



# Allergen immunotherapy: from EBM to doctors' and patients' need

**Moscow, Marriott Hotel  
February 28th, 2019**

**Dr. Franco Frati**

**Medical Department**

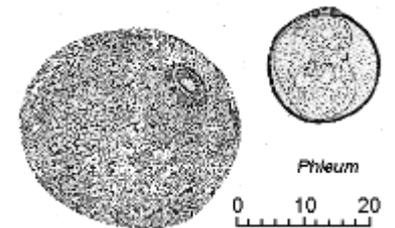
 **Lofarma** Milan, Italy

# From the recognition of the pollen to in vivo tests



Charles Harrison Blackley (1820-1900)  
**Hay Fever: Its Causes, Treatment, and  
Effective Prevention, Experimental  
Researches**  
London

**1880**



# Immunotherapy :

## The first severe side effects

**POLLANTIN**  
(passive  
immunization)



William Dunbar

Pollantin



<sup>3</sup> W. P. Dunbar: Zur Ursache und spezifischen Heilung des Heufiebers, München, 1903.

# Anaphylaxis during pollantin



1911



# THE LANCET

[www.thelancet.com](http://www.thelancet.com)

## Reprint

Prophylactic inoculation against hay fever

L. Noon, B.C. Cantab, F.R.C.S. Eng.  
*Lancet* 1911; June 10: 1572-3



**Conclusion: the result of these experiments demonstrates that the sensibility of hay fever patients may be decreased by properly directed dosage. (Noon L. et al The Lancet 1911)**

# Bad year for the SCIT

# 1988

## CSM UPDATE

### Desensitising vaccines

**D**ESENSITISATION THERAPY (hyposensitisation or immunotherapy) has been used to treat allergic disorders since the early 1900s. It aims to reduce the susceptibility of patients to symptoms induced by specific environmental allergens to which they have been found to be sensitive. The two types of desensitising vaccines most commonly used in the United Kingdom are extracts of house dust mite and grass pollen. Extracts of a large variety of other allergens, including bee and wasp venoms, are also available and are given either singly or in combination. A confusing number of different units are used to express the allergen content of the products currently marketed. The absence of a standard unit means that products containing the same allergen are not interchangeable. Treatment usually entails subcutaneous injections of increasing concentrations of allergen(s). These are usually given at intervals of seven to 14 days before any likely natural exposure to the allergen(s), for seasonal allergic disorders, or at any time for perennial allergens. The number of injections in a course of treatment varies from three to 18, depending on the products used. In addition, maintenance injections of allergen, usually at monthly intervals, are advocated for perennial allergies.

There is convincing evidence of efficacy for some vaccines. These include the rag weed extract used in the United States, where rag weed is a common cause of allergy; the vaccines used to protect against anaphylaxis induced by some antibiotics; and the bee and wasp venoms. The efficacy of other vaccines is more difficult to assess. In double blind placebo controlled studies carried out in patients with hay fever and asthma there is some evidence that by the end of a course of grass pollen extracts some patients will be less susceptible to

TABLE 1—Number of cases and incidence (per course of treatment) of serious adverse reactions to desensitising agents reported in the UK. Figures given as percentages after each agent are number of courses still during the stated period

	Allergens			
	Anaphylaxis	Bronchospasm	bronchospasm+	Death
<i>Form of house dust mite</i>				
Merck (18000, 1979-80)				
No. of cases	38	19	58	2
Estimated incidence	1/415	1/150	1/412	1/2000
Mega (110400, 1973-80)				
No. of cases	19	30	52	4
Estimated incidence	1/631	1/347	1/230	1/2450
<i>Pollen extracts</i>				
Merck Grass (10 500, 1979-80)				
No. of cases	14	18	28	0
Estimated incidence	1/302	1/122	2/151	
Pollens (50 500, 1974-80)				
No. of cases	50	27	57	2
Estimated incidence	0.21/310	1.07/311	1.91/289	1/11750
Alexis P. (20 500, 1979-80)				
No. of cases	3	7	10	0
Estimated incidence	0.11/156	1/942	0/998	
Spectolign Pollen (500, 1982-8)				
No. of cases	1	7	8	0
Estimated incidence	1/500	1/71	1/62.7	
<i>A mixture of many different allergens</i>				
Novartis (27 000, 1979-80)				
No. of cases	17	8	25	0
Estimated incidence	1/941	1/121	1/240	
Centax (1150, 1981-8)				
No. of cases	1	0	1	0
Estimated incidence	1/1800	1/420	1/117	
Allyria (189 000, 1979-80)				
No. of cases	14	17	28	0
Estimated incidence	0.0001	0.0002	0.0002	



