L'immunoterapia specifica: attualita' e prospettive future

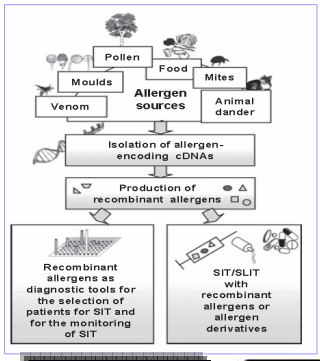
Salvatore Leonardi
Ricercatore dell'Universita' di Catania
Dipartimento di Scienze Mediche e Pediatriche
UNIVERSITÀ DEGLI STUDI DI CATANIA
DIPARTIMENTO DI PEDIATRIA

Antigen-directed therapy of hypersensitivity diseases

- In 1911, Drs John Freeman and Leonard Noon published an account of a novel treatment for hay fever. Their method of desensitisation consisted of injecting increasing doses of an extract of pollen subcutaneously until the hypersensitivity reaction was diminished or abolished
- "there seems little doubt that there has been a distinct amelioration of symptoms. This improvement took several forms; a greater freedom from attack, the attack not so bad as in former years, and the attack sooner over, the constitutional disturbance not so great"

1. Noon, L. Prophylactic innoculation against hay fever. Lancet i, 1572-1573. 1911
2. Larche, M. and Wraith, D.C. Peptide Vaccines for Allergic and Autoimmune Diseases Nature Medicine (2005) 11: 69-76

Leonard Noon John Freeman



Allergy 2011

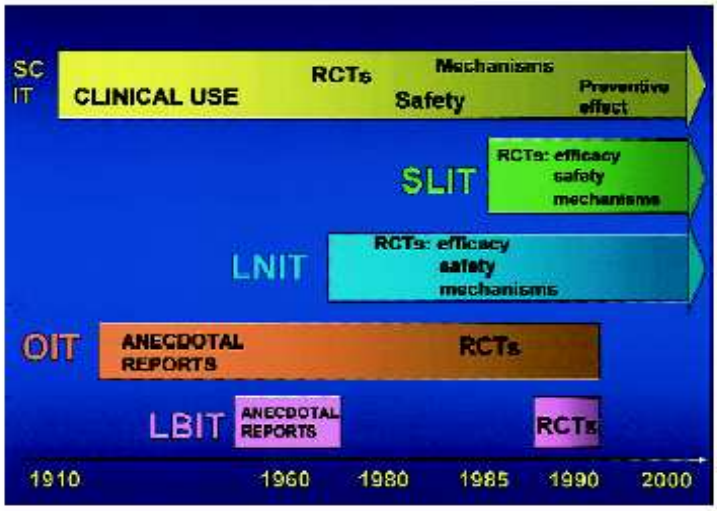


FIG 1. The chronology of the different modalities of immunotherapy. *RCTs*, Randomized controlled trials.

Canonica G, et al. J.Allergy clin.Immunol,2003

Kind of local immunotherapy	Status
Local bronchial immunotherapy	Withdrawn
Local nasal immunotherapy	Withdrawn
Oral immunotherapy	Withdrawn
Sublingual immunotherapy	In use*

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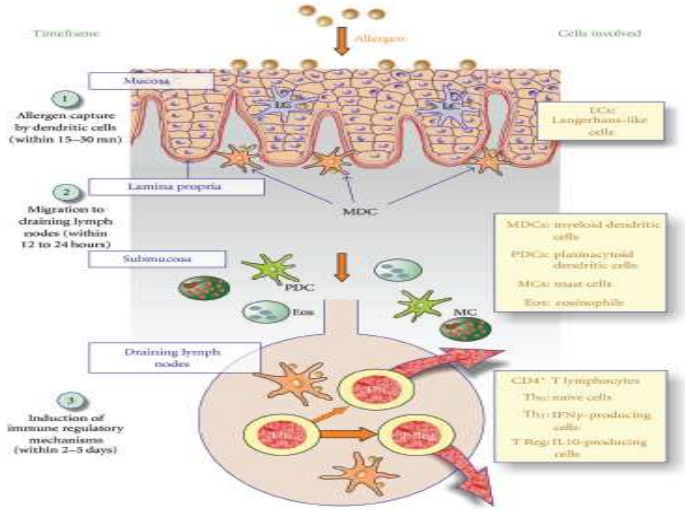
DIPARTIMENTO DI PEDIATRIA

Induction of Tolerance via the Sublingual Route: Mechanisms and Applications

Philippe Moingeon and Laurent Mascarell



Organizzazione Mondiale della Sanità
World Health Organization

Position Paper

IMMUNOTERAPIA ALLERGENE-SPECIFICA: I VACCINI PER LE MALATTIE ALLERGICHE

ALLERGEN IMMUNOTHERAPY: THERAPEUTIC VACCINES FOR ALLERGIC DISEASES

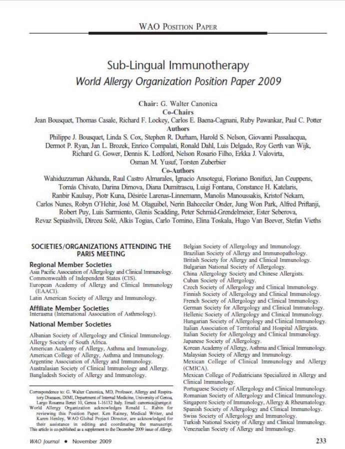
American Academy of Allergy, Asthma and Immunology (AAAAI)
European Academy of Allergology and Clinical Immunology (EAACI)
European Society of Pediatric Allergy and Clinical Immunology (ESPACI)
IUIS/IAACI Sub Committee on Allergen Standardization
Japanese Society of Allergology
National Institute of Allergy and Infectious Diseases (NIAID),
World Health Organization (W.H.O.)

Approvato da:
American College of Allergy, Asthma and Immunology (ACAAI)
International Association of Asthmology (Interasma)

…… l'ITS costituisce l'unica opzione in grado di modificare la "Storia naturale" delle malattie allergiche e di prevenire lo sviluppo di nuove sensibilizzazioni (1998)

WAO Sublingual Position Paper 2009

EFFICACIA CLINICA DELLA SLIT



WAO Position Paper

Sub-Lingual Immunotherapy

World Allergy Organization Position Paper 2009

Chair: G. Walter Canonica

Co-Chairs

Jean Bousquet, Thomas Casale, Richard F. Lockey, Carlos E. Baena-Cagnani, Ruby Pawankar, Paul C. Potter

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SOCIETIES/ORGANIZATIONS ATTENDING THE PARIS MEETING

Regional Member Societies

Asia Pacific Association of Allergology and Clinical Immunology.
Commonwealth of Independent States (CIS).
European Academy of Allergy and Clinical Immunology (EAACI).
Latin American Society of Allergy and Immunology.

Affiliate Member Societies

Interasma (International Association of Asthmology).

National Member Societies

Albanian Society of Allergology and Clinical Immunology.
Allergy Society of South Africa.
American Academy of Allergy, Asthma and Immunology.
American College of Allergy, Asthma and Immunology.
Argentine Association of Allergy and Immunology.
Australasian Society of Clinical Immunology and Allergy.
Bangladesh Society of Allergy and Immunology.
Belgian Society of Allergology and Immunology.
Brazilian Society of Allergy and Immunopathology.
British Society for Allergy and Clinical Immunology.
Bulgarian National Society of Allergology.
China Allergology Society and Chinese Allergists.
Cuban Society of Allergology.
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Venezuelan Society of Allergy and Immunology.

Correspondence to: G. Walter Canonica, MD, Professor, Allergy and Respiratory Diseases, DIMI, Department of Internal Medicine, University of Genoa, Largo Rosanna Benzi 10, Genoa 1-16132 Italy. Email: canonica@unige.it
World Allergy Organization acknowledges Ronald L. Rabin for reviewing this Position Paper. Ken Rainey, Medical Writer, and Karen Henley, WAO Global Project Director, are acknowledged for their assistance in editing and coordinating the manuscript.
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WAO Journal • November 2009 233

- Fino a Giugno 2009, erano stati pubblicati 60 DBPC-RCTs sulla SLIT, di questi, 41 condotti con estratti di acari o pollini di graminacee. La maggior parte di questi studi è eterogenea per dose allergenica, durata e selezione dei pazienti.
- 48 studi forniscono risultati complessivamente positivi mentre 12 sono completamente o pressoché completamente negativi
- La letteratura nel suo complesso suggerisce che la SLIT è efficace nonostante esistano differenze tra i vari allergeni
- Le metanalisi disponibili sono in favore della SLIT nonostante le conclusioni siano limitate dalla grande eterogeneità degli studi analizzati
- L'efficacia clinica e la dose-dipendenza sono state dimostrate in importanti DBPC-RCTs sulla rinocongiuntivite da polline di graminacee → la dose di mantenimento ottimale per le graminacee è stata identificata in circa 600 µg di allergene maggiore
- Studi di dose-finding e grossi studi con obiettivi definiti ed un adeguato campione (numero di pazienti coinvolti) sono necessari per altri rilevanti singoli allergeni

I riunione di ciclo
11-15 Gennaio 2010

INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 24, no. 4 (S), 0-0 (2011)

