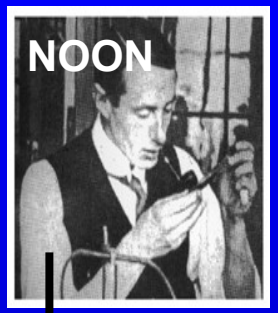
RECOMMENDATIONS FOR APPROPRIATE SLIT TRIALS

Giovanni Passalacqua

Allergy & Respiratory Diseases
Dept.Internal Medicine-
IRCCS S.Martino – IST -
University of Genoa ITALY

CHICAGO-WAO-2013



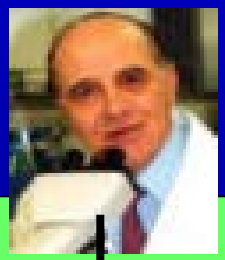
UK CSM

1986 2012

EMPIRICAL USE IgE Randomized trials

1928 1960

ROMAGNANI



SLIT

Allergoids

Th1/Th2

Peptides

Mechanisms

Recombinants

WHO

Pos Pap

DNA-

ITS

Liposomes

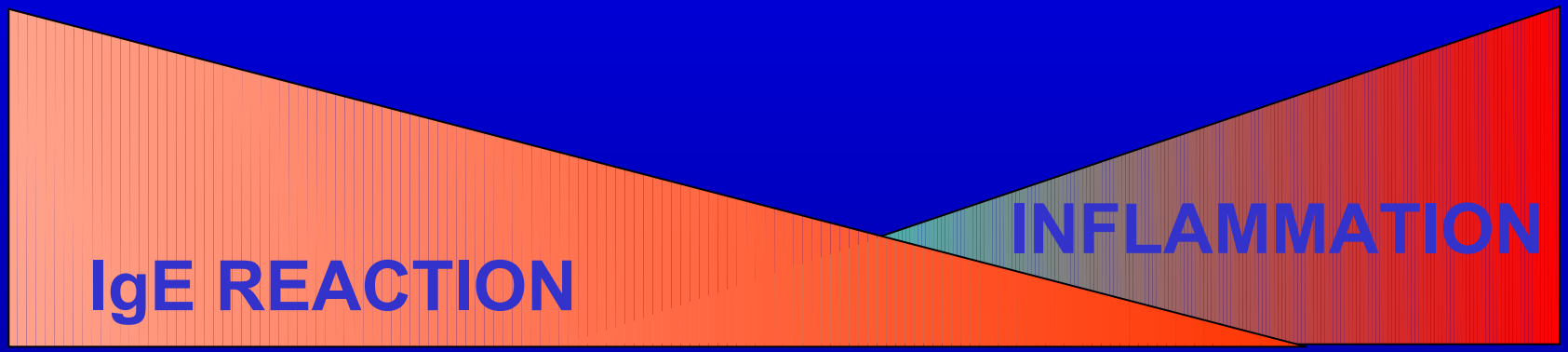
Adjuvants

ILIT

EPIT

1986 1990 1998 2012

Where does IT preferentially works?



Hymenoptera Allergy

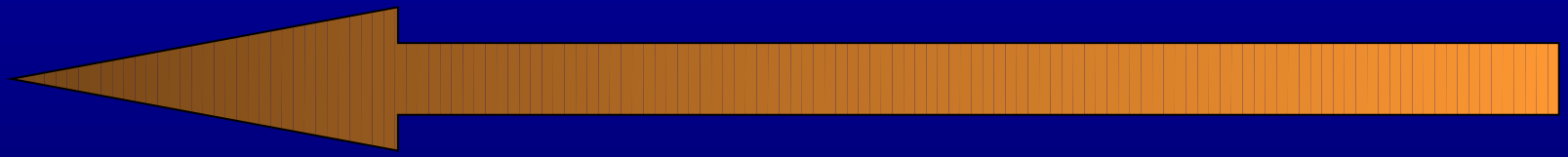
Food Allergy

Seasonal rhinitis

Perennial rhinitis

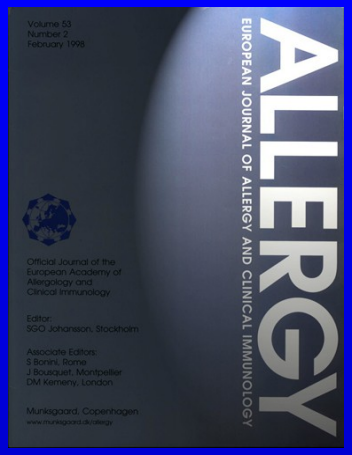
Atopic dermatitis

Asthma



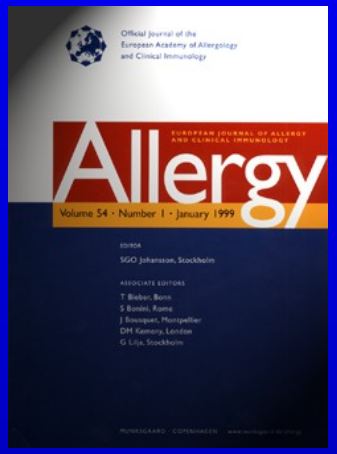
Factors to be evaluate in SIT prescription