TABLE 1—Details of 26 patients\* who died from anaphylaxis induced by desensitising agents†

	No		No
Indication for treatment:		Adverse reactions reported to previous injections in final course of treatment:	
Asthma	16	Yes	6
Hay fever	1	No	20
Unknown	9		
Type of treatment:		Time of onset of reaction:	
Normal course	16‡	<10 minutes	14
Maintenance injections	4	<30 minutes	4
Unknown	6	<90 minutes	2
		Unknown	6

# First DBPCs SLIT



*Clinical Allergy*, 1986, Volume 16, pages 483–491

## Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite

GLENIS K. SCADDING and J. BROSTOFF

*Department of Immunology, Middlesex Hospital Medical School, London, W1P 9PG*

*(Received in original form 4 December 1985 and in revised form 25 April 1986; accepted for publication 28 April 1986)*

### Summary

In a double-blind placebo-controlled cross-over trial, low dose sublingual therapy with house dust mite was effective in relieving symptoms in 72% of the group of patients with perennial rhinitis due to house dust mite ( $P < 0.03$ ). Following active treatment, there was a significant increase in morning peak nasal inspiratory flow rate ( $P < 0.01$ ) in those who improved (thirteen out of eighteen) and resistance to nasal provocation with house dust mite also increased, in some cases up to 1000-fold ( $P < 0.05$ ). Oral therapy is safe and avoids the side effects of desensitizing injections which can be serious. The potential for oral desensitization is great and further studies on this form of treatment are needed.



**SLIT therapy is safe and avoids the side effects of desensitizing injections which can be serious. (Scadding G.: CEA 1986)**

# Allergic inflammation in the target organs

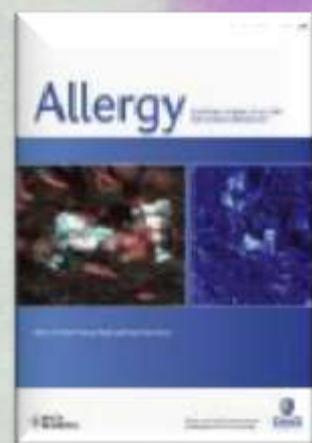


**AIT**



**AntiH1**

**CTS**



# Which product to choose?



**EFFICACY**

**SAFETY**

**SLIT IN RESPIRATORY ALLERGY**

## Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses

Enrico Compalati, MD; Martin Penagos, MD; Francesco Tarantini, MD; Giovanni Passalacqua, MD; and Giorgio Walter Canonica, MD