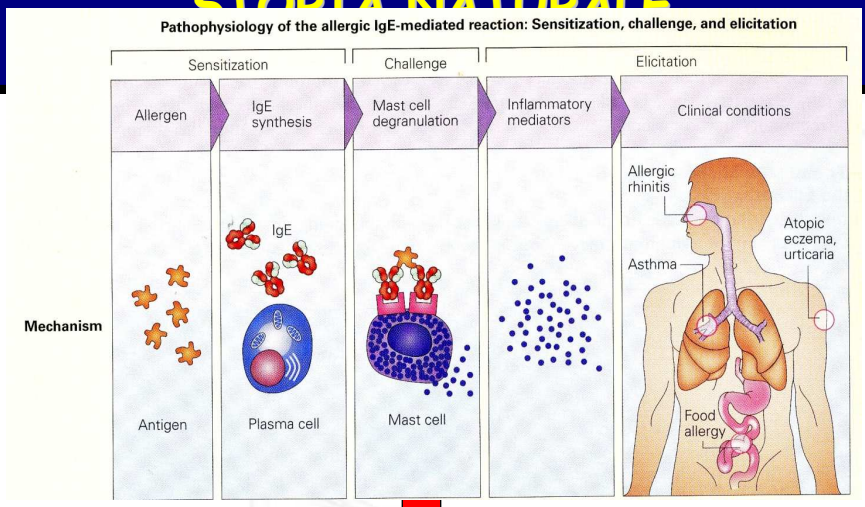
SPECIFIC IMMUNOTHERAPY IN CHILDREN: THE EVIDENCE

LA ROSA M°, LIONETTI E °, LEONARDI S°, SALPIETRO A*, BIANCHI L§, SALPIETRO C*, MIRAGLIA DEL GIUDICE M.^ CIPRANDI G,**MARSEGLIA GL§

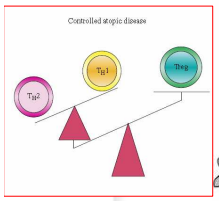
Ig-E mediated mechanism	La malattia
Role of allergen in related-disease	
Time of duration of disease	
Age of patient	Il paziente
Response to pharmacological treatment	
Expected response	
Possibility to use standardized vaccine	
Controindications to use of vaccine	Il vaccino
Safety of vaccine	
Costs	
Compliance of patient and parents	

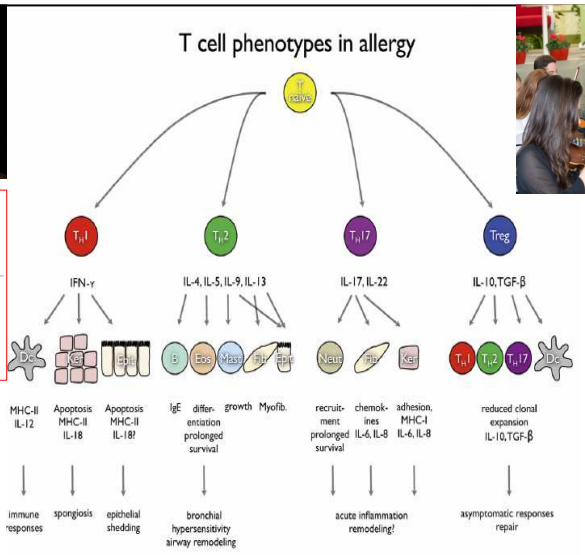
Table 3 – Considerations for the prescription of immunotherapy.

STORIA NATURALE



COMPLICANZE



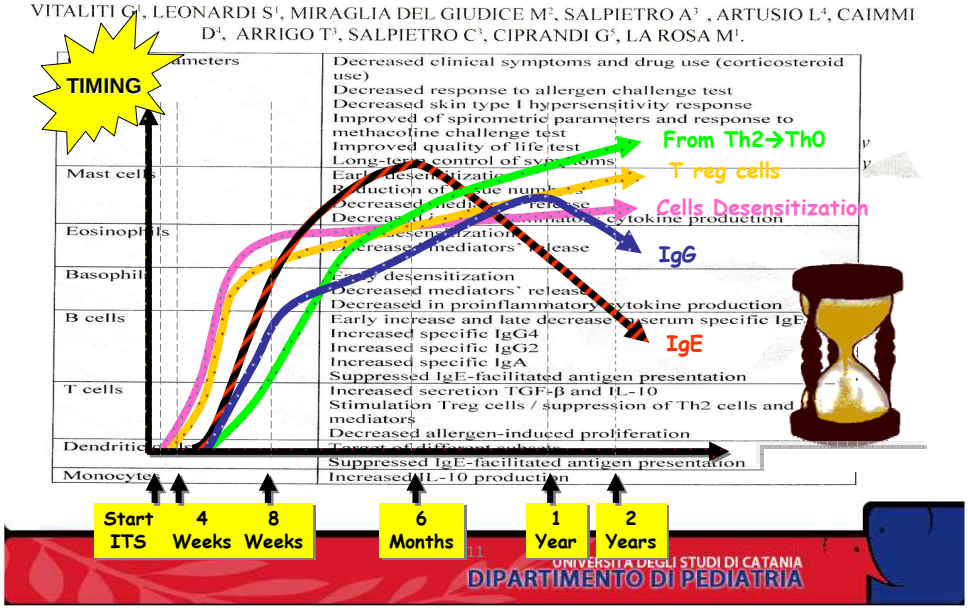


DISREGOLAZIONE IMMUNOCITOCHINICA

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 26, no. 1 (S), 0-0 (2012)

MUCOSAL IMMUNITY AND SUBLINGUAL IMMUNOTHERAPY IN RESPIRATORY DISORDERS

VITALITI G[1], LEONARDI S[1], MIRAGLIA DEL GIUDICE M[2], SALPIETRO A[3] , ARTUSIO L[4], CAIMMI D[4], ARRIGO T[3], SALPIETRO C[3], CIPRANDI G[5], LA ROSA M[1].



UNIVERSITÀ DEGLI STUDI DI CATANIA
DIPARTIMENTO DI PEDIATRIA

Applicazioni cliniche

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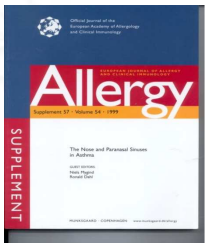
DIPARTIMENTO DI PEDIATRIA

L'ITS e' efficace nell'asma ?



Immunotherapy in asthma : an update systematic review
M.Abramson et al Allergy 1999
Obiettivi dello studio:

A-Reperire tutti gli studi randomizzati controllati relativi alla ITS nell'asma allergico

B-Valutare l'accuratezza metodologica di tali studi

C-Valutare l'efficacia della ITS sui sintomi asmatici,sul consumo farmaci,sulla funzionalita' respiratoria,sulla broncoreattività specifica ed aspecifica

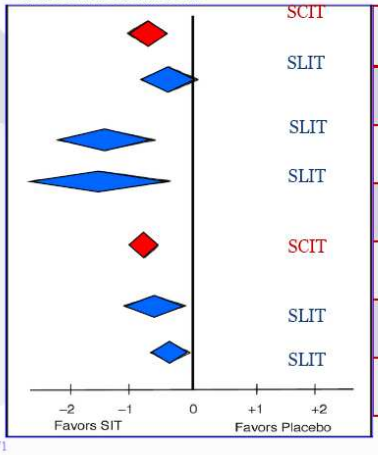
D-Confrontare l'efficacia della ITS per i vari allergeni

Conclusioni :..l'attenta analisi di tutti i lavori conferma l'indiscussa efficacia della ITS , specie per quello che riguarda ***il consumo di farmaci e la broncoreattività specifica*****……**

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

Compalati E et al, Ann Allergy Asthma Immunol 2009 (modificata)

Meta analisi: sintomi



Abramson 2010	Asthma	A-C	p< 0.00001
Calamita 2006	Asthma	A-C	P= 0.07
Penagos 2008	Asthma	C	P= 0.02
Olaguibel 2005	Asthma /Rhinitis	C	P= 0.01
Calderon 2007	Rhinitis	A	p< 0.01
Penagos 2006	Rhinitis	C	p= 0.02
Radulovic 2010	Rhinitis	A-C	p= 0.00001

A = adults C = children

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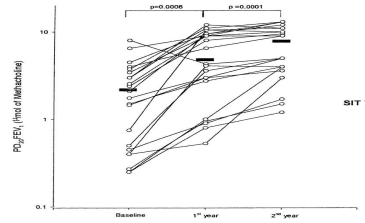
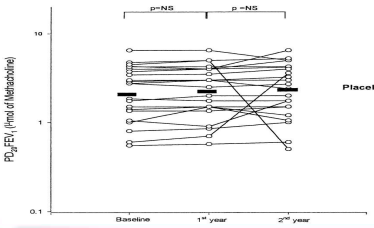
DIPARTIMENTO DI PEDIATRIA

Effects of Specific Immunotherapy in Allergic Rhinitic Individuals with Bronchial Hyperresponsiveness

Grembiale RD et al, Am. J. Respir. Crit. Care Med 2000



Dopo il 1 anno di trattamento si e' osservato un miglioramento di 2.88 volte del PD20FEV1 (p<0.001) che aumento' fino a 4 volte alla fine del 2 anno di trattamento (p<0.001)



Evaluation of the antiinflammatory and clinical effects of sublingual immunotherapy with carbamylated allergoid in allergic asthma with or without rhinitis. A 12-month perspective randomized, controlled, trial.