1 IgE mediated disease
2 Clear identification of the responsible allergen
3 Severity and duration of symptoms
4 Efficacy of pharmacological treatment
5 Compliance
6 Availability of standardized products
7 demonstration of the efficacy



WHO Pos Pap. Therapeutical vaccines for allergic diseases
Allergy 1998

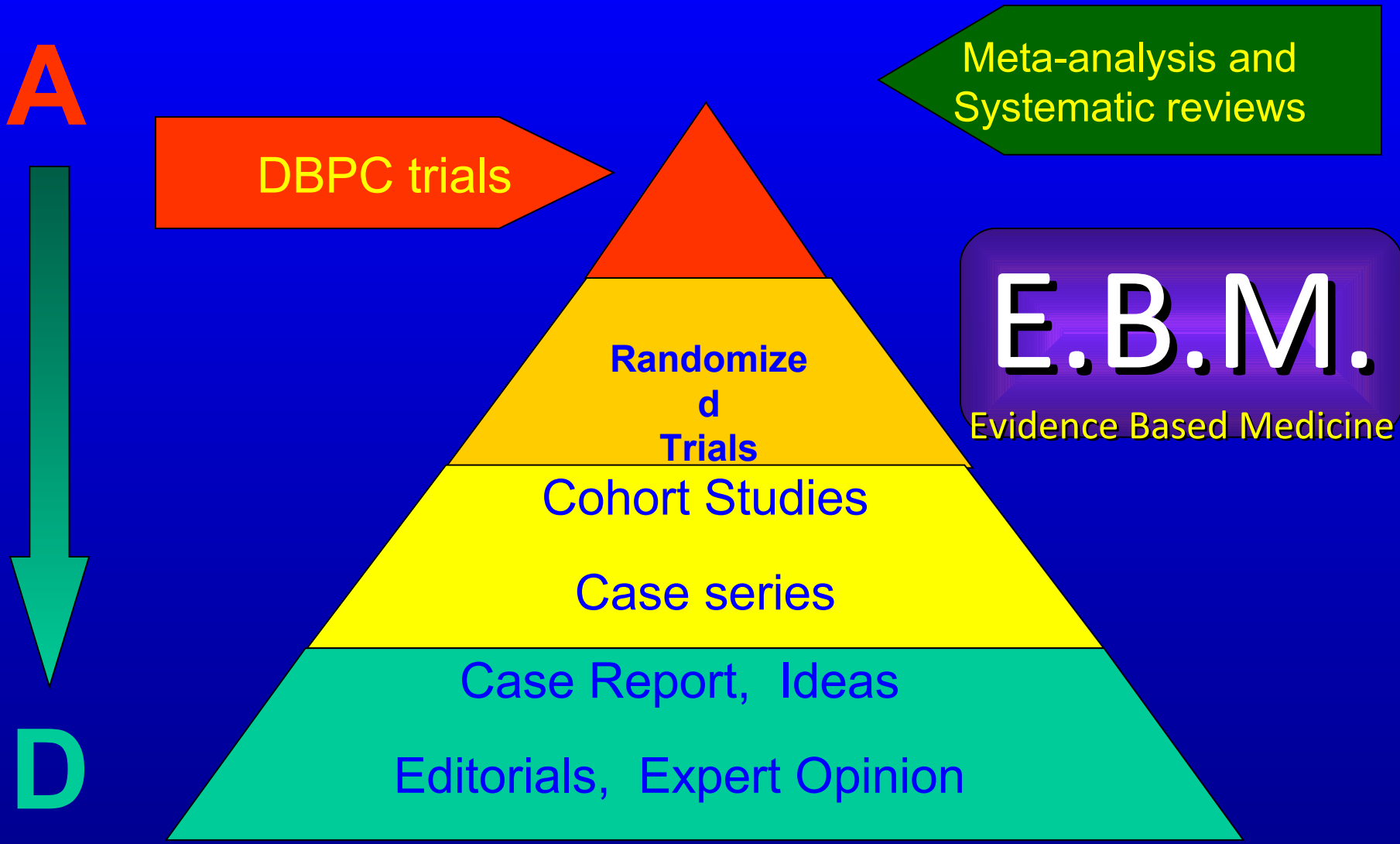
Standards for practical allergen-specific immunotherapy.
Allergy 2006



