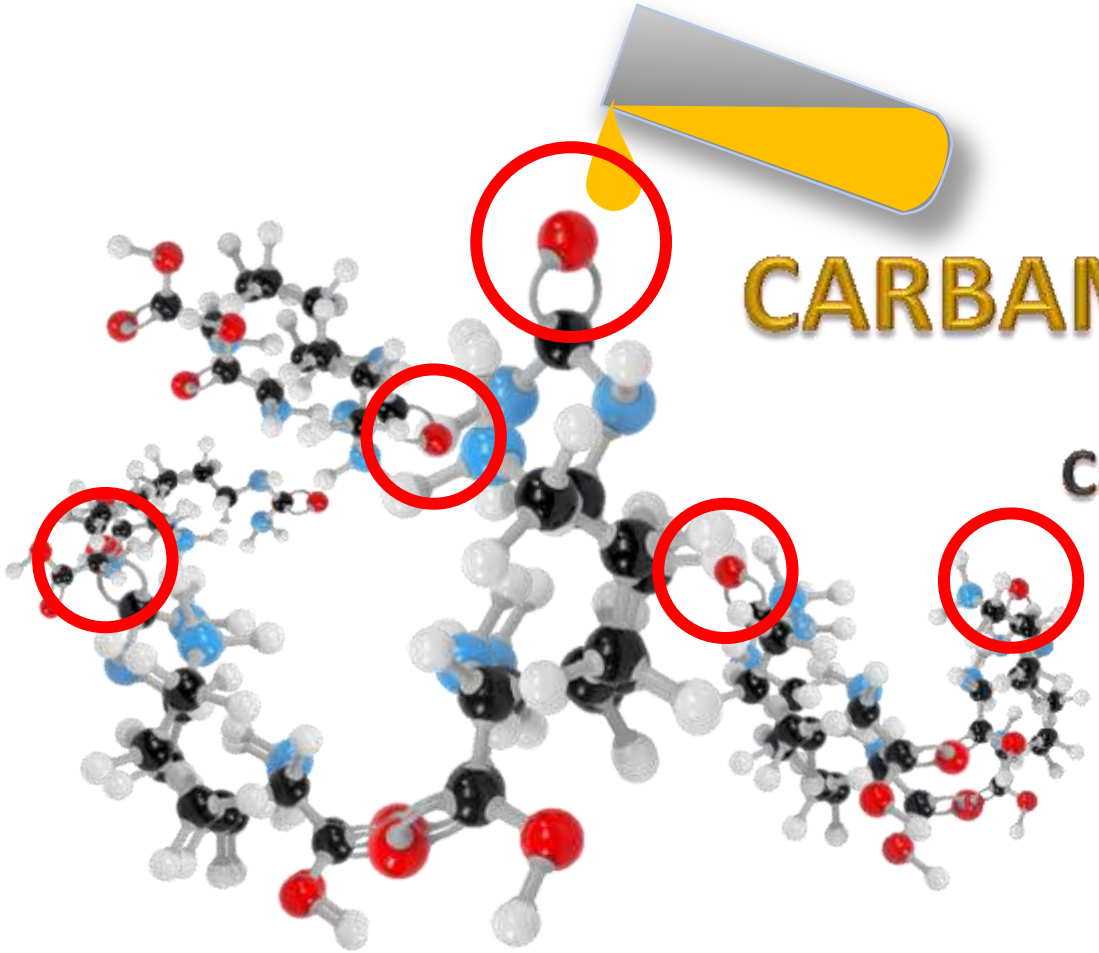
Accepted for publication 14 September 1995





KcNO

CARBAMYLATION

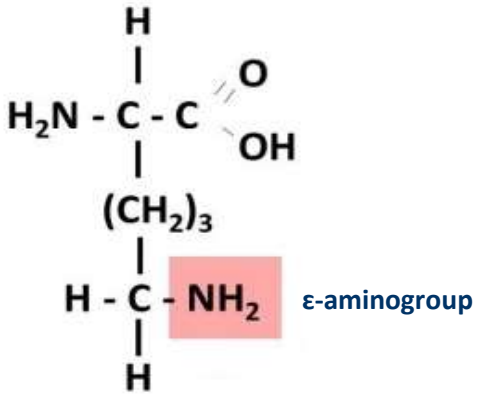
Carbamylated
Allergoid

The Monomeric Carbamylated Allergoid

The Monomeric Carbamylated Allergoid is obtained by selective carbamylation with potassium cyanate at alkaline pH, a reaction that leads to a marked substitution of ε-amino groups of allergen lysine residues, that allows a **reduced interaction with specific IgE** and a particular resistance to proteolytic enzymes.

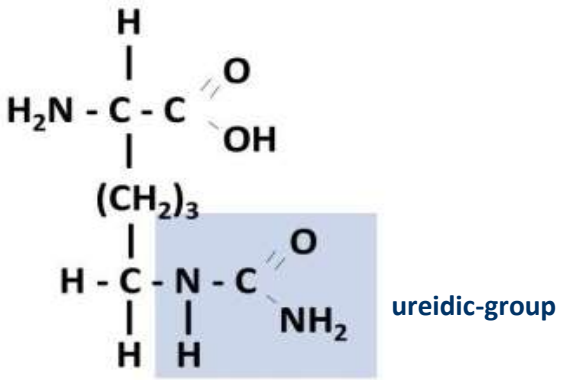
from allergen

to allergoid



Lysine

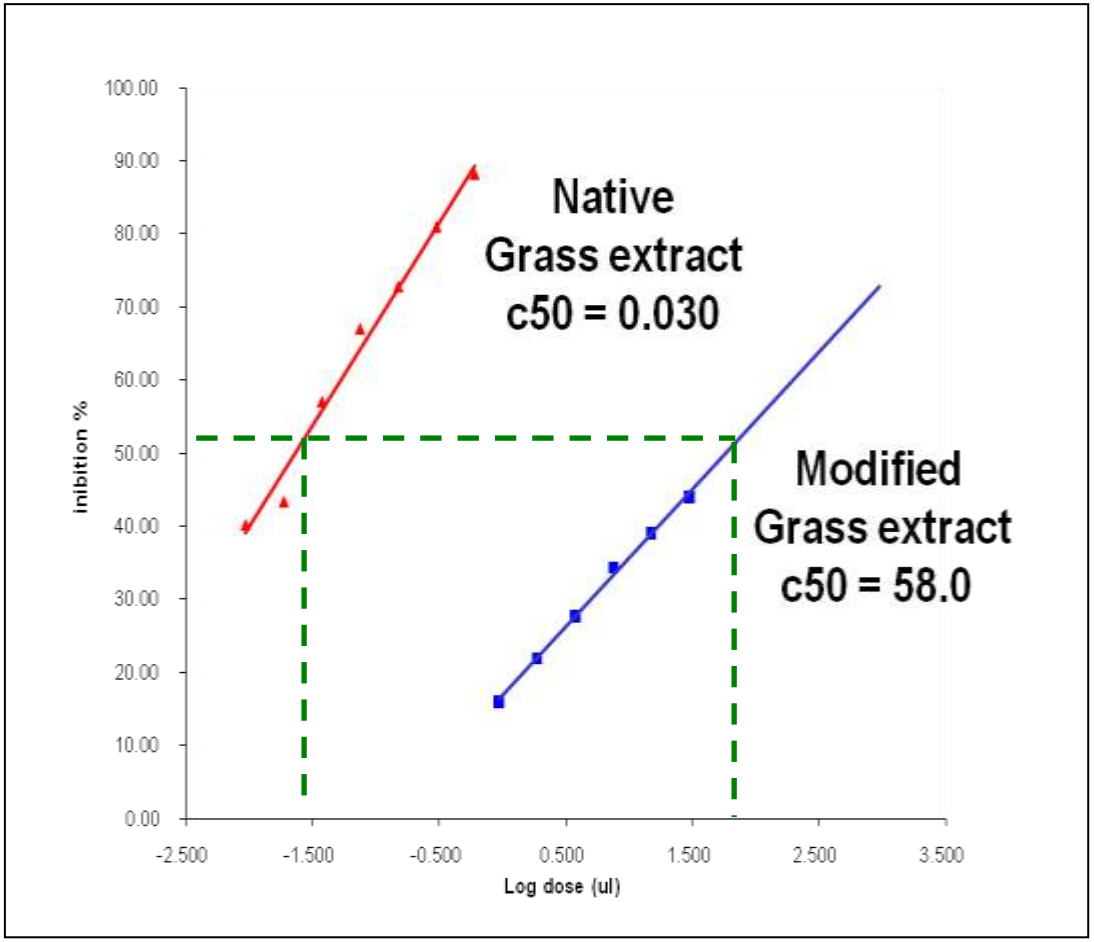
+ KCNO



Homocytrulline

CARBAMYLATED ALLERGOID: REDUCED LINKING with IgE

Comparison between native and modified grass extract by EAST-inhibition



Mistrello et al. Allergy. 1996 Jan;51(1):8-15

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

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Safety of sublingual immunotherapy with monomeric all_ergoid in adults: multicenter post-marketing surveillance study

C. Lombardi, S. Gargioni, A. Melchiorre, A. Tiri, P. Falagiani, G. Walter Canonica, G. Passalacqua

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	-

Dose-finding study of carbamylated monomeric allergoid tablets in grass-allergic rhinoconjunctivitis patients

Ralph Mösges*,1,2, Christina Rohdenburg[1], Andrea Eichel[3], Gregor Zadoyan[1], Elena-Manja Kasche[1], Kija Shah-Hosseini[1], Walter Lehmacher[1], Petra Schmalz[4] & Enrico Compalati[5]
[1]Institute of Medical Statistics, Informatics and Epidemiology, Medical Faculty, University of Cologne, Cologne, Germany

158 randomized adults

300 UA/day (n = 36),
600 UA/day (n = 43),
1000 UA/day(n = 39),
2000 UA/day (n = 37)

applied preseasonally for 12 weeks (3 months)

Immunotherapy

Immunotherapy. 2017 Nov;9(15):1225-1238.