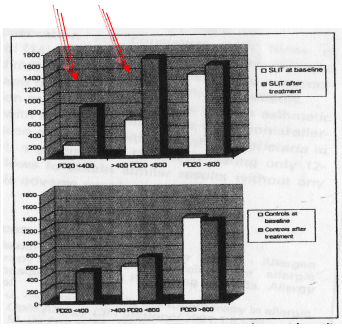
Leonardi S, La Rosa M et al. Eur Ann Allergy Clin Immunol. 2007

	Allergoid SLIT	Controls	P Value
Patients	33	23	NS
Mean age (years)	15.4	21.8	NS
Range	8 - 44	7 - 68	
Sex (M/F)	22/11	13/10	NS
Methacholine PD_{20} (µg)	626.4 ± 526.19	616.1 ± 578.08	NS
Nasal eosinophils (grading)	2.0 ± 1.14	2.1 ± 0.52	NS

Table 1: Demographic data at baseline.

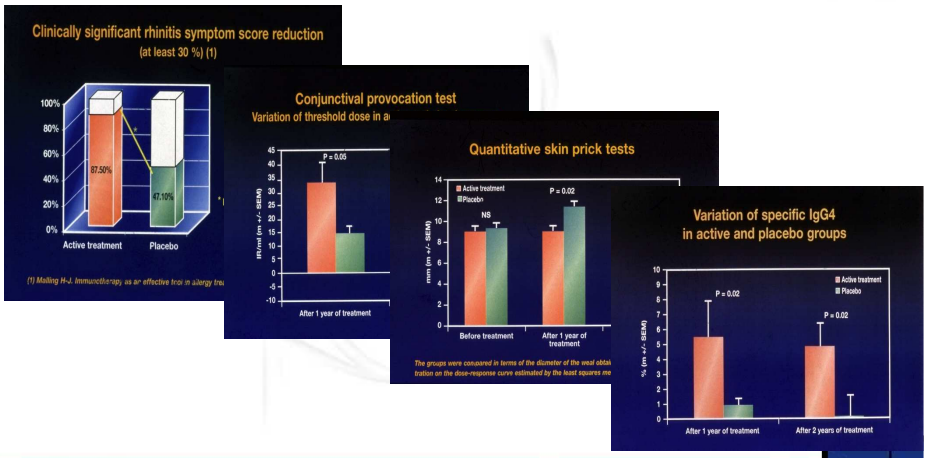
	Allergoid SLIT	Controls
Methacholine PD20 (µg) at baseline	626.4 ± 526.19	616.1 ± 578.08
Methacholine PD20 (µg) after treatment	1277.7 ± 963.51	860.3 ± 732.39
P Value	0.001	0.08

Table 2: Methacholine PD mean values (µg) at baseline and after treatment in the two groups.



Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis.

La Rosa M, Ranno C, Andre' C, Carat F, Tosca MA, Canonica GW.

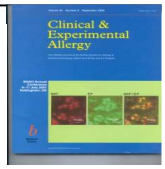


J.Allergy Clin.Immunol 1999

Clin Exp Allergy 2003; 33:206–210

Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study

V. Di Rienzo, F. Marcucci*, P. Puccinelli†, S. Parmiani†, F. Frati*, L. Sensi*, G. W. Canonica‡ and G. Passalacqua‡
*Clinica Villa Benedetta, Rome, *Clinica Pediatrica, University of Perugia, Perugia, †ALK-Abellò, Lainate, Milan and ‡Allergy and Respiratory Diseases, DIMI, University of Genoa, Genoa, Italy*



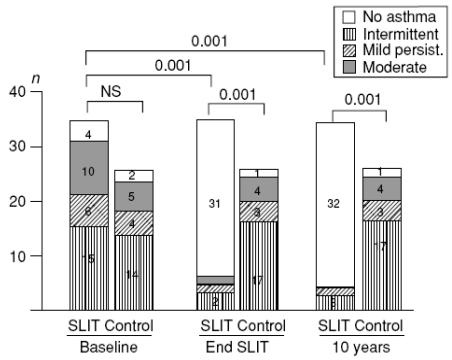
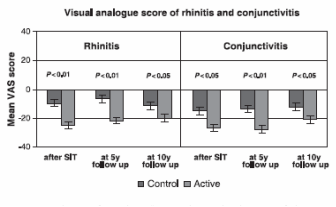


Fig. 1. Number of patients with different asthma severity, or without asthma, at the three time points. Significant intragroup and intergroup *P*-values are indicated upon the bars.

Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study

The PAT investigator group. Allergy 2007



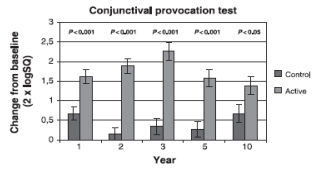


Figure 5. Change from baseline and standard error of the mean for the conjunctival provocation test. For children allergic to both grass and birch, the challenge with both allergens is included.

SCIT

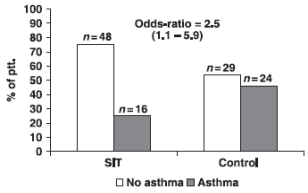


Figure 3. The percentage of children with and without asthma 7 years after termination (10-year follow-up) of specific immunotherapy. Based on the patients without asthma before treatment (n = 117). The absolute number of children is shown above the bars.

Conclusion: A 3-year course of SIT with standardized allergen extracts has shown long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment.
Clinical implication: Specific immunotherapy has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhino conjunctivitis up to 7 years after treatment termination.

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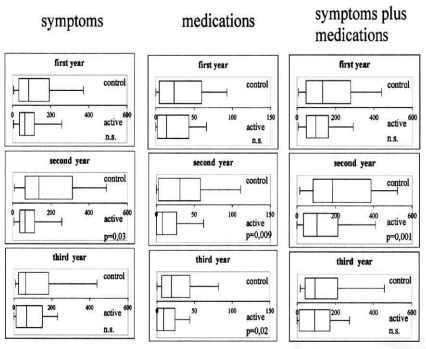
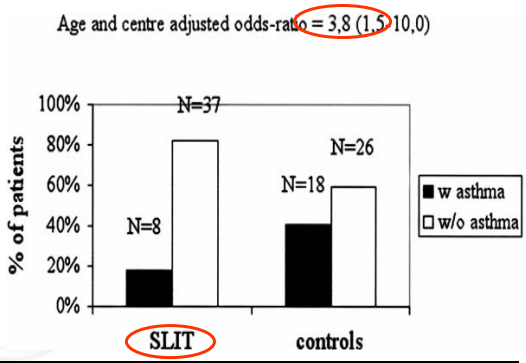
Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis

Novembre E. et al. (Rome, Parma, Pisa, Milan, Grosseto, and Florence, Italy)

J Allergy Clin. Immunol 2004.





Conclusions: **Development of asthma after 3 years was 3.8 times more frequent (95% confidence limits, 1.5-10.0) in the control subjects. Three years of coseasonal SLIT to grass pollen improves seasonal allergic rhinitis symptoms and reduces the development of seasonal asthma in children with hay fever.**

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DIPARTIMENTO DI PEDIATRIA

Studi epidemiologici su popolazione generale

ECHRS (Europa) 11.355 soggetti: adulti *Ann Epidemiol 2010*		57-67% Non sensisibilizzati 16-19.6% Monosensibilizzati 12.8-25.3% Polisensibilizzati
NHANES II e III (USA) 10.863 soggetti: adulti *JACI 2005*		45.7% Non sensibilizzati 15.5% Monosensibilizzati 38.8% Polisensibilizzati
Studio Olandese *PAI 2011*	9044 bambini:	60.1% Non sensibilizzati 12.4% Monosensibilizzati 27.5% Polisensibilizzati

STRATEGIES FOR ALLERGEN IMMUNOTHERAPY
IN POLYSENSITIZED PATIENTS

2 correnti di pensiero: Europea e USA

- In Europa la maggior parte delle formulazioni sono basate su un singolo estratto

- Negli USA le preparazioni contengono una miscela media di 8 allergeni

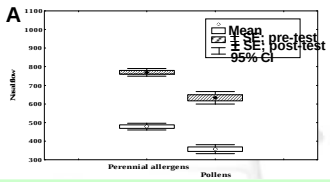
1) un soggetto polisensibilizzato non è necessariamente un poliallergico

2) sulla base della stagionalità delle diverse esposizioni allergeniche, una poliallergia non sempre costituisce un problema clinico

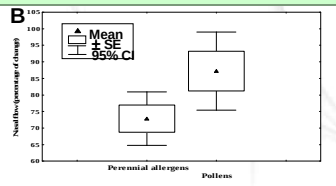
- **L'atteggiamento americano è di trattare il maggior numero possibile di pazienti sensibilizzati/allergici, usando tutti gli allergeni rilevanti.**