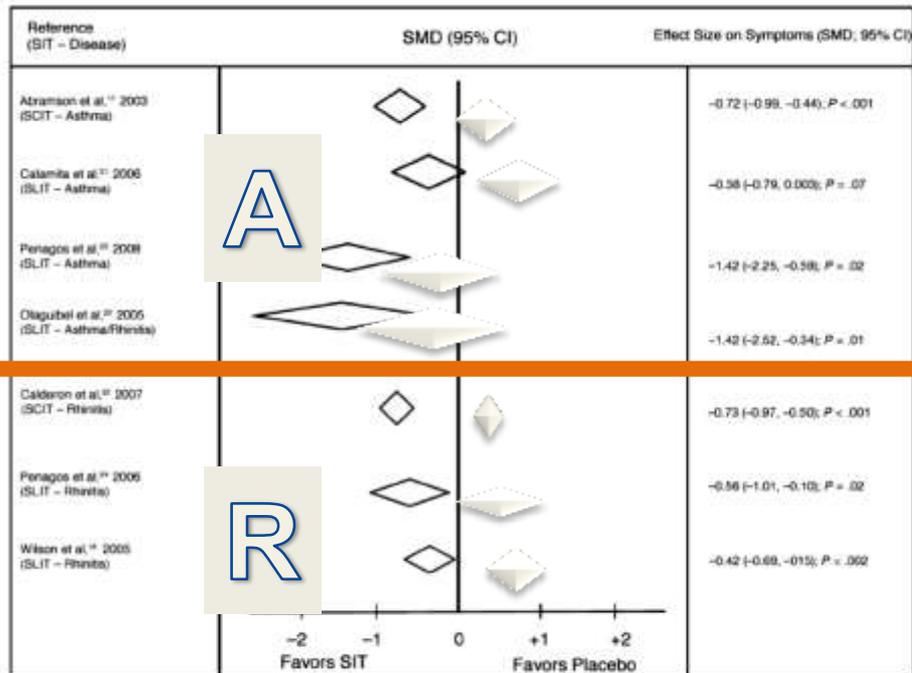
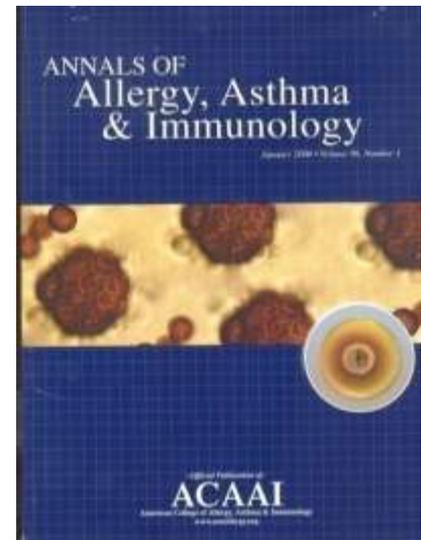


Figure 1. Efficacy of specific immunotherapy (SIT). Summary of meta-analysis results expressed as effect size on symptoms. CI indicates confidence interval; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; and SMD, standardized mean difference.

According to evidence-based criteria, AIT can be recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms. Also, future methodological approaches that consider safety and costs should corroborate this positive evaluation

Compalati E. et al AAAI 2009

# 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



## History of DBPCs in ITS

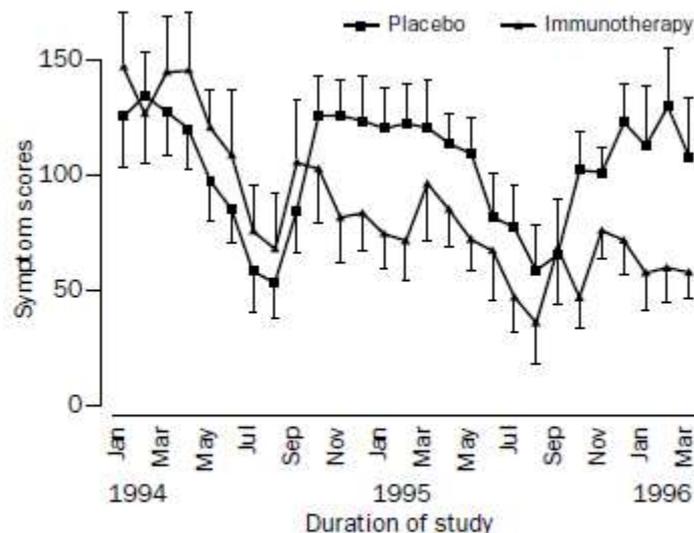


Figure 2: Mean (95% CI) symptom scores in the immunotherapy (n=10) and placebo (n=9) groups

## THE LANCET

"A staggering tripling of diagnosed cases of diabetes in the USA, from 6.2 million cases in the late 1980s to 21.1 million cases in the early 2010s."