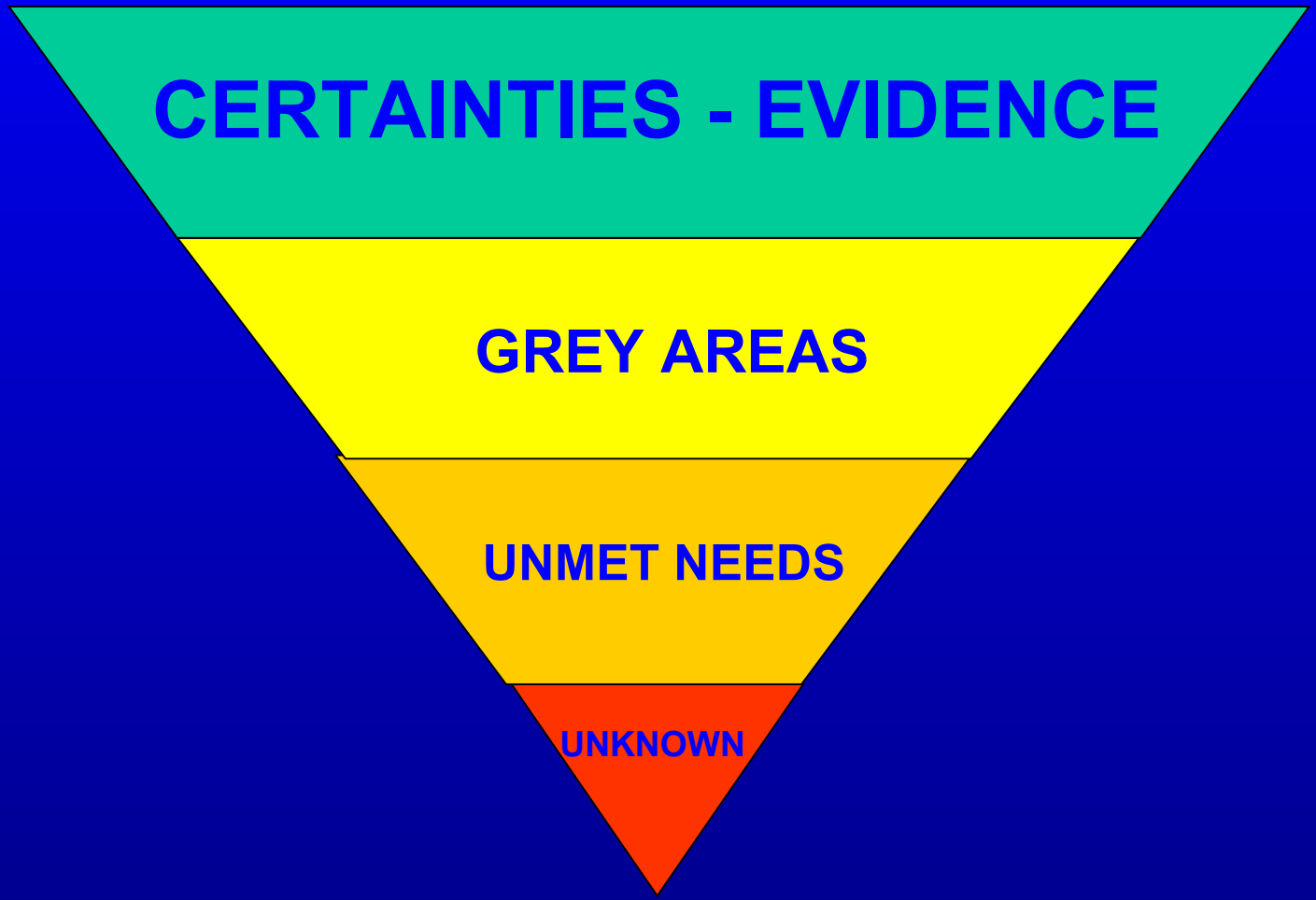
Allergen immunotherapy: A practice parameter second update
JACI 2011