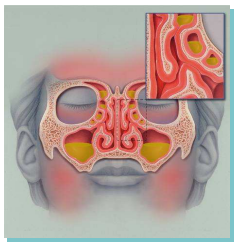
Persistent allergic rhinitis includes different pathophysiological types.
Giorgio Ciprandi, Ignazio Cirillo, Angela Pistorio

Laryngoscope (2008)



Flusso aereo nasale
Basale e Post-decongestione



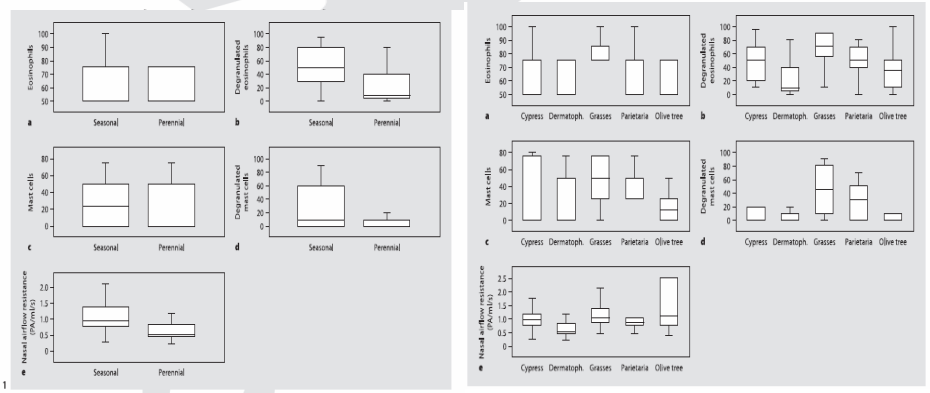


Nell'ambito della PER esistono vari fenotipi in funzione della specificità allergenica.

International Archives of Allergy and Immunology
Int Arch Allergy Immunol 627
DOI: 10.1159/0000XXXXX
Receive
Accept
Publish

Nasal Resistance and Allergic Inflammation Depend on Allergen Type

Matteo Gelardi[a] Alessandro Maselli Del Giudice[a] Teresa Candreva[a]
Maria Luisa Fiorella[a] Michaela Allen[b] Catherine Klersy[b] Gian Luigi Marseglia[b]
Giorgio Ciprandi[c]



INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 22, no. 3, 0-0 (2009

IMMUNOGLOBULIN PRODUCTION PATTERN IS ALLERGEN-SPECIFIC IN POLYSENSITIZED PATIENTS

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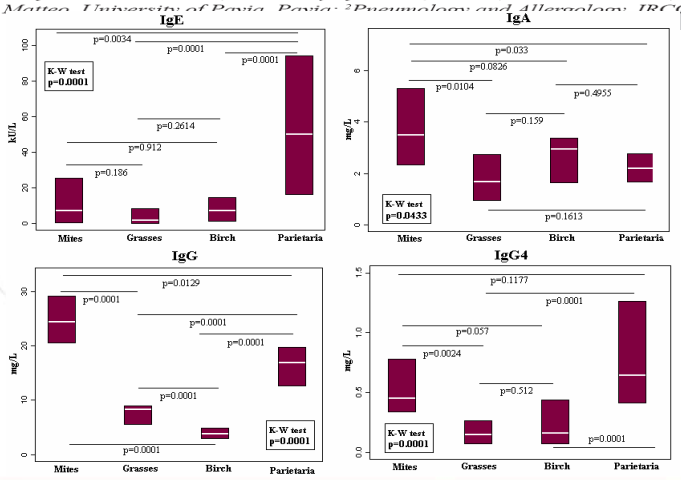


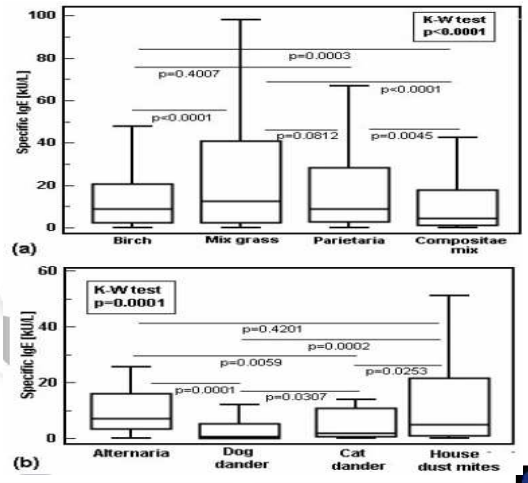
INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 23, no. 4, 0-0 (2010)

LETTER TO THE EDITOR

COMPARISON OF SERUM SPECIFIC IGE AND SKIN PRICK TEST IN POLYSENSITIZED PATIENTS.

G. CIPRANDI, M. DE AMICI[1], V. GIUNTA[1] and G.L. MARSEGLIA[1]

- Tutti i pazienti
- avevano la stessa reazione cutanea:
- SPT ++++



How molecular diagnosis can change allergen-specific immunotherapy **prescription in a complex pollen area.**

- **BACKGROUND:**
- The identification of disease-eliciting allergens is a prerequisite for accurate prescription of allergen-specific immunotherapy (SIT). The aim of this study was to determine whether molecular diagnosis (MD) may change indication and allergen prescription of SIT.
- **METHODS:**
- A total of 141 patients with allergic rhinoconjunctivitis and/or asthma sensitized to pollen with or without concomitant food allergy were included. Skin prick testing with a panel of aeroallergens and a microarray-based panel of allergens (ISAC(®) ; Phadia, Sweden) was performed in all patients. Prior to learning the results of molecular diagnosis, three of the authors reached a consensus on the indication of SIT and use of allergens following EAACI recommendations, basing their judgment on clinical history and skin prick test results before and after obtaining the ISAC results. The agreement coefficient (kappa index) was used to analyze the results.
- **RESULTS:**
- Fifty-nine percent of the patients were women with a mean age of 31 ± 13.63. Agreement in SIT indication before and after ISAC(®) results was found in only 62 (46%) patients (kappa = 0.1057 ± 0.0413). Concerning allergens used in the most common prescriptions before and after MD results, we obtained the following results: κ = 0.117 ± 0.0825 for grass; κ = 0.1624 ± 0.0639 for olive; κ = 0.0505 ± 0.0548 for olive and grass; κ = 0.1711 ± 0.0471 for grass and cypress; κ = 0.1897 ± 0.0493 for grass and London plane; κ = 1 ± 0.0842 for olive and cypress, and κ = 0.3586 ± 0.0798 for other combinations.
- **CONCLUSIONS:**
- There was very low agreement concerning indication and use of allergens for SIT before and after performing MD. This discrepancy emphasizes the usefulness of MD, at least in areas of complex sensitization to pollen, in determining correct indication of SIT.

Sastre JJ et al. Allergy 2012

Rostrum

Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: Looking at the published evidence

Moisés A. Calderón, MD, PhD,[a] Linda Cox, MD,[b] Thomas B. Casale, MD,[c] Philippe Moingeon, PhD,[d] and Pascal Demoly, MD, PhD[e] *London, United Kingdom, Davie, Fla, Omaha, Neb, and Antony and Montpellier, France*

Key messages

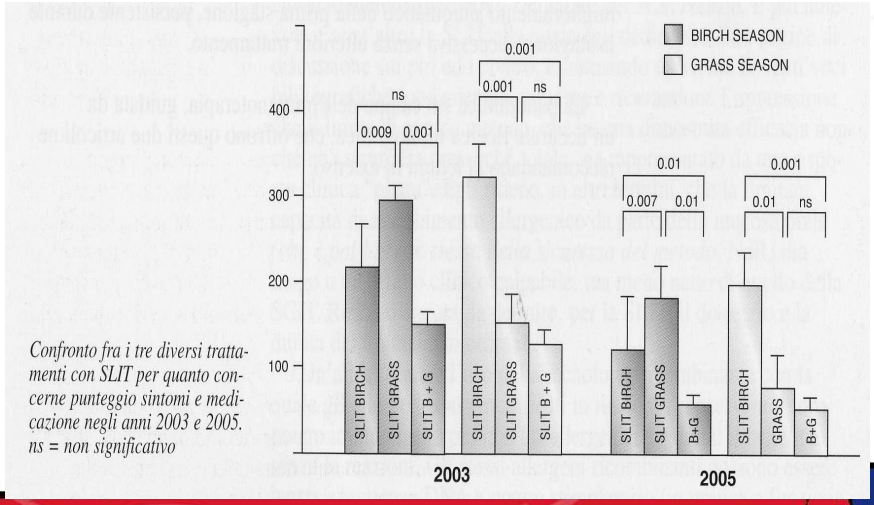
- Epidemiologic and clinical trial data show that 51% to 81% of US and European patients are polysensitized (according to skin prick test results, IgE assay results, or both). However, a polysensitized patient is not necessarily clinically polyallergic.
- In Europe most allergen immunotherapy formulations are single-allergen extracts (even for polysensitized patients), whereas preparations in the United States contain an average of 8 different components.
- In recent, large, well-designed, well-powered clinical trials, single-allergen immunotherapy with grass pollen extract has proved to be as safe and effective in polysensitized patients as in monosensitized patients.
- Sublingual or subcutaneous multiallergen immunotherapy in polysensitized patients needs more supporting data from large clinical trials to validate it as a treatment option.