# The most famous study

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



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

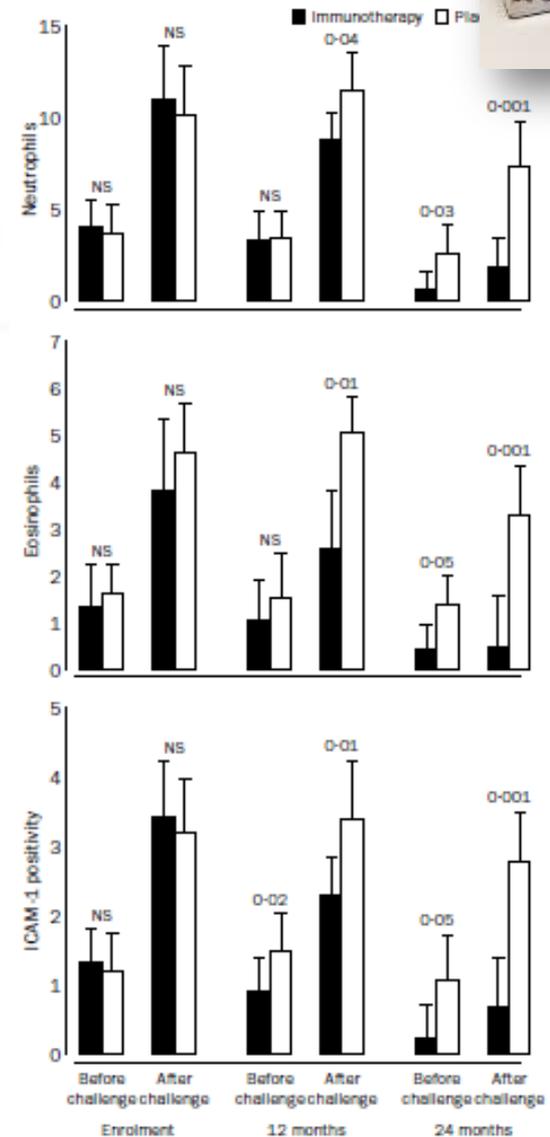


Figure 3: Inflammatory conjunctival variables (mean [95% CI]) before and after challenge at enrolment, 12 months, and 24 months

## Anti inflammatory effect

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

Samuele E. Burastero, MD\*; Gianni Mistrello, PhD†; Paolo Falagiani, DVM†; Clara Paolucci, PhD\*; Daniela Breda, BSc\*; Daniela Roncarolo, PhD†; Stefania Zanotta, PhD†; Giorgio Monasterolo, MD‡; and Renato E. Rossi, MD§

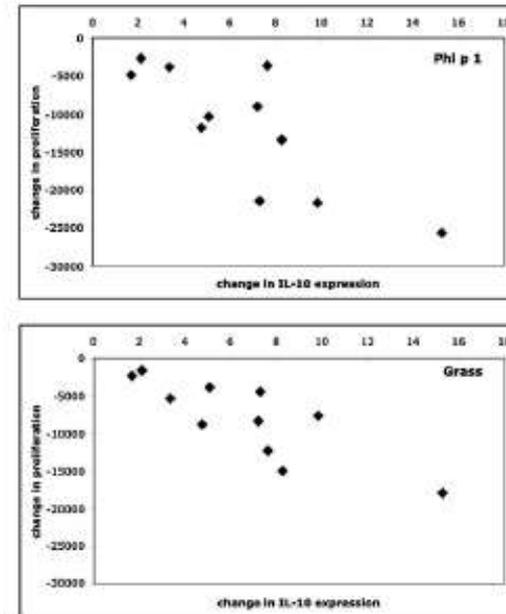
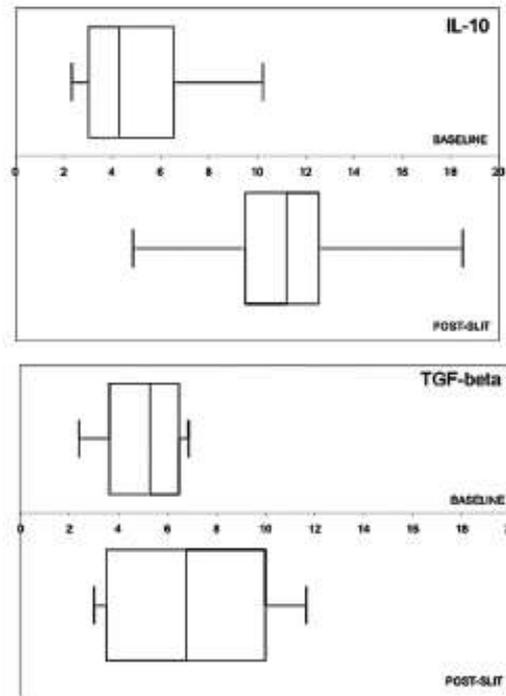
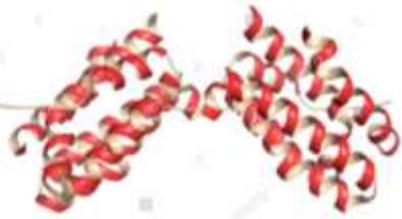