Table 6. Distribution of treatment-related adverse events.

Type of adverse event	Total	300 UA/day	600 UA/day	1000 UA/day	2000 UA/day
Local	5	1	0	2	2
Gastrointestinal	7	1	4	1	1
Mild systemic	9	4	1	1	3
Unspecific	5	1	2	1	1
Other	12	7	0	2	3
Total	38	14	7	7	10

UA: Unit of allergy.

No serious AEs
No occurrence of anaphylaxis
No need to apply epinephrine
Of all 155 exposed patients, 106 subjects (68.4%) did not experience any AEs at all
38 treatment-related (TRAE), which corresponds to 3 AEs per 1000 tablets taken

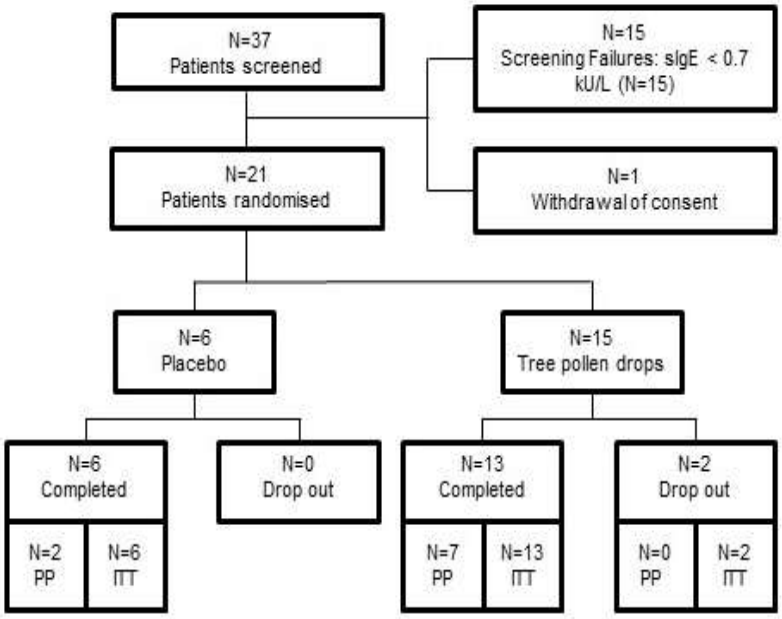
Most common TRAEs:
diarrhea (n = 5; 3.2%),
rhinoconjunctival symptoms (n = 4; 2.6%),
swelling of one eye (n = 3; 1.9%),
hypertension (n = 3; 1.9%),
tiredness/fatigue (n = 2; 1.3%)

bronchitis (n = 2; 1.3%),
headache (n = 2; 1.3%)
abdominal pain (n = 2; 1.3%)

Dose escalation using carbamylated monomeric tree pollen drops is well tolerated in patients with allergic rhinoconjunctivitis and points towards clinical effects

– Letter to the Editor

E Raskopf, S Allekotte, E Compalati , J Singh, C Acikel, R Mösges



Day	Visit	Number of drops	Concentration of Lais® Frühblüher sublingual drops [UA/mL]	Dose of placebo [UA]	Dose of Lais® Frühblüher sublingual drops [UA]
1	V2[a]	2	20,000	0	2,000
		5	20,000	0	5,000
		2	100,000	0	10,000
2 to 3	[b]	2	100,000	0	10,000
4	V3[a]	3	100,000	0	15,000
		5	100,000	0	25,000
5 to 7	[b]	5	100,000	0	25,000
8	V4[a]	10	100,000	0	50,000
9 to 71	[b]	10	100,000	0	50,000

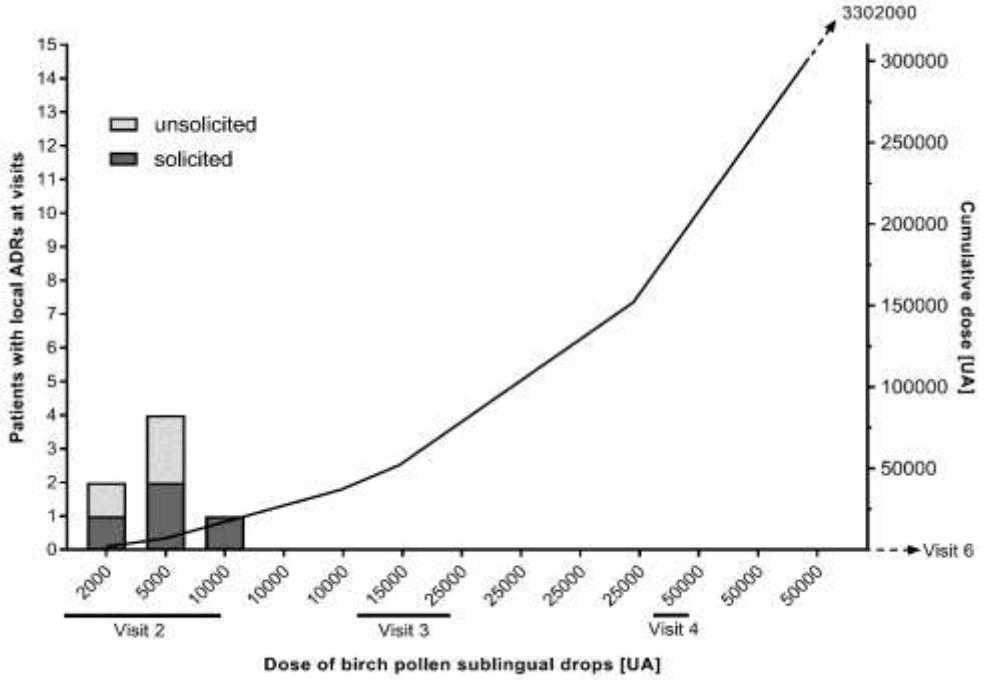
- Phase: IIa
- Design: double-blind, randomized
- Median treatment duration: 68.0 days (min: 8 days, max: 77 days)
  [8 days induction, 60 days maintenance]

- Solicited and unsolicited local reactions occurred in 1.4% of the 920 administrations

- 4 solicited and 3 unsolicited local reactions were documented for 2 patients 30 min after up-dosing