Key Message

SIT limited to one to two allergen extracts may be prescribed to polysensitized patients and is effective and safe

Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients.

Marogna M, Spadolini I, Massolo A, Zanon P, Berra D, Chiodini E, Canonica WG, Passalacqua G.
Ann.Allergy Asthma Immunol. 2007



Confronto fra i tre diversi trattamenti con SLIT per quanto concerne punteggio sintomi e medicazione negli anni 2003 e 2005. ns = non significativo

GRADO DI EVIDENZA SPERIMENTALE PER IMMUNOTERAPIA SOTTOCUTANEA (SCIT) E SUBLINGUALE (SLIT)

	SCIT	SLIT
Efficacia clinica (rinite)	Ia	Ia
Efficacia clinica (asma)	Ia	Ia
Efficacia clinica bambini (rinite)	Ib	Ia
Efficacia clinica bambini (asma)	Ib	Ia
Prevenzione sensibilizzazioni	Ib	IIa
Prevenzione asma	Ib*	Ib*
Effetto a lungo termine	Ib	IIa

* Un solo studio randomizzato in aperto.

IA: evidenza di metanalisi di lavori controllati e randomizzati
IB: da almeno 1 lavoro controllato e randomizzato
IIA: da almeno 1 lavoro controllato senza randomizzazione.
*** 1 singolo lavoro,controllato e randomizzato in aperto.**

Passalacqua e Durham, JACI 2007, modificata

RINITE LIEVE

RINITE MODERATA
PIU' CONGIUNTIVITE

RINITE SEVERA
PIU' CONGIUNTIVITE

PROFILASSI ALLERGICA (QUANDO POSSIBILE)

CONSIDERARE IMMUNOTERAPIA

ASMA
INTERMIRTTENTE

ASMA LIEVE
PERSISTENTE

ASMA
PERSISTENTE
MODERATO

ASMA
PERSISTENTE
GRAVE

FARMACOTERAPIA

CONSIDERARE IMUNOTERAPIA

IMMUNOTERAPIA SPECIFICA
DOSAGGI E DURATA OTTIMALI ?

IL DOSAGGIO E LA DURATA DELL'E.A. COSTITUISCE LA PARTE PIU' "EMPIRICA", MA PIU' IMPORTANTE E NECESSARIA DELLA ITS LA CUI EFFICACIA E' *DOSE E TEMPO DIPENDENTE*

NESSUNA TERAPIA E' PIU' "INDIVIDUALE" DELLA IMMUNOTERAPIA SPECIFICA !!!

High-dose sublingual immunotherapy in children at 8-year follow-up.

Leonardi S , La Rosa M et al. Ann Allergy Asthma Immunol. 2009

Characteristics	Formerly active	Formerly placebo	Comparison
No. of patients	10	11	
Sex, M/F	6/4	4/7	$\chi^2 = 0.41$
Current mean age, y	21.7	22.9	NS
Asthma (intermittent/mild persistent)	6 (4/2)	7 (5/2)	$\chi^2 = 0.078$
Mean (SD) FEV_1, % predicted	97.5 (11.2)	92.6 (16.4)	$t = 0.79$
No. of patients with FEV_1 <80%	1	3	NS
Mean (SD) $FEF_{25\%-75\%}$	79.9 (22.1)	69.9 (16.4)	$t = 1.18$
No. of patients with $FEF_{25\%-75\%}$ <80%	3	7	$\chi^2 = 1.21$
No. of new sensitizations	19	20	NS

Abbreviations: $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75%; FEV_1, forced expiratory volume in 1 second; NS, not significant.

Conclusions: Finally it is apparent that two years of high dose SLIT seem ineffective to modify significantly the natural history of respiratory allergy to *Parietaria* pollen, looking at the persistence of rhinitis, the prevention of asthma and the appearance of new sensitizations. When the study was conducted from 1995 to 1997, the knowledge on SLIT effects was rather limited, and in particular it was not yet stated that 3-5 years may represent an optimal duration (1).

1) Canonica GW, Passalacqua G. Noninjections routes for immunotherapy. J Allergy Clin Immunol 2003.

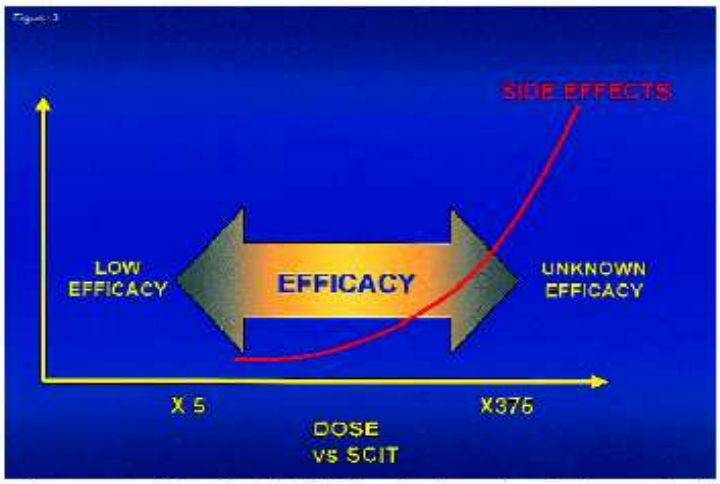


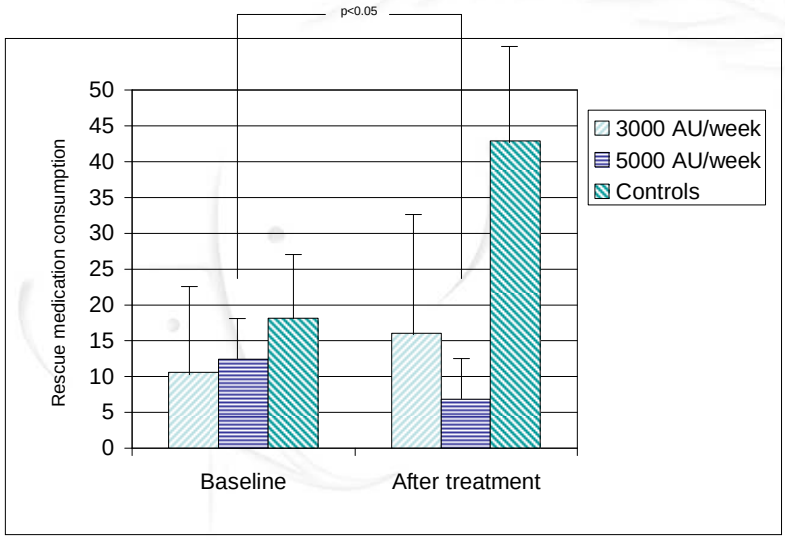
FIG 3. The dose-response relationship with SLIT. Efficacy has been shown for doses ranging between 20 and 375 times those of SCIT. Gastrointestinal side effects increase when the dosage rises.

Canonica G, et al. J.Allergy Clin.Immunol,2003

Olea sublingual allergoid immunotherapy administered with two different treatment regimens

	3000 AU/WEEK (for 10 weeks)	5000 AU/WEEK (for 6 weeks)	CONTROLS
Patients (n.)	11	10	12
Sex (M/F)	7/4	2/8	5/7
Mean Age	26±14	24±13	23±14
Weight	58±19	51±15	52±21
Height	166±6	156±19	160±19
Disease			
Rhinitis with asthma	*8*	*6*	*7*
Rhinitis without astma	*3*	*4*	*5*

Leonardi S et al. Allergy & Asthma Proceedings 2010



UNIVERSITÀ DEGLI STUDI DI CATANIA
DIPARTIMENTO DI PEDIATRIA

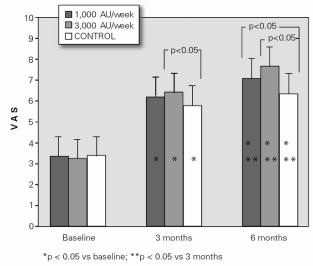
Parietaria sublingual allergoid immunotherapy with a co-seasonal treatment schedule

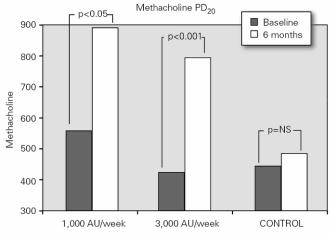
Leonardi S, La Rosa M et al. Allergol. et Immunopathol 2007

Table I

Patients' characteristics at baseline

	1,000 AU/week	3,000 AU/week	Control
Patients	24	21	21
Sex (M/F)	16/8	12/9	12/9
Mean age	26.3 ± 11.1	20.9 ± 8.8	27.9 ± 13
Weight	75.1 ± 40.0	58.6 ± 14.6	60.3 ± 13
Height	164.5 ± 13.9	162.8 ± 16.2	159.4 ± 13
Disease			
Asthma	6	6	7
Rhinitis and asthma	18	15	14
Allergen			
Parietaria	24	21	21
Dermatophagoides	18	15	16
Grass	3	–	2
Compositae	1	1	–
Olive	2	2	1
Dog	2	1	–
Cat	4	1	1
Birch	–	–	–
Alternaria	–	2	–
Aspergillus	–	1	–