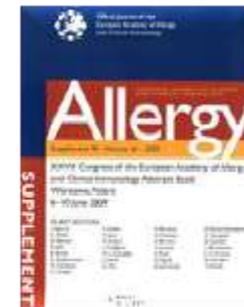
Figure 3. Correlations of the observed changes in allergen-dependent interleukin 10 (IL-10) expression after sublingual immunotherapy (SLIT) (post-SLIT minus pre-SLIT values) with the corresponding allergen-dependent changes in proliferation. Results obtained with comparison of proliferation



# 2000

## Original article

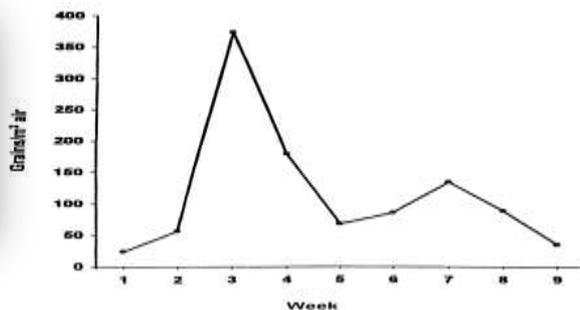
### Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial



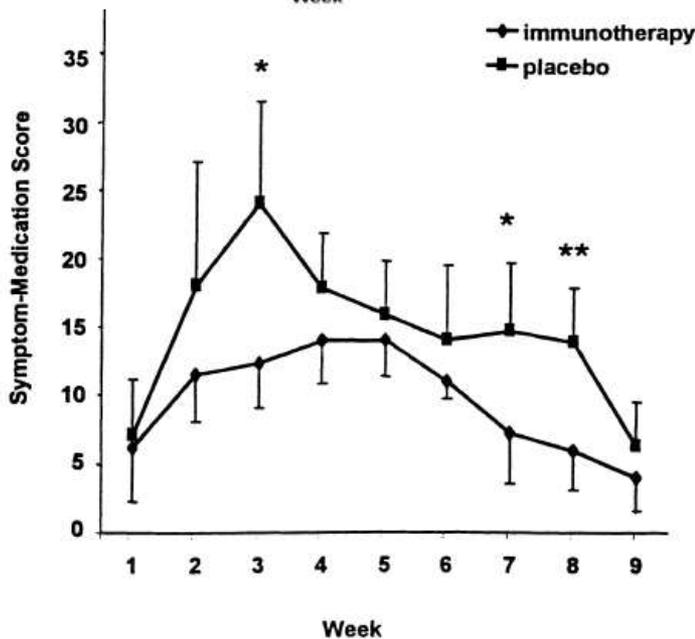
**Background:** We assessed the efficacy of preseasonal local allergoid immunotherapy in a group of children with asthma and/or rhinitis and/or

**C. Caffarelli**

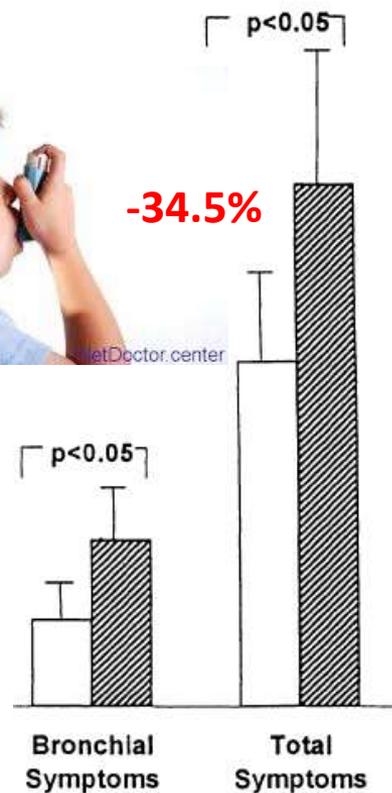
Pediatric Department, Parma



1° double-blind, placebo-controlled, randomized study with grass tablets in children