- No systemic reaction grade II or higher was recorded

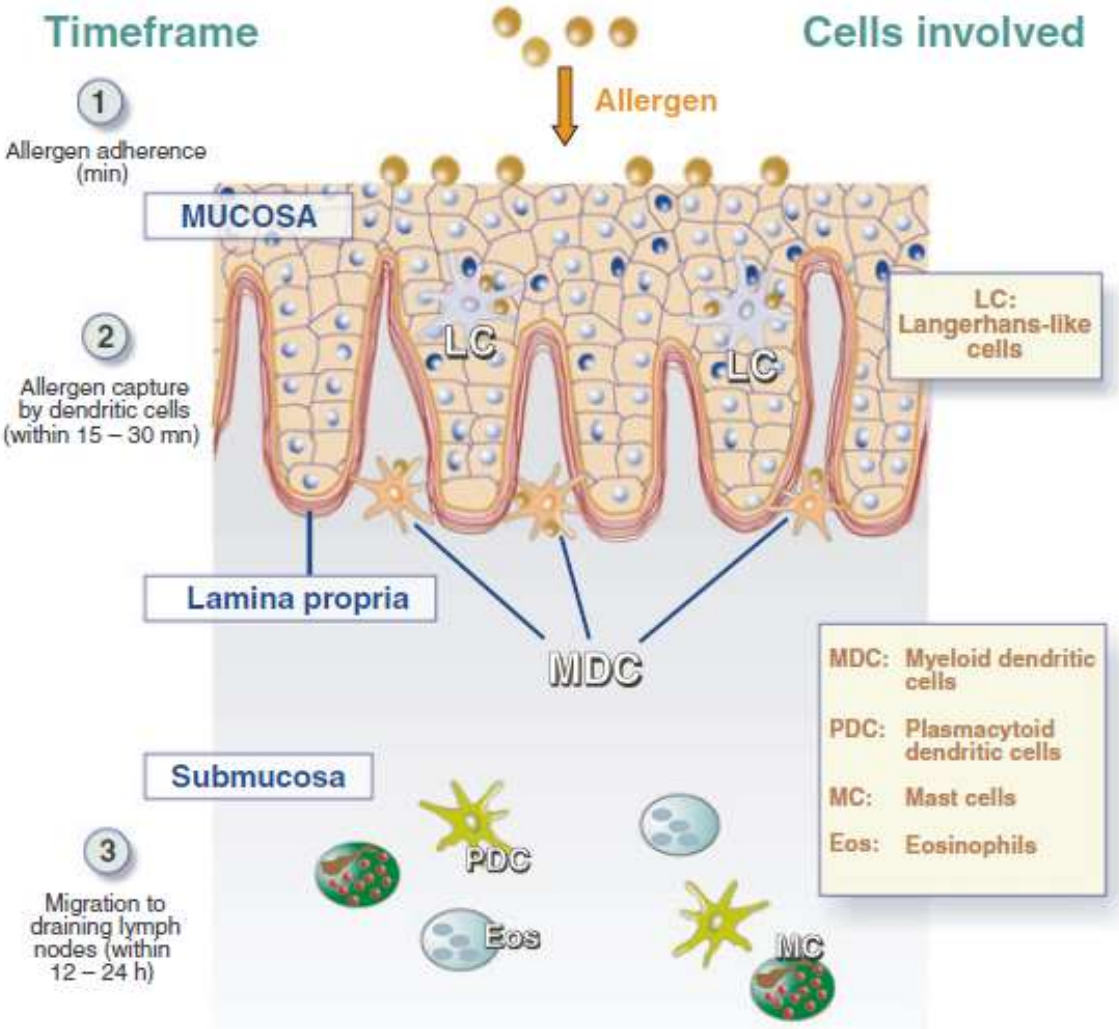
- Systemic allergic reactions for 1 actively treated patient (drop out): after updosing to 25,000 UA, the patient experienced 6 systemic reactions (rhinitis) grade I and 6 local reactions.



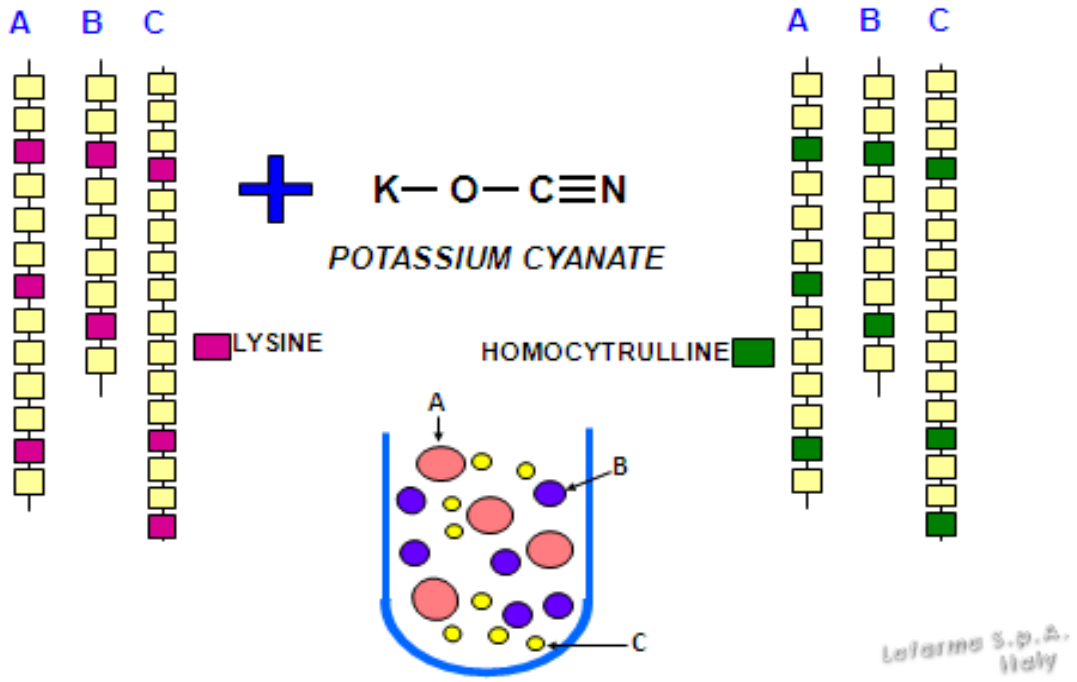
Why using an allergoid ?

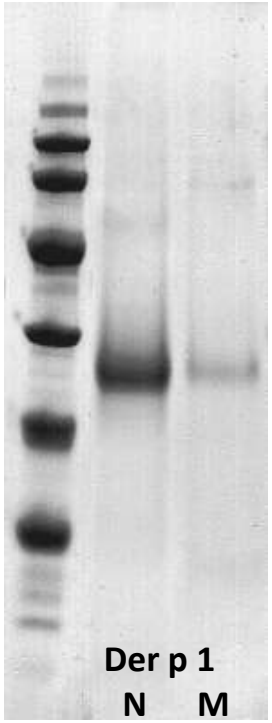
Because it is safer and better tolerated

Sublingual Immunotherapy (SLIT)



Monomeric Allergoid





MONOMERIC

~40 kda

Why using an allergoid ?

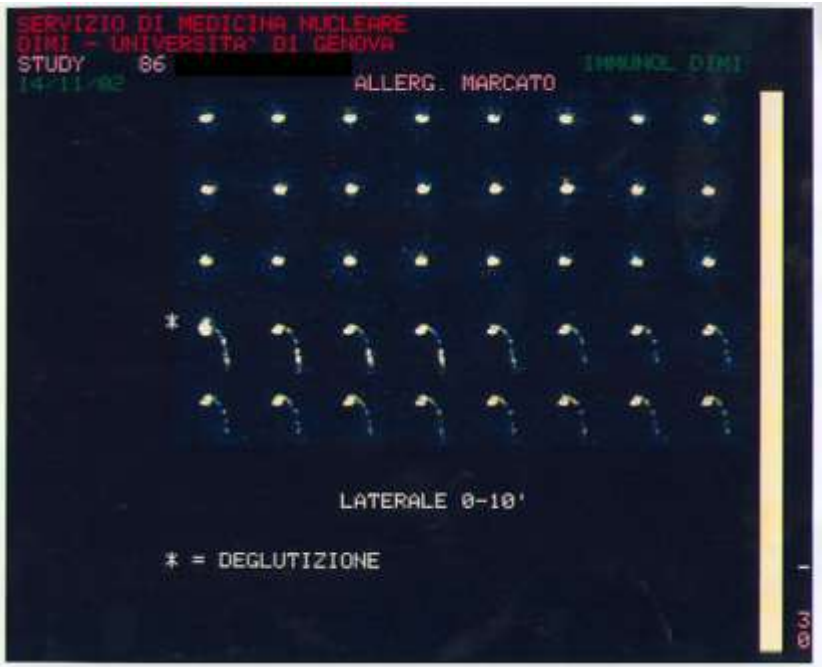
Because it suitable for sublingual route

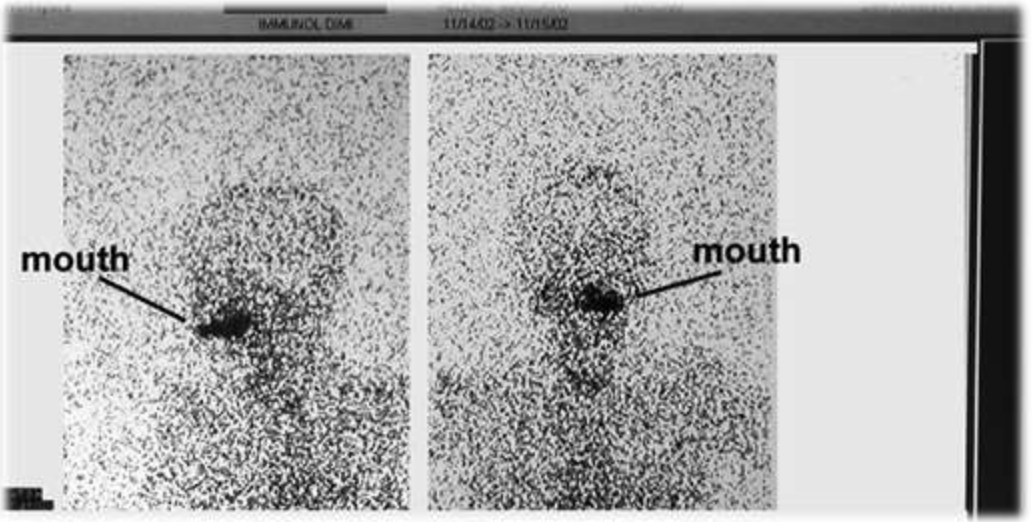
Clinical and Experimental Allergy, 2001, Volume 31, pages 54–60