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DIPARTIMENTO DI PEDIATRIA

Clin Exp Allergy 2005; 35:565–571 doi:10.1111/j.1365-2222.2005.02240.x

The safety of sublingual-swallow immunotherapy: an analysis of published studies

G. B. Gidaro*, F. Marcucci†, L. Sensi†, C. Incorvaia‡, F. Frati*,† and G. Ciprandi§

Table 6. Ratio AE/number of SLIT doses and ratio SLIT/SCIT defining low and high allergen doses in the 25 studies included in the analysis

Author	Reference	AE/10,000 doses	Ratio SLIT/SCIT
Horack	[31]	80.8	1
Casanovas	[40]	55.6	1.2
Ippoliti	[33]	0.0	3
Voltolini	[32]	79.1	3
Pajno	[18]	16.7	4
Ariano	[35]	0.0	5
Hirsch	[36]	26.9	5
Tari	[37]	51.5	5
Passalacqua	[38]	0.0	7
Bufe	[17]	3	10
Hordijk	[34]	72.5	10
Troise	[39]	4.1	20
TorresLima	[16]	320.8	40–50
Sabbah	[19]	44.9	50
Bahceciler	[20]	0.0	70
Pradalier	[21]	32.8	150
André	[22]	50.2	200
Tonnel	[25]	0.0	200
Bousquet	[23]	9.8	200
Guez	[24]	1.7	200
Grosclaude	[26]	27.6	257
Vourdas	[27]	13.2	300
La Rosa	[28]	25.8	375
Mortemousque	[29]	1.9	375
Clavel	[30]	19.0	500

AE, adverse events; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

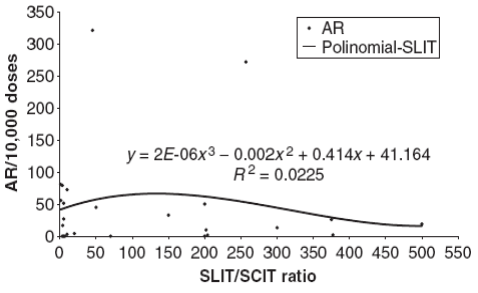

Fig. 1. Lack of correlation between adverse events (AE) and magnitudo of sublingual immunotherapy (SLIT) doses. Regression curve obtained by interpolating the points corresponding to the incidence of AE occurred for each dose expressed as SLIT to subcutaneous immunotherapy (SCIT) ratio.

UNIVERSITÀ DEGLI STUDI DI CATANIA
DIPARTIMENTO DI PEDIATRIA

Clin Exp Allergy 2005; 35:565–571 doi:10.1111/j.1365-2222.2005.02240.x

The safety of sublingual-swallow immunotherapy: an analysis of published studies

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Table 2. Local reactions evaluated concerning the allergen dose

	Local reactions			
	High allergen dose		Low allergen dose	
	Active	Placebo	Active	Placebo
Sample (No. patients)	445	405	302	285
Buccolingual	159	15	417	36
Gastrointestinal	50	10	6	1
Total	209	25	423	37
Reaction per patient	0.47	0.06	1.4	0.13

$P<0.0001$

Table 3. Systemic reactions evaluated concerning the allergen dose

	Systemic reactions			
	High allergen dose		Low allergen dose	
	Active	Placebo	Active	Placebo
Sample (No. patients)	445	405	302	285
Ocular itching	3	1	8	3
Cutaneous	11	8	5	3
Respiratory reactions	43	33	40	16
Others (headache, dizziness, tiredness)	10	12	7	7
Total	67	54	60	29
Reaction per patient	0.15	0.13	0.20	0.10

NS

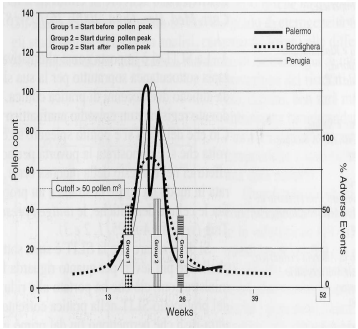
NS, non-significant.

Conclusions: There is evidence that AE occurrence is substantially not dose-dependent. This fact highlights two main clinical aspects: the elevated tolerability of SLIT in general and the safety of HAD regimen.

Safety of sublingual immunotherapy started during the pollen season.

Ariano R, Incorvaia C, La Grutta S, Marcucci F, Pajno G, Sensi L, Di Cara G, Sieber J, Yacoub MR, Frati F. Curr Med Res Opin. 2009

- **BACKGROUND:** The aim of this study was to assess the **safety of ultra-rush SLIT** in pollen-allergic children according to different timing of administration in relation to the pollen season.
- **METHODS:** In total, 34 children with pollen-induced rhinitis and 36 with pollen-induced asthma and rhinitis, were enrolled and assigned to three study groups:
- **group 1 (n = 17 patients): conventional pre-seasonal-SLIT treatment;**
- **group 2 (n = 23 patients), seasonal SLIT ended before the pollen seasonal peak;**
- **group 3 (n = 30 patients), SLIT began after the pollen seasonal peak and ended after the pollen season**
- **RESULTS: In all, 54 adverse events (AEs) were reported: 12 in nine patients in group 1 (9/17, 52.9%), 22 in 14 patients in group 2 (14/23, 60.9%), and 20 in 13 patients in group 3 (13/30,**



CONCLUSIONS: This study suggests that SLIT with pollen extracts may be safely started at the beginning and also during the pollen season, with a tolerability profile comparable to the conventional pre-seasonal SLIT.

Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis

H-J. Malling*, A. Montagut†, M. Melac‡, G. Patriarca§, P. Panzner¶, E. Seberova‖ and A. Didier**

2008 Blackwell Publishing Ltd, *Clinical and Experimental Allergy*, **39**: 387–393

Table 1. Distribution of patients in the four sensitivity subgroups

Population	Treatment group	IgE ⩾ 17.5 kU/L (Group 1) n	%	RRTSS ⩾ 15 (Group 2) n	%	SPT weal diameter ⩾ 10.5 mm (Group 3) n	%	Any of Group 1, 2 or 3 (Group 4) n	%
Safety population (n = 628)	100 IR	62	22.2	67	27.5	37	23.6	117	25.5
	300 IR	69	24.7	52	21.3	36	22.9	112	24.5
	500 IR	66	23.7	66	27.0	44	28.0	117	25.5
	Placebo	82	29.4	59	24.2	40	25.5	112	24.5
	All	279	100.0	244	100.0	157	100.0	458	100.0
ITT population (n = 569)	100 IR	55	21.9	61	27.2	34	23.9	105	25.4
	300 IR	59	23.5	47	21.0	32	22.5	100	24.2
	500 IR	57	22.7	60	26.8	39	27.5	103	24.9
	Placebo	80	31.9	56	25.0	37	26.1	105	25.4
	All	251	100.0	224	100.0	142	100.0	413	100.0

IR, index of reactivity; ITT, Intent-to-Treat; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

Conclusioni: i gruppi caratterizzati da particolare gravita' raggiungono un effetto protettivo statisticamente significativo; inoltre il profilo di sicurezza nei confronti di reazioni avverse di questi pazienti "gravi" non si discosta da quello dei pazienti "normali"

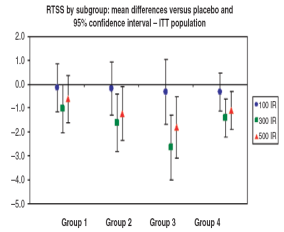


Fig. 1. Average Rhinoconjunctivitis Total Symptom Score (RTSS) (mean±SD) during the pollen season according to sensitivity subgroup (Intent-to-Treat (ITT) population).

Table 5. Proportion of patients with treatment-emergent adverse events according to sensitivity subgroup (safety population)

	Placebo	100 IR	300 IR	500 IR
G1 = Specific IgE ⩾ 17.5 kU/L	46	68	61	70
G2 = RRTSS ⩾ 15	46	64	67	59
G3 = Weal diameter ⩾ 10.5 mm	63	70	64	64
G4 = G1, or G2, or G3	49	67	63	63
Overall study population	49	69	63	64

IR, index of reactivity; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

DIP

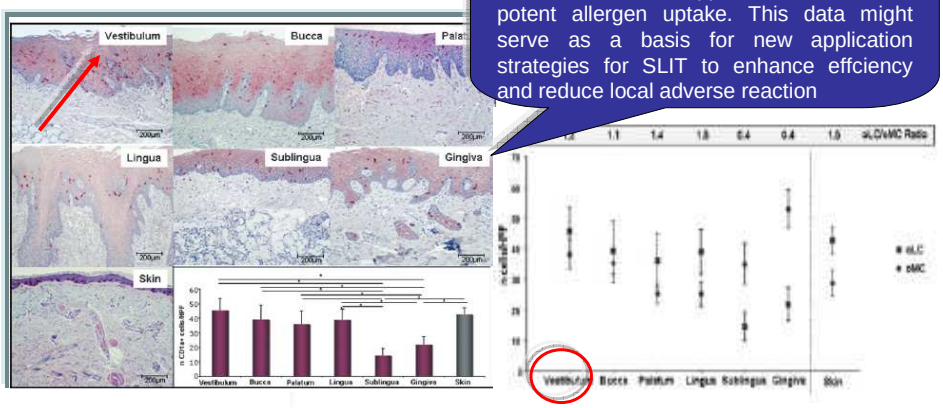
WAO Sublingual Position Paper 2009

SICUREZZA DELLA SLIT

- La SLIT sembra essere meglio tollerata della SCIT
- La SLIT dovrebbe venir prescritta unicamente dallo specialista
- Istruzioni specifiche dovrebbero esser fornite al paziente in merito alla gestione di eventuali reazioni avverse, di interruzioni non previste del trattamento ed in merito alle situazioni nelle quali la SLIT dovrebbe essere interrotta
- La maggior parte delle reazioni avverse legate alla SLIT sembrano verificarsi durante la fase iniziale del trattamento
- Alcuni casi di anafilassi legata alla SLIT sono stati riportati ma nessun caso di morte
- I fattori di rischio per lo sviluppo di reazioni avverse severe alla SLIT non son stati ancora stabiliti
- C'È IL BISOGNO DI UN SISTEMA ACCREDITATO E GLOBALMENTE ACCETTATO DI REPORTING DELLE REAZIONI AVVERSE E DELLE ANAFILASSI

Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy?