WORLD ALLERGY ORGANIZATION

Sub-lingual Immunotherapy: WAO Position Paper 2009



EBM Hierarchy


CERTAINTIES - EVIDENCE
GREY AREAS
UNMET NEEDS
UNKNOWN

Sublingual Immunotherapy for Allergic Respiratory Diseases: Efficacy and Safety

Giovanni Passalacqua*, Giorgio Walter Canonica

Table 2
Meta-analyses on SLIT

Author	Patients	Disease	Trials	Effect Size on Symptoms	Comment
Calamita et al,[22] 2006	303 adults + children	Asthma	5 pollens 4 mite	−0.38 (P = .07)	No change in symptom score Significant reduction medication score
Wilson et al,[21] 2005	959 adults + children	Rhinitis	16 pollens 6 mite	−0.42 (P = .002)	Decreased symptoms and medications for rhinitis Asthma not evaluable
Penagos et al,[24] 2006	484 children	Rhinitis	5 pollens 4 mite	−0.56 (P = .02)	Decreased symptoms and medications for rhinitis No subanalysis feasible
Penagos et al,[23] 2008	441 children	Asthma	3 pollen 3 mite	−1.42 (P = .02)	Decreased symptoms and medications for asthma
Compalati et al,[28] 2009	858 adults + children	Rhinitis Asthma	Mite 8 rhinitis 9 asthma	Rhinitis, −0.95 Asthma, −0.95 (P = .02)	Significant effect on symptoms and drug intake for both rhinitis and asthma
Di Bona et al,[29] 2010	2791 adults + children	Rhinitis	19 grass	−0.32 (P<.0001)	Decreased symptoms and medications for rhinitis Greater effect in adults

Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report

A. Wesley Burks, MD,[a] Moises A. Calderon, MD, PhD,[b] Thomas Casale, MD,[c] Linda Cox, MD,[d] Pascal Demoly, MD, PhD,[e] Marek Jutel, MD,[f] Harold Nelson, MD,[g] and Cezmi A. Akdis, MD[h] *Chapel Hill, NC, London, United Kingdom, Omaha, Neb, Davie, Fla, Montpellier, France, Wroclaw, Poland, Denver, Colo, and Davos, Switzerland*

JACI 2013

TABLE E1. Symptom scores

Disease	Author	Studies (no.)	Population	Participants: Active (no.)	Participants: Placebo (no.)	Effect size, SMD (95% CI)*
SCIT						
Rhinitis	Calderon,[E1] 2007	15	Adults	597	466	−0.73 (−0.97 to −0.50)
Asthma	Abramson,[E2] 2010	34	Adults and children	727	557	−0.59 (−0.83 to −0.35)
SLIT						
Rhinitis	Wilson,[E3] 2003	21	Adults and children	484	475	−0.42 (−0.69 to −0.15)
Rhinitis	Penagos,[E4] 2006	10	Children	245	239	−0.56 (−1.01 to −0.10)
Rhinitis	Radulovic,[E5] 2011	49	Adults and children	2333	2256	−0.49 (−0.64 to −0.34)
Asthma	Calamita,[E6] 2006	9	Adults and children	150	153	−0.38 (−0.79 to 0.03)
Asthma	Penagos,[E7] 2008	9	Children	232	209	−1.14 (−2.10 to −0.18)
Conjunctivitis	Calderon,[E8] 2011	36	Adults and children	1725	1674	−0.41 (−0.53 to −0.28)
House dust mites	Compalati,[E9] 2009	8	Adults and children	194	188	−0.95 (−1.77 to −0.14)
Grass allergens	Di Bona,[E10] 2010	19	Adults and children	1518	1453	−0.32 (−0.44 to −0.21)

*Effect size (SMD): poor, <−0.20; medium, −0.50; high, >−0.80.

†Heterogeneity (I^2) = 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.

Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma

A Systematic Review

Sandra Y. Lin, MD
Nkiruka Erekosima, MD, MPH
Julia M. Kim, MD, MPH
Murugappan Ramanathan, MD
Catalina Suarez-Cuervo, MD
Yohalakshmi Chelladurai, MBBS
Darcy Ward, BA
Jodi B. Segal, MD, MPH

Importance Allergic rhinitis affects up to 40% of the US population. To desensitize allergic individuals, subcutaneous injection immunotherapy or sublingual immunotherapy may be administered. In the United States, sublingual immunotherapy is not approved by the Food and Drug Administration. However, some US physicians use aqueous allergens, off-label, for sublingual desensitization.

Objective To systematically review the effectiveness and safety of aqueous sublingual immunotherapy for allergic rhinoconjunctivitis and asthma.

Evidence Acquisition The databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials were searched through December 22, 2012. English-language randomized controlled trials were included if they compared sub-