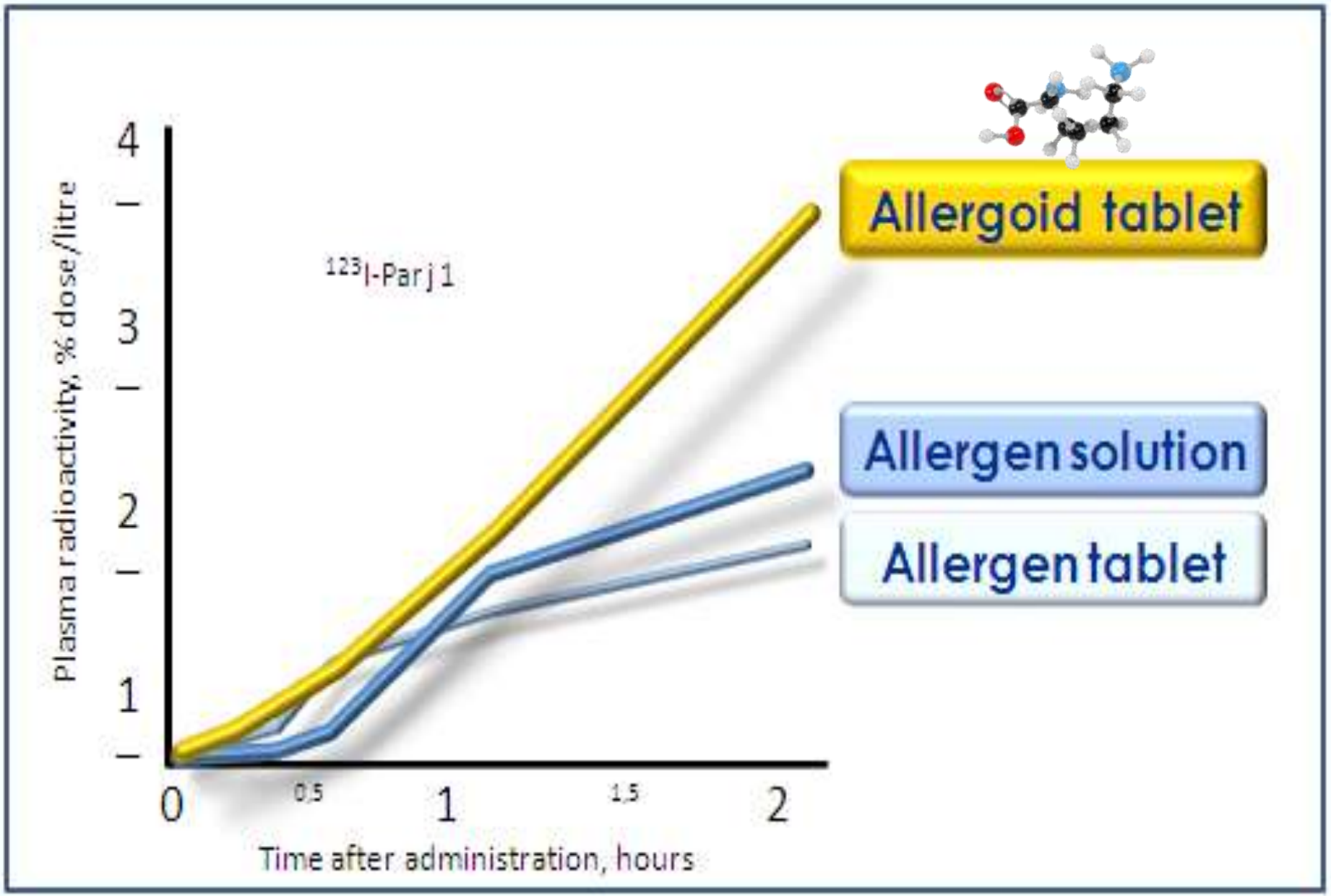
Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers

M. BAGNASCO, G. PASSALACQUA*, G. VILLA†, C. AUGERI†, G. FLAMIGNI†, E. BORINI, P. FALAGIANI‡, G. MISTRELLO‡, G.W. CANONICA* and G. MARIANI†

*Allergy and Clinical Immunology and *Allergy and Respiratory Diseases and † Nuclear Medicine Service, Department of Internal Medicine, Genoa, ‡Lofarma S.p.A., Milan, Italy*



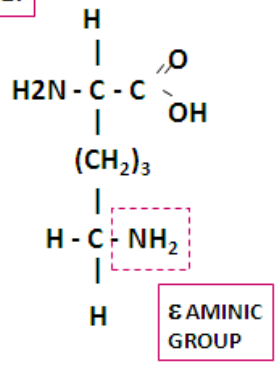



Plasma radioactivity, % dose/litre
4
3
2
1
0
0,5
1
1,5
2
Time after administration, hours
^{123}I-Parj 1
Allergoid tablet
Allergen solution
Allergen tablet

Resistence to enzymatic degradation

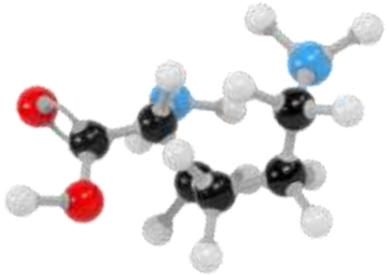
NATIVE ALLERGEN

LYSINE:



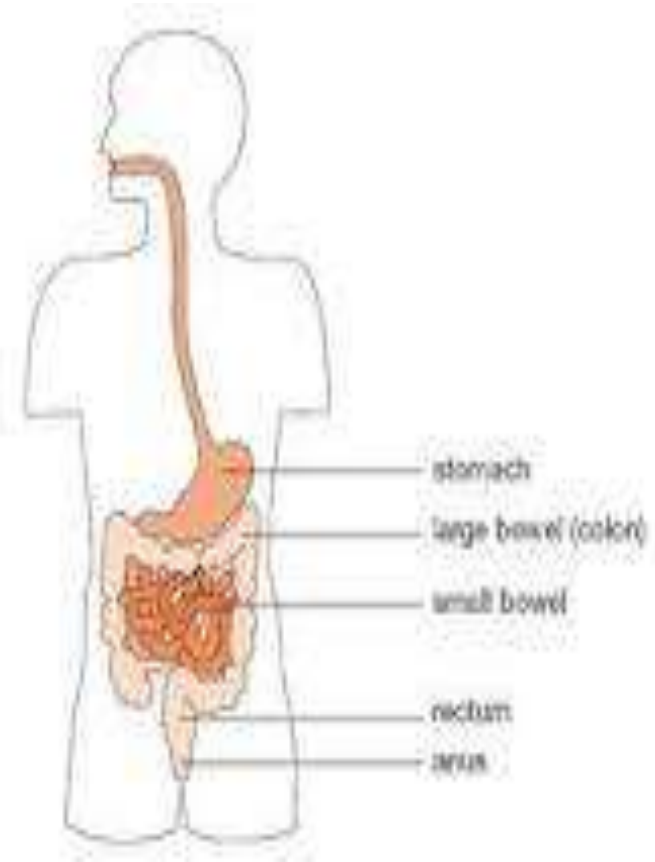
degradation

Enzymes

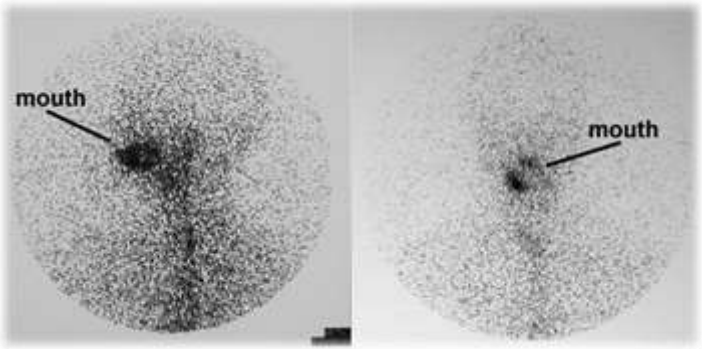


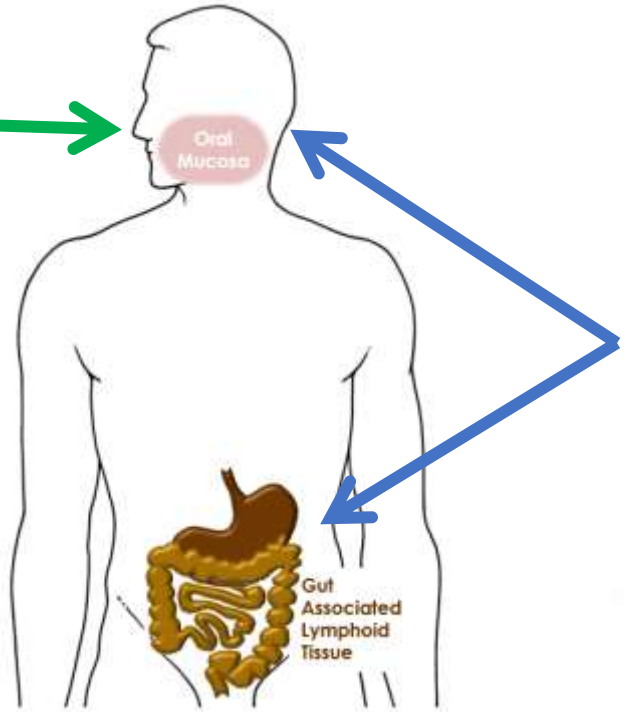
Enzymes

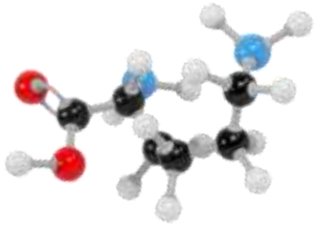
Low degradation



Biologically active dose







Why using an allergoid ?

Because the given dose is more efficient

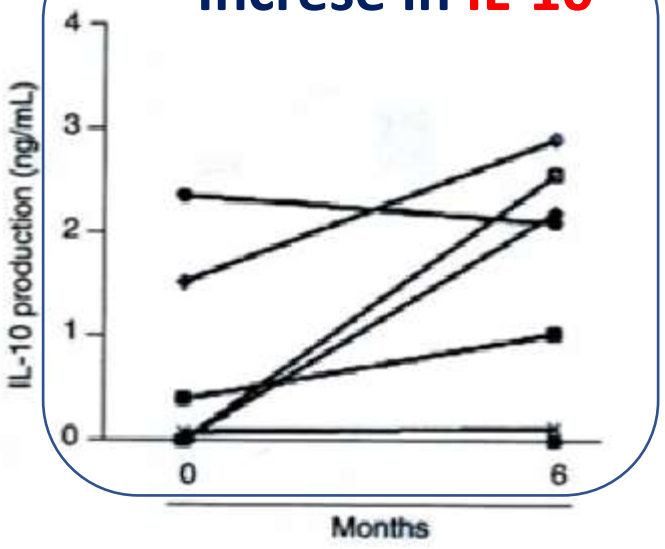
doi: 10.1111/j.1365-2222.2006.02429.x
Clinical and Experimental Allergy, 36, 261–272

ORIGINAL PAPER

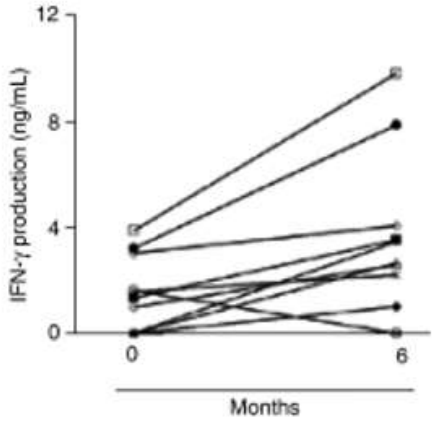
Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-γ- and interleukin-10-production

L. Cosmi[1]*, V. Santarlasci[1]*, R. Angeli*, F. Liotta*, L. Maggi*, F. Frosali*, O. Rossi*, P. Falagiani†, G. Riva†, S. Romagnani*, F. Annunziato* and E. Maggi*
*Center of Research, Transfer, High Education 'DENOthe', University of Florence, Firenze and †Laboratorio Allergeni, SpA, Milano, Italy

Increse in IL-10

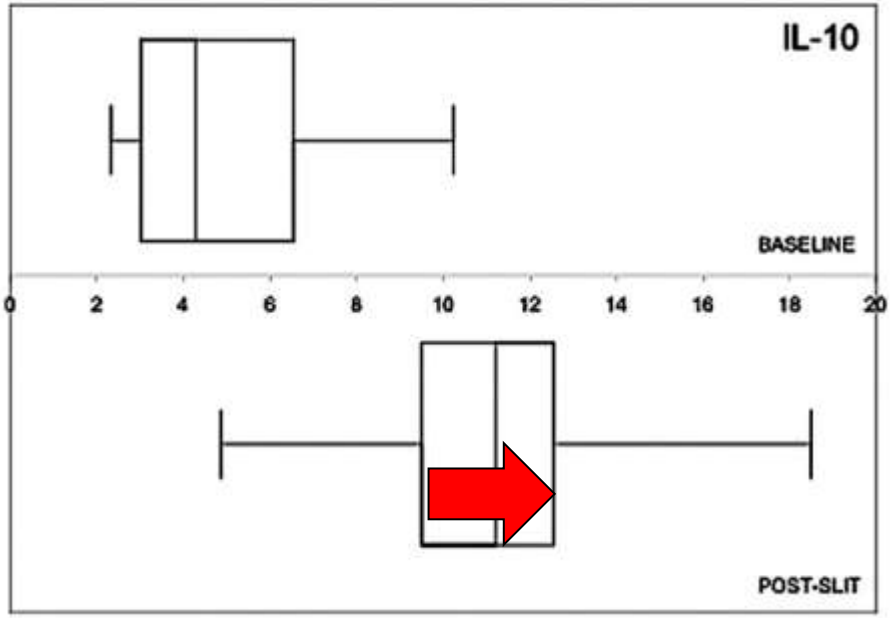


Increase in IFN-g



Cosmi - Maggi - Romagnani . Clin Exp Allergy2006

Effect of sublingual immunotherapy with grass monomeric allergoid on allergen-specific T-cell proliferation and interleukin 10 production



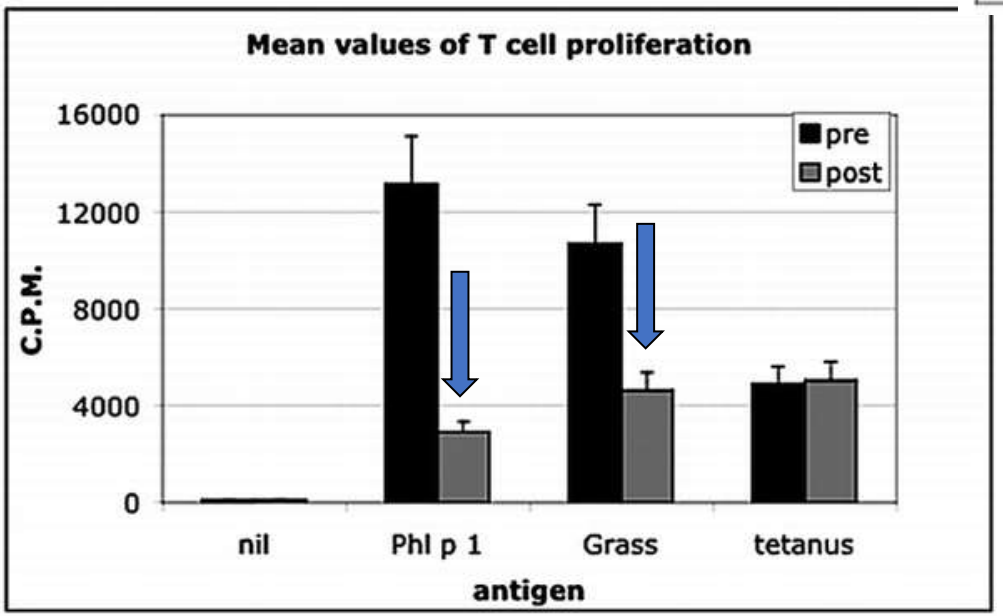


Table 2. Percentage of IL-10–Positive Cells Among CD3⁺ T Lymphocytes[a]

Donor	Before SLIT	After SLIT
1	0.68	1.22
5	0.71	3.29
7	2.18	4.63
8	0.90	2.98
11	1.42	5.49
Median	0.90	3.29
Interquartile range	0.71–1.42	2.98–4.63