Conclusions: different mucosal regions such as the vestibulum might represent alternative SLIT application sites with potent allergen uptake. This data might serve as a basis for new application strategies for SLIT to enhance effciency and reduce local adverse reaction



J.P.Allam et al. Allergy 2008

Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma

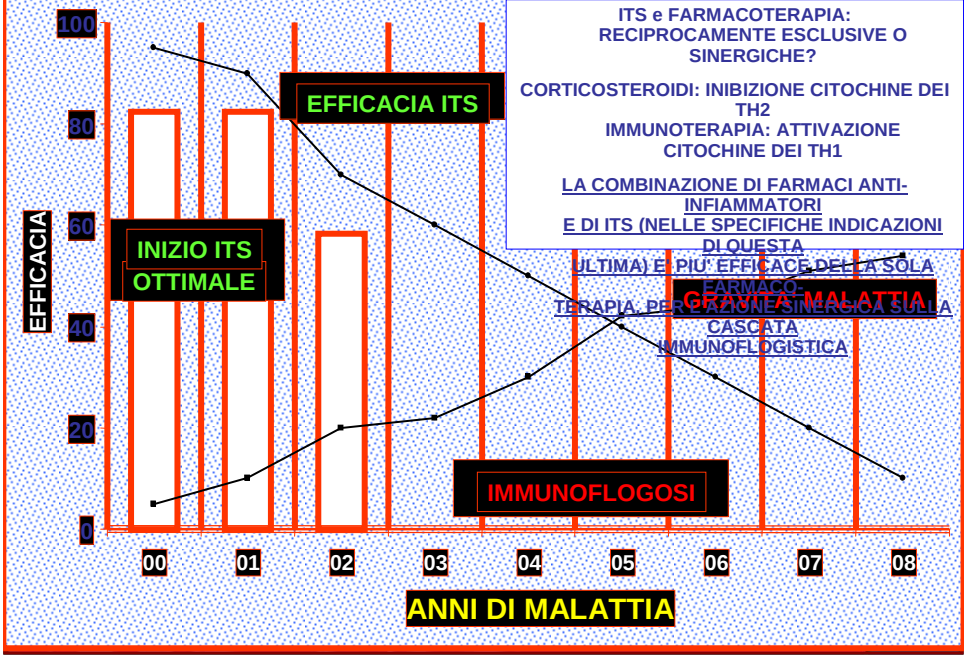
Ariano R, Berto P, Incorvaia C, Di Cara G, Boccardo R, La Grutta S, Puccinelli P, Frati F.
Ann Allergy Asthma Immunol. 2009

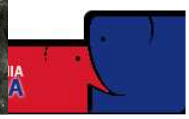
- Seventy patients with perennial allergic asthma, sensitized to dust mites, were enrolled; 50 of these patients were treated with SLIT against house dust mites and 20 were treated with symptomatic drugs. The patients were evaluated for 2 years after discontinuing immunotherapy, which was performed for 3 years, to obtain a more complete follow-up
- **RESULTS:** Patients treated with SLIT plus drugs had a higher mean annual cost in the first year of SLIT treatment compared with patients only receiving drug treatment, but the mean annual cost became significantly lower since the end of SLIT both in the whole population and in the subgroups defined by disease severity.
- **CONCLUSION: The economic advantage measured along side this prospective observational study was long lasting and still present at the fifth year of the follow-up (2 years after discontinuing SLIT)** and could positively be related to the persistent good clinical control of patients.

Immunoterapia specifica: punti chiave

- L'ITS riduce l'infiammazione allergene-specifica dell'organo bersaglio. L'entità di tale effetto è in rapporto alla dose di allergene somministrata ed alla dose di allergene a cui il paziente è esposto.
- L'effetto clinico dell'ITS è duplice:
  - riduzione l'impatto clinico (es.attenuazione dei sintomi e del consumo dei farmaci) sia nel corso del trattamento sia per alcuni anni dopo la sua sospensione
  - interferenza sulla storia naturale dell'allergopatia respiratoria riducendo nei pazienti rinitici il rischio di evoluzione ad asma.
- L'efficacia sui sintomi e sul consumo dei farmaci dell'asma è stata confermata anche da studi di metanalisi. Le prove di efficacia più consistenti sono per l'ITS sottocutanea utilizzata per singoli allergeni (in particolare acari, pollini e derivati allergizzanti di animali). Non è ancora disponibile un indicatore predittivo di efficacia dell'ITS.
- L'ITS e il trattamento farmacologico non sono mutuamente esclusivi.

I.T.S.: NECESSITA' DI INIZIO TEMPESTIVO





Food allergy, anaphylaxis, dermatology, and drug allergy

Update review

Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis?

Caroline Bussmann,[a] Anette Böckenhoff, PhD,[b] Henning Henke,[b] Thomas Werfel, MD,[c] and Natalija Novak, MD[a] *Bonn, Dortmund, and Hannover, Germany*

House dust mite (HDM) allergens are perennial indoor allergens, which may play a role as allergic trigger factors in atopic dermatitis (AD). Facilitated by their high enzymatic activity, HDM allergens are capable of penetrating the impaired epidermal skin barrier in patients with AD, gaining access to immune cells. In this way, HDM allergens induce both allergic reactions of the immediate type and allergic reactions of the delayed type, which contribute to impairment of AD. Because allergen reduction achieved by encasing strategies does not always lead to significant improvement of clinical symptoms, specific immunotherapy (SIT) might represent an attractive therapeutic option for long-time treatment of this subgroup of patients with AD. However, systematic studies on the effectiveness of SIT in patients with AD are rare. Furthermore, data on the immunologic changes induced by SIT in patients with AD are not well studied. In this review, we provide an overview of the pathogenic impact of HDM allergens as an example for aeroallergens on the course of AD. In addition, we discuss prophylactic and therapeutic options for the treatment of HDM allergy in patients with AD, including a summary of the current data available on SIT as a potential therapeutic option for patients with AD. (J Allergy Clin Immunol 2006;118:1292-8.)

Abbreviations used
AD: Atopic dermatitis
HDM: House dust mite
PAR: Proteinase-activated receptor
SIT: Specific immunotherapy

been rising in prevalence in Western societies. It is well known that a subgroup of atopic patients goes through an atopic march during their lifetime, which usually starts with AD in early childhood (between the 1st and 7th years of life), followed by the development of allergic bronchial asthma (between the 3rd and 9th years of life) and the manifestation of allergic rhinoconjunctivitis later (between the 7th and 13th years).[3] Many attempts have been made to explain the modern trend toward allergic diseases. One of the most accepted explanatory approaches for this development is the so-called hygiene hypothesis. According to this concept, the high incidence of atopic

J ALLERGY CLIN IMMUNOL
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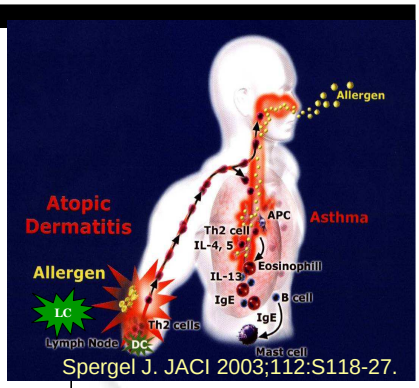

Spergel J. JACI 2003;112:S118-27.