-34.5%



# Which product to choose?



**EFFICACY**

**SAFETY**

**SLIT IN RESPIRATORY ALLERGY**

# Safety of sublingual immunotherapy in children

Franco Frati<sup>†</sup>, Erminia Ridolo, Nicola Fuiano, Salvatore Barberi, Ilaria Dell'Albani, Massimo Landi, Luisa Ricciardi, Guglielmo Scala & Cristoforo Incorvaia

<sup>†</sup>*Sublergenes, Medical and Scientific Department, Milan, Italy*

**Introduction:** Sublingual immunotherapy (SLIT) was introduced as a safer option to subcutaneous immunotherapy (SCIT) which was associated with the possible occurrence of systemic reactions including anaphylaxis and, though very rarely, fatalities. Some anaphylactic reactions to SLIT are reported, mainly in adults but also in children. It is therefore important to investigate the risk factors related to such reactions.

**Areas covered:** Data from the literature on the safety of SLIT in children were reviewed. The data reviewed concerned the application of this treatment to patients with respiratory allergy and also possible new indications such as food allergy, atopic dermatitis and latex allergy. Reports of anaphylactic reactions were analyzed to identify the potential risk factors.

**Expert opinion:** SLIT is a well tolerated treatment, the common side effect being local reactions in the mouth. Systemic reactions, concerning the skin and the airway, are rare and anaphylactic reactions are extremely rare.

**Keywords:** children, major allergen, safety, sublingual immunotherapy

*Expert Opin. Drug Saf. [Early Online]*



SLIT is a well tolerated treatment, the common side effect being local reactions in the mouth. **Systemic reactions**, concerning the skin and the airway, are rare and **anaphylactic reactions rare extremely rare.** (Frati et al EOD&S 2014)



# Safety of SLIT with a **monomeric carbamylated allergoid** in very young children

*F. Agostinis et al. 2005*

## 33 children

Follow-up : 2 years

Mite (19), grass (17)