Burastero et al, Ann Allergy Asthma Immunol. 2008;100:343–350

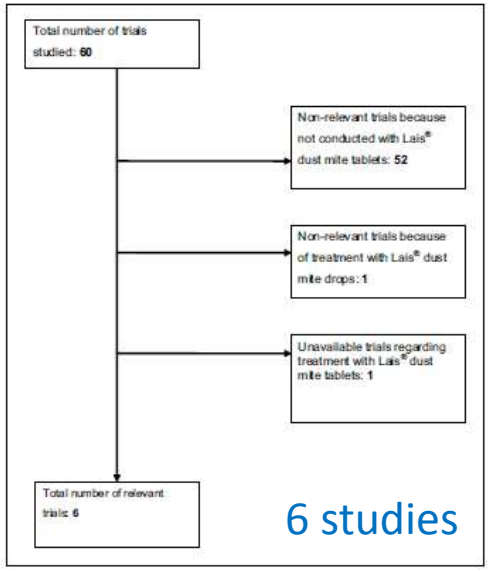
KEY Message

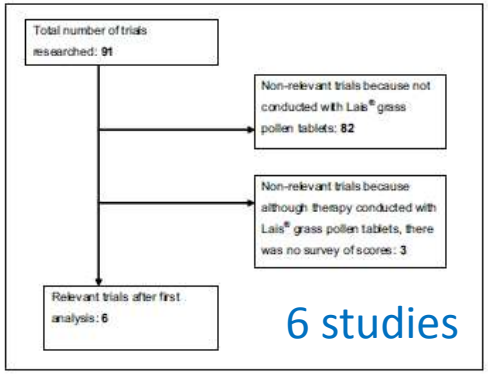
- Monomeric Allergoid Lais® aims to fulfil the need for better risk –benefit ratio
- Lais® has allergenic reactivity strongly reduced
- Lais® mantains molecular size of native allergens
- Lais® has enhanced profile of bioavailability
- Lais® work on the immune system in a pro-tolerogenic way

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





DBPCRT, observational studies, randomized controlled trials, open controlled studies, and retrospective trials

Grass Monomeric Allergoid Vs PLACEBO:

-34% in symptoms reduction

-48% in medication use reduction

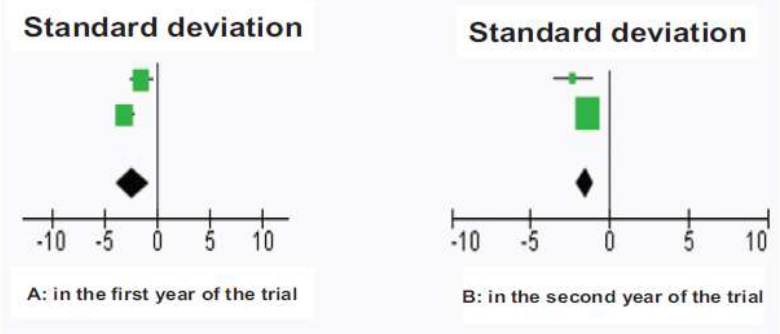
Published trials of the treatment of grass pollen induced allergic rhinoconjunctivitis

Author	Method	Study participants				Outcomes	
		Allergoid tablets	Placebo, control	Duration	Intervention	Relative improvement in symptom score	Relative improvement in medications score
V Bordignon (1994)	Double-blind, placebo-controlled trial	30	30	3 yrs	SLIT vs. placebo	38.5% ($p < 0.05$)	74.60% ($p < 0.001$)
C Caffarelli (2000)	Double-blind, placebo-controlled trial	24	20	1 yr	SLIT vs. placebo	31.66% ($p < 0.01$)	n.s.
G Cavagni (1996)	Double-blind, placebo-controlled trial	24	20	2 yrs	SLIT vs. placebo	30.45% ($p < 0.01$)	22.63% ($p<0.05$)
C Lombardi (2001)	Open controlled trial	26	25	3 yrs	SLIT vs. control	Rhinitis: 17.27% ($p=0.01$) Asthma: 60.47% ($p=0.01$)	Rhinitis: 55.55% ($p = 0.01$) Asthma: 68.43% ($p = 0.01$)
ML Pacor (1996)	Observational study	34		2 yrs	SLIT	$p<0.001$	n.s.
AG Palma-Carlos (2006)	Double-blind, placebo-controlled trial	17	16	2 yrs	SLIT vs. Placebo	$p<0.03$	$p<0.02$

Mites Monomeric Allergoid Vs PLACEBO:

-22% in symptoms reduction

-24% in medication use reduction

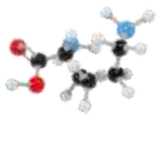


Published trials of the treatment of dust mite induced allergic rhinoconjunctivitis.

Author	Method	Study participants		Duration	Intervention	Outcomes	
		Allergoid tablets	Placebo, control			Relative improvement in symptom score	Relative improvement in medications score
L Cosmi (2006)	Open, parallel group design	11	9	2 yrs	SLIT vs. control	2.44% ($p < 0.05$)	39.51% ($p < 0.05$)
M La Rosa (1996)	Randomized trial, parallel group design	30	21 SCIT	19 mos	SLIT vs. SCIT	n.s.	n.s.
M Marogna (2007)	Retrospective trial	53	12	1–4 yrs	SLIT vs. control	$p < 0.001$	$p < 0.001$
ML Pacor (1995)	Open observational study	14		2 yrs	SLIT	n.s.	n.s.
G Passalacqua (1998)	Double-blind, placebo-controlled trial	10	9	23 mos	SLIT vs. placebo	48.4% ($p < 0.0002$)	n.s.
G Passalacqua (2006)	Double-blind, placebo-controlled trial	28	28	3 yrs	SLIT vs. placebo	13.9% ($p < 0.05$)	7.83% ($p = 0.036$)

Note: *n.s. = not specified*

World Allergy Organization Consensus Document



1986
Scadding et al
1st DBPC trial

1997
Tari et al
1st pediatric trial

Bagnasco et al.
Absorption and kinetics of radiolabelled allergen

1998
Passalacqua et al
1st study with tablets

1998
Lombardi et al, DiRienzo et al.
Postmarketing studies on SLIT Safety in Adults & Children

1998
WHO accepts SLIT for adults

2001
ARIA - *Bousquet et al.*
SLIT for adults and children

2004
Wilson et al.
1° METANALYSIS

2004
Novembre et al.
Preventive effect

2005-2006
Cosmi et al, Durham et al., Bohle et al.
SLIT Mechanims

2005- 2007
DiRienzo et al., Fiocchi et al., Agostinis et al.
SLIT safety in children below 5 years

2006-2008
Penagos et al.
Meta-analyses in children

2006
Cox et al.
1° USA review

2006-2009
Large RCTs with tablets in Adults &Children

REGISTRATION in Europe of SLIT Grass Tablets as Drug


Лайс Грасс
Таблетки подъязычные
300 АЕ / 1000 АЕ
Начальный курс
для сублингвальной иммунотерапии
40 таблеток подъязычных
10 табл.: 300 АЕ
30 табл.: 1000 АЕ
Лофарма
Лайс Грасс


Лайс
Дерматофагоидес
Таблетки подъязычные
1000 АЕ
Поддерживающий курс
для сублингвальной иммунотерапии
30 таблеток подъязычных
30 табл.: 1000 АЕ
Лофарма
Лайс
Дерматофагоидес

УДК: 616-08-039.71

Опыт применения карбамилированного мономерного аллергоида Lais® для сублингвальной иммунотерапии пациентов с аллергическим риноконъюнктивитом, вызванным пыльцой злаковых трав

И.В. Данилычева, Н.И. Ильина, А.Е. Шульженко
ФГБУ «ГНЦ Институт иммунологии» ФМБА России, г. Москва

Ключевые слова: аллергический риноконъюнктивит, сублингвальная иммунотерапия, карбамилированный мономерный аллергоид

GRASS

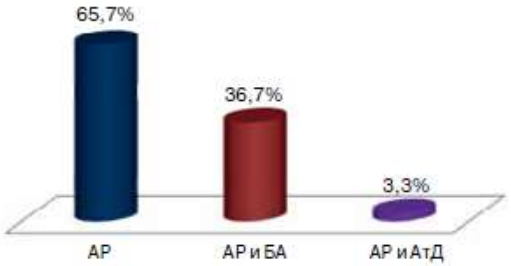


Рис. 1. Распределение пациентов, принявших участие в исследовании, по нозологическим формам.
АР – аллергический ринит; БА – бронхиальная астма; АтД – атопический дерматит