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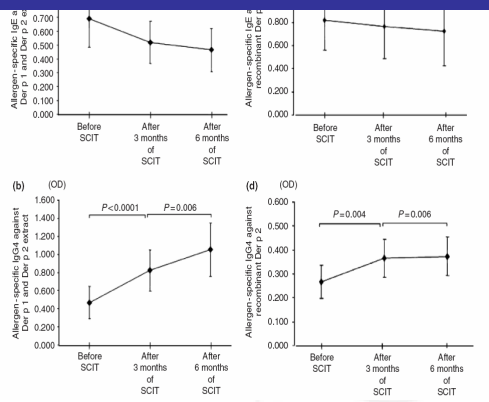
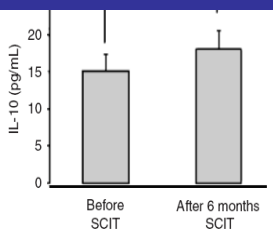
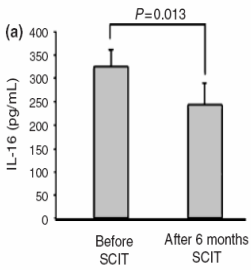
Clinical improvement and immunological changes in atopic patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study

C. Bussmann, et al. Clinical and Experimental Allergy 2007







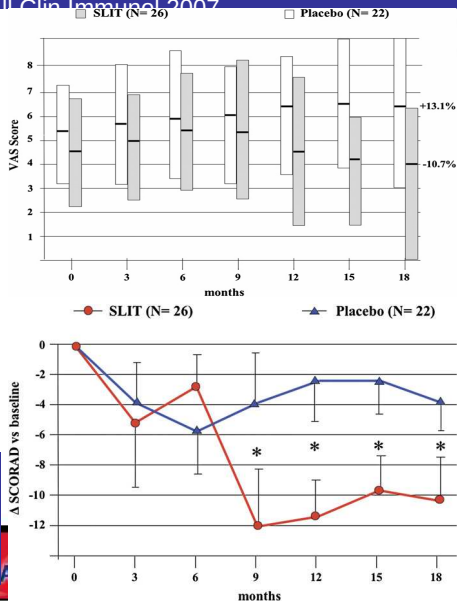
In summary, we could show that SCIT with an HDM allergoid might lead to a significant improvement in subjective and objective clinical symptoms of AD patients, combined with serological and immunological changes that mirror the therapeutic effect. Furthermore, our data provide evidence for the induction of the mechanisms that might contribute not only to the development of allergen-specific tolerance but, besides these, to overall changes in the AD-related immune state. Together, these immunolo-

Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: A randomized, double-blind, placebo-controlled study

Paino GB et al. J All Clin Immunol 2007

TABLE I. Demography and clinical characteristics of the enrolled children at baseline

	SLIT	Placebo
N	28	28
Sex (male/female)	15/13	12/16
Mean age (y)	10	11
Age range (y)	5-16	5-16
Duration of AD, mean ± SD (y)	6.7 ± 2.3	6.9 ± 2.5
Mild-moderate AD with SCORAD > 40	14	14
SCORAD in mild-moderate patients	32 ± 7	29 ± 5
Total IgE, mean ± SD (kU/L)	560 ± 85	486 ± 51
Rhinitis, n (%)	3 (10.7)	4 (14.2)
Rhinitis + intermittent asthma, n (%)	4 (14.2)	2 (7.1)
Only intermittent asthma, n (%)	7 (25.0)	6 (21.4)
HDM specific IgE, means ± SDs (kU/L)	10.6 ± 2.8	9.2 ± 1.6
Sensitization to foods, n (%)	9 (32.1)	11 (39.3)
Milk	5	6
Egg	3	3
Milk + egg	1	2
Other + ties to aeroallergens, n (%)	5 (18)	2 (7)



Conclusioni: SLIT sembra risultare efficace in bambini con DA lieve-moderata mentre sembra risultare inefficace nelle forme gravi. Questo risultato e' similare a quello osservato nell'asma grave.

ORIGINAL ARTICLE

ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis

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Abstract

Background The diagnosis of atopic dermatitis (AD) is made using evaluated clinical criteria. Management of AD must consider the symptomatic variability of the disease.

Methods EADV eczema task force developed its guideline for atopic dermatitis diagnosis and treatment based on literature review and repeated consenting group discussions.

Results and Discussion Basic therapy relies on hydrating topical treatment and avoidance of specific and unspecific provocation factors. Anti-inflammatory treatment based on topical glucocorticosteroids and topical calcineurin antagonists is used for exacerbation management and more recently for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, but the topical calcineurin inhibitors, tacrolimus and pimecrolimus are preferred in certain locations. Systemic anti-inflammatory treatment is an option for severe refractory cases. Microbial colonization and superinfection may induce disease exacerbation and can justify additional antimicrobial/antiseptic treatment. Systemic antihistamines (H1) can relieve pruritus, but do not have sufficient effect on eczema. Adjuvant therapy includes UV irradiation preferably of UVA1 wavelength or UVB 311 nm. Dietary recommendations should be specific and given only in diagnosed individual food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programmes have been proven to be helpful.

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Keywords
atopic dermatitis, eczema, guideline, therapy

Conflict of Interest
Authors declare that they have no conflict of interest.

Allergen-specific immunotherapy to aeroallergen may be useful in selected cases

Introduction and definitions

Atopic dermatitis (AD, atopic eczema, eczema) is an inflammatory, chronically relapsing and intensely pruritic skin disease occurring often in families with atopic diseases (AD, bronchial asthma and/or allergic rhino-conjunctivitis). Eczema is a non-contagious inflammation of epidermis and dermis with characteristic clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in synchronous or

[†]See Appendix.

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REVIEW ARTICLE

Immunotherapy for Food Allergy

Kazuyuki Kurihara[1]

ABSTRACT

Although the curren… hope of possible g… promising approach… gens has shifted fo… derlying mechanism… plied. Easy and un… bated food allergy, …

…f the trigger foods with …l immunotherapy is a …tolerance to food anti… …ed to elucidate the un… …therapy should be ap… …ncreased and exacer… …equired.

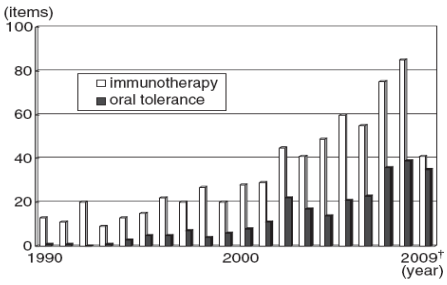

Fig. 1 The numbers of published papers on immunotherapy or oral tolerance for food allergy. The numbers of published papers found by searching PubMed with keywords of "food allergy & immunotherapy" or "food allergy & oral tolerance" since 1990 are shown. †Searched on September 1, 2009.

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ORIGINAL ARTICLE

Rush Specific Oral Tolerance Induction in School-Age Children with Severe Egg Allergy: One Year Follow Up

Naoka Itoh[1,2], Yasuharu Itagaki[3] and Kazuyuki Kurihara[1]

Table 2 Rush SOTI for egg allergy: Background of subjects and the results. Six new cases are added to the original data cited as reference 20.

Subject number	Sex	Age	Age of last anaphylaxis by cooked egg	Complications	Threshold		Days of rush SOTI†	Symptoms during treatment
					before (g)	after (g)		
001	F	9y8m	9y2m	BA, AD	0.360	>60	18 (13)	WH, UR, AP
002	M	8y5m	8y0m	BA, AD, AR	0.012	>60	13 (9)	UR
003	M	12y0m	11y3m	BA, AD, AR	0.296	>60	9 (7)	AP
004	F	7y2m	6y9m	BA, AD, AC	0.200	>60	10 (8)	WH, UR
005	M	9y4m	8y10m	BA, AD	0.088	>60	15 (11)	AP, DI
006	M	11y4m	10y10m	BA, AD	0.104	>60	11 (9)	AP, DI
007	M	11y3m	10y10m	AD, AR, AC	0.144	>60	15 (10)	WH, UR, AP
008	F	11y2m	11y0m	AD	0.752	>60	10 (8)	UR, AP
009	M	6y9m	6y4m	BA, AD, AR	0.752	>60	14 (9)	WH, UR, DI
010	M	7y8m	7y6m	BA	0.011	>60	15 (11)	WH, UR
011	F	7y9m	3y0m	BA, AD	0.030	>60	15 (11)	WH, UR
012	M	6y9m	3y2m	BA	0.013	>60	15 (11)	WH, UR, AP, DI
Median		8y7m			0.124 (raw EW)	>60 (cooked egg)	14.5 (9.5)	

SOTI, specific oral tolerance induction; EW, egg white; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis; WH, wheezing; UR, urticaria; AP, abdominal pain; DI, diarrhea.

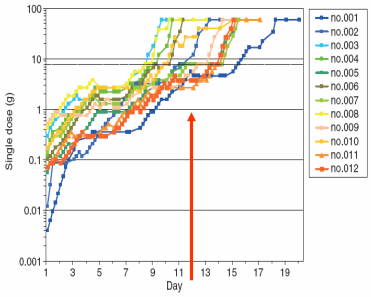

Fig. 2 The individual process of rush SOTI for egg allergy to reach a whole egg. The abscissa expresses the days after starting rush SOTI. The ordinate expresses the single doses of egg plotted in logarithmic scale. Rush SOTI was started with powdered raw egg white, and when the dose reached 8 g, it was changed to cooked egg. Six new cases are added to the original figure which has been shown in the reference 21.

A novel approach in allergen-specific immunotherapy: Combination of sublingual and subcutaneous routes

Sevgi Keles, MD,* Elif Karakoc-Aydiner, MD,* Ahmet Ozen, MD,[b] Ayse Gul Izgi, MS,* Ayzer Tevetoglu, MS,* Tunc Akkoc, PhD,* Nerin N. Bahceciler, MD,* and Isil Barlan, MD* *Istanbul, Turkey*