Aqueous LAIS® drops - Oral intake

Parents's diary card for 22.2 months follow-up

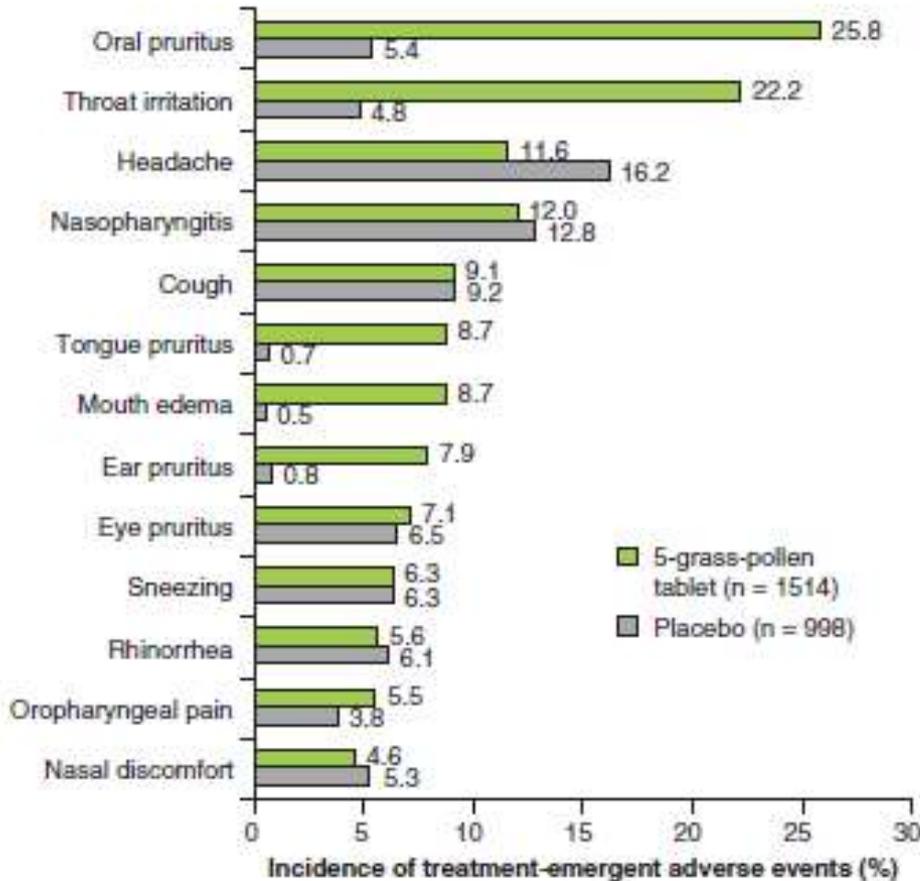


Age range: 1,5 - 3,5 y

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

NEWS

## Safety of grasses high dose tablet



Over 6 years of 5-grass pollen tablet use, 12 cases of **severe anaphylactic reactions** considered by physicians as possibly related to treatment have been reported

**Safety and tolerability of 5-grass pollen tablet sublingual immunotherapy: pooled analysis and clinical review** (Didier A. Drug Safety Evaluation Bons 2015)

# FDA approves Odactra for house dust mite allergies



The most commonly reported adverse reactions were nausea, itching in the ears and mouth, and swelling of the lips and tongue.

The prescribing information includes a **boxed warning** that severe allergic reactions, some of which can be life-threatening, can occur



# Safety of **sublingual immunotherapy with carbamylated monomeric allergoid**: an Italian pharmacovigilance study

E.Compalati, M.Bruno, S.Urbano, P.Strada and F.Frati

## FLORENCE

Palazzo dei Congressi & Palazzo degli Affari

DECEMBER, 6-9 2018

**20 Years**

**15.000.000 doses**

**(MITES and GRASSES)**

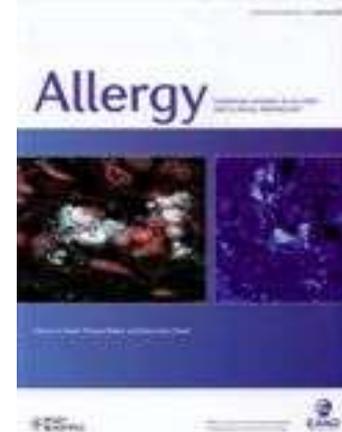
**Adult and Children**

**0.00000 side effects)**



**LAIS NEW DATA 2018**

**Results:** A number of 10.071.390 doses were administered with the Dermatophagoides allergoid and 5.096.930 with the Grass pollen allergoid. Only two reactions were serious consisting of tachycardia (1) and throat oedema (1), completely resolved. The huge disproportion between the large number of administered doses and the very low number of ADRs, and particularly the low presence of serious reactions, **reaching up to 10%** of treated patients or even more in other studies with different tablets, confers evidence of a very appreciable safety profile for the to the **carbamylated monomeric allergoid**.



Accepted: 20 September 2017

DOI: 10.1111/all.13317



WILEY | Allergy

## Recommendation:

patients receiving SLIT have to be informed about possible occurrence of particularly severe reactions and be instructed on their recognition and management

F. Timmermans | O. Tsilochristou | E.-M. Varga | J. N. Wilkinson | A. Williams  
L. Zhang<sup>40</sup> | I. Agache<sup>41</sup> | E. Angier<sup>42</sup> | M. Fernandez-Rivas<sup>43</sup> | M. Jutel<sup>44,45</sup> | S. Lau<sup>46</sup> |  
R. van Ree<sup>47</sup> | D. Ryan<sup>48</sup> | G. J. Sturm<sup>49,50</sup> | A. Muraro<sup>51</sup>

# Final considerations

1. For more than 100 years, **specific immunotherapy** has played a fundamental role in the treatment of respiratory allergies with EBM results.
2. Considering the side effects (even serious) injective therapy has been progressively joined by **sublingual immunotherapy** which immediately proved to be **easy to perform** and **safe in adults and children**.
3. The use of some recent formulations with natural allergen in tablets (grasses and mites) with high allergenic doses have also caused serious side effects (also anaphylaxis).
4. The introduction of **innovative sublingual allergoids (LAIS)** appears to definitively solve this issue both in **adult and children**.

**Thank you**  
**for your attention!**

**Спасибо за внимание!**

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