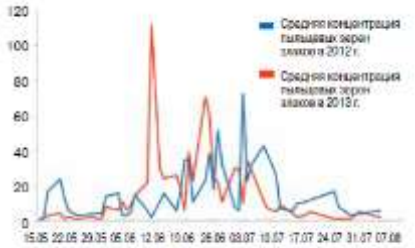


Рис. 2. Концентрации пыльцевых зерен злаков в Москве в сезоны 2012 и 2013 годов

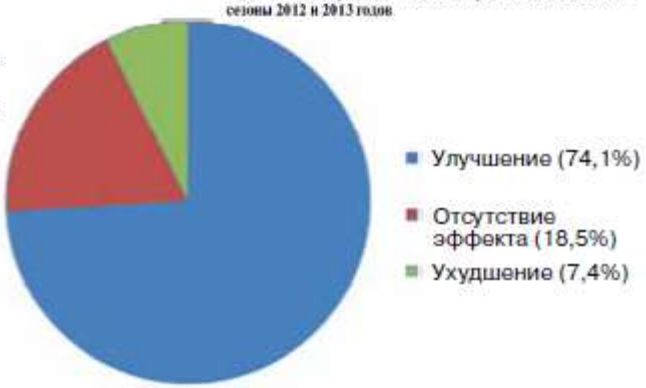


Рис. 3. Эффективность СЛИТ аллергоидом Lais® (злаковые травы)

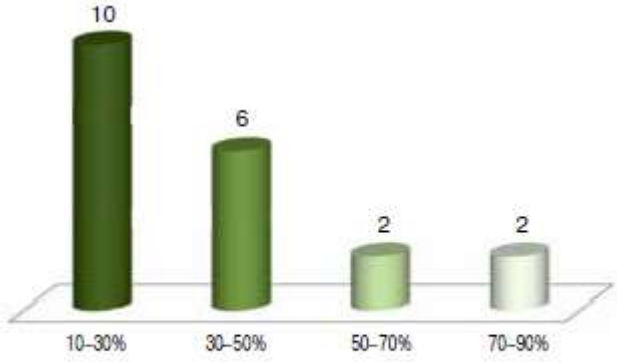


Рис. 4. Субъективная оценка пациентами эффективности СЛИТ аллергоидом Lais® (злаковые травы). Над столбиками указано абсолютное число пациентов

УДК: 616.211-002

Опыт применения карбамилированного мономерного аллергоида LAIS® для сублингвальной иммунотерапии пациентов с аллергическим риноконъюнктивитом, вызванным пыльцой злаковых трав и клещами *Dermatophagoides pteronyssinus* и *Dermatophagoides farinae*

И.В. Данилычева, Н.И. Ильина, А.Е. Шульженко
ФГБУ «ГНЦ Институт иммунологии» ФМБА России, г. Москва

Ключевые слова: аллергический риноконъюнктивит, сублингвальная иммунотерапия, карбамилированный мономерный аллергоид

DERMA

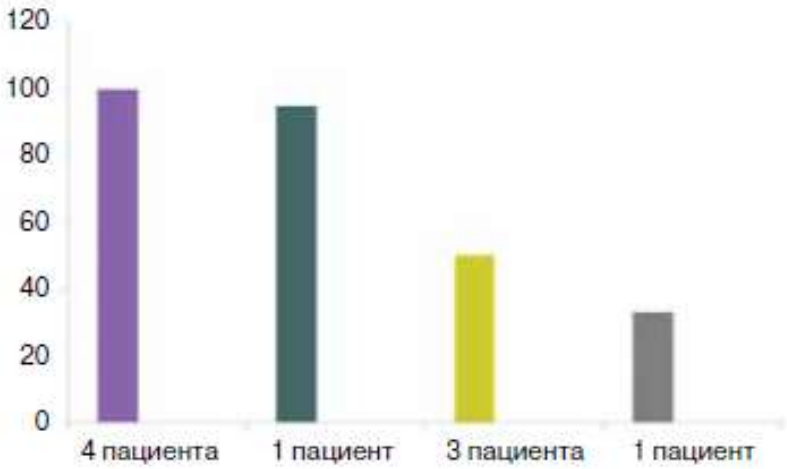


Рис. 5. Снижение потребности в деконгестантах (%)

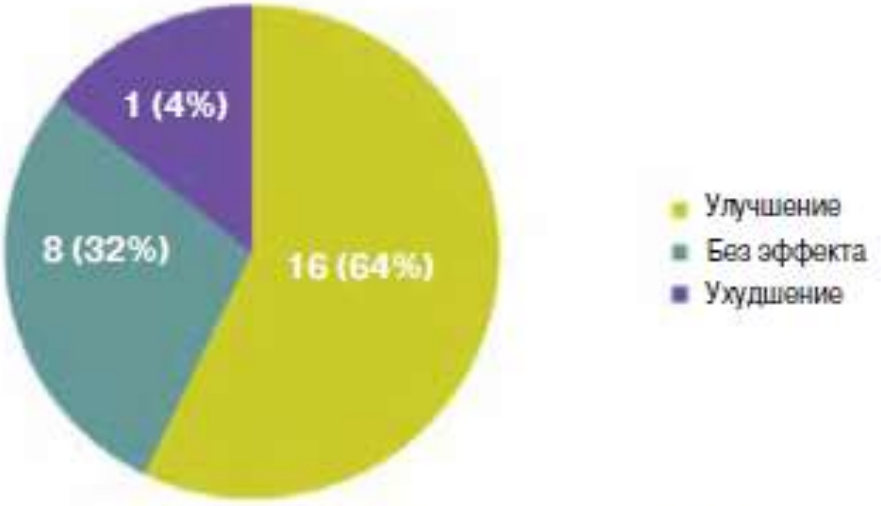


Рис. 4. Эффективность СЛИТ аллергоидом Лайс® (клещи домашней пыли)

1. препараты является высокоэффективными для лечения пациентов с аллергическим ринитом и конъюнктивитом с сенсибилизацией к пыльце злаковых трав и клещам домашней пыли;

2. обладают хорошим профилем безопасности;

3. обеспечивают высокую приверженность к лечению.

Препараты могут быть рекомендованы для широкого использования в лечении пациентов с аллергическим ринитом и конъюнктивитом с сенсибилизацией к пыльце злаковых трав и ринитом у пациентов с сенсибилизацией к клещам домашней пыли.

KEY Message

- Monomeric Allergoid Lais® showed clinical efficacy and adult and children affected by allergic rhinitis and asthma
- Lais® largely contributed to the SLIT international literature
- Lais® is available for GRASS pollen and HOUSE DUST MITES in Russia
- Lais® for GRASS and HOUSE DUST MITES was successfully used in Russia

Why using an allergoid ?

Safe, well tolerated,
efficient,
with consolidated use and satisfaction

Frequently asked questions

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

Does the chemical modification impair the vaccine content of allergens ?

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Allergen identification and characterisation of lysine modification in monomeric allergoids

Waschl, CC[1]; Steiner, M[1]; Mistrello, G[2]; Briza, P[1]; Ferreira-Briza, F[1]; Himly, M[1]
[1]Molecular Biology, Paris Lodron University of Salzburg, Salzburg, Austria; [2]Lofarma spa, Research and Development, Milan, Austria

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Mass spectrometry
+ liquid chromatography

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

Phleum partense,
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

Which patient is candidate to LAIS®?

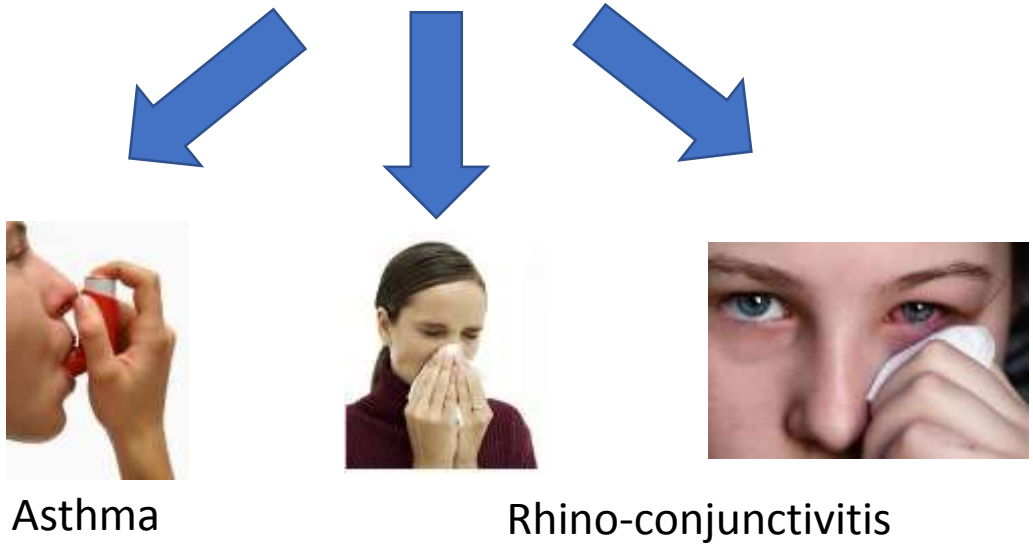
Monomeric Allergoid SLIT: Indications

- **Grass extract**

(Phleum pratense 33%, Holcus lanatus 33%, Poa Pratensis 33%)

- **Mites extract**

(Dermatophagoides pteronissinus 50%, Dermatophagoides farinae 50%)



Asthma

Rhino-conjunctivitis

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

Схема лечения*

За 2 месяца до начала сезона цветения и во время него.

Таблетки держат под языком до полного рассасывания (1-2 минуты).

- Фаза определения максимальной терапевтической дозы:

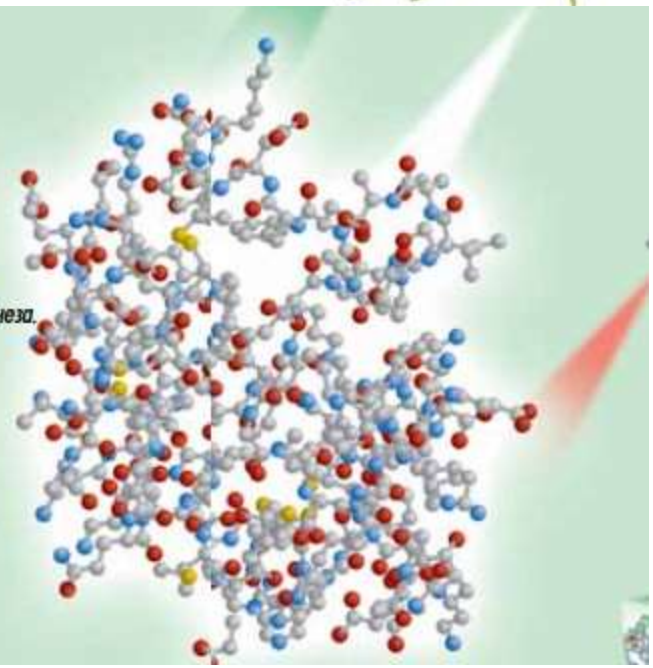
1-й день – 1 табл. (300 АЕ), 2-й день – 2 табл. (600 АЕ),
3-й день – 3 табл. (900 АЕ), 4-й день – 4 табл. (1200 АЕ).

- Фаза лечения:

по 1 табл. (1000 АЕ) в день 5 раз в неделю (например, с понедельника по пятницу).

АСИТ рекомендовано проводить от 3 до 5 лет.

** Предложенные схемы лечения приведены исключительно в качестве рекомендаций. Схему приема препарата определяет врач-аллерголог на основании наблюдений и анамнеза.*



Лофарма

Производитель: «Лофарма С.п.А.»
20143, Италия, Милан, Виале Кассала, д. 40.

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- Фаза лечения:

по 1 табл. (1000 АЕ), от 2 до 5 раз в неделю по усмотрению врача.

АСИТ рекомендовано проводить от 3 до 5 лет.

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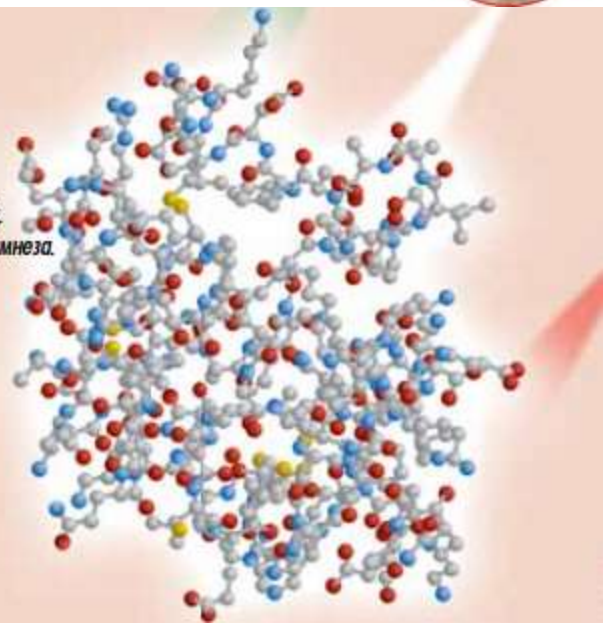


Лофарма

Производитель: «Лофарма С.п.А.»
20143, Италия, Милан, Виале Кассала, д. 40.

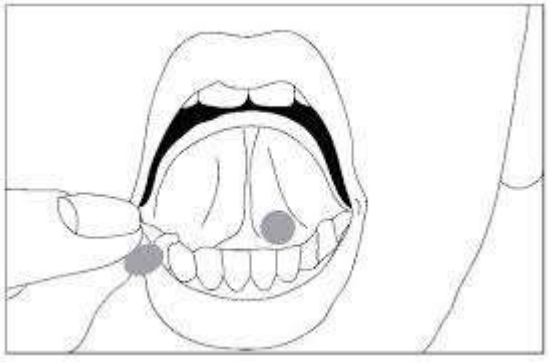
Factors to be considered for correct prescription

1. IgE mediated mechanism (skin test/serum CAP)
2. Clear causal relationship exposure-symptoms
3. Exclusion of other causes
4. Impact of symptoms on QoL, work and school activity
5. Low response to standard pharmacotherapy
6. Side effect with pharmacotherapy
7. Refuse injections (SCIT)
8. Compliance to long term treatment
9. Absence of contraindications

Contraindications

- lactose intolerance,
- severe systemic diseases,
- active autoimmune disease,
- immunodeficiency,
- chronic inflammatory diseases,
- heart failure,
- neoplasia,
- viral infection,
- severe uncontrolled asthma,
- FEV1 <70%
- contraindication to adrenaline

Intake modalities



- Sublingual-swallow modality

keep under the tongue for a couple of minutes
on empty stomach, then swallow residues

- Take the tablets away from meals

- The first dose can be administered under medical superivision

- Patient should be instructed to seek immediate medical care and discontinue therapy in case of severe systemic reactions.

Special precautions

Avoid alcoholics and
strong physical exercise

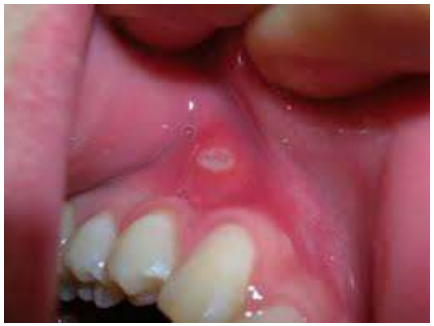
A sensation of fatigue is likely to be experienced after administration.
Alert on the ability to drive and use machines

Special precautions

Do not start in pregnancy and breastfeeding

Concomitant acute illnesses (fever, flu..): temporary interruption until recovery

Oral inflammation: in patient with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of treatment should be postponed



Special precautions

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

Consider alternative drugs or benefits/risk ratio

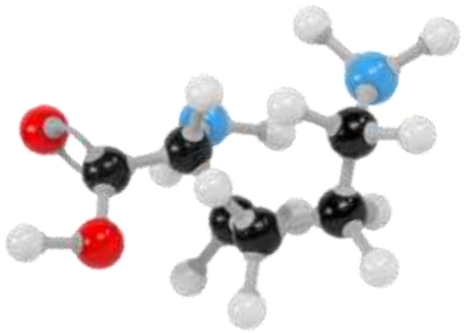
Before starting a specific immunotherapy, allergy symptoms must be eventually stabilized with an appropriate pharmacological treatment.

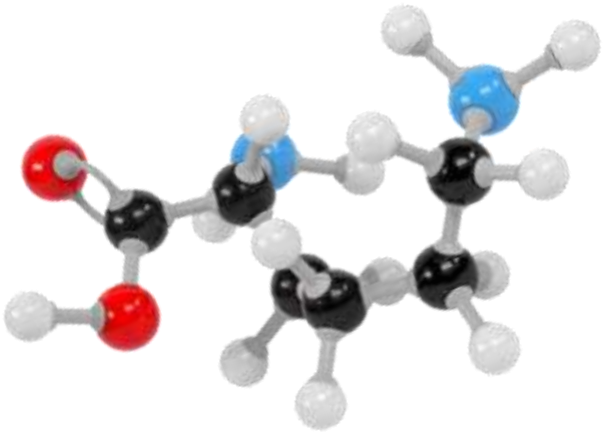
Special precautions

In asthmatic patients
SLIT should initially be used in addition to the pharmacologic therapy for asthma and not as a substitute of a pre-existing therapy.

It is recommended **not to discontinue abruptly a medicine used to control asthma**

Gradual reduction of the medicine used to control asthma under medical supervision and according to the guidelines for asthma treatment.



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E RICERCA
MADE IN Italy

Thank you
for your attention!

за внимание!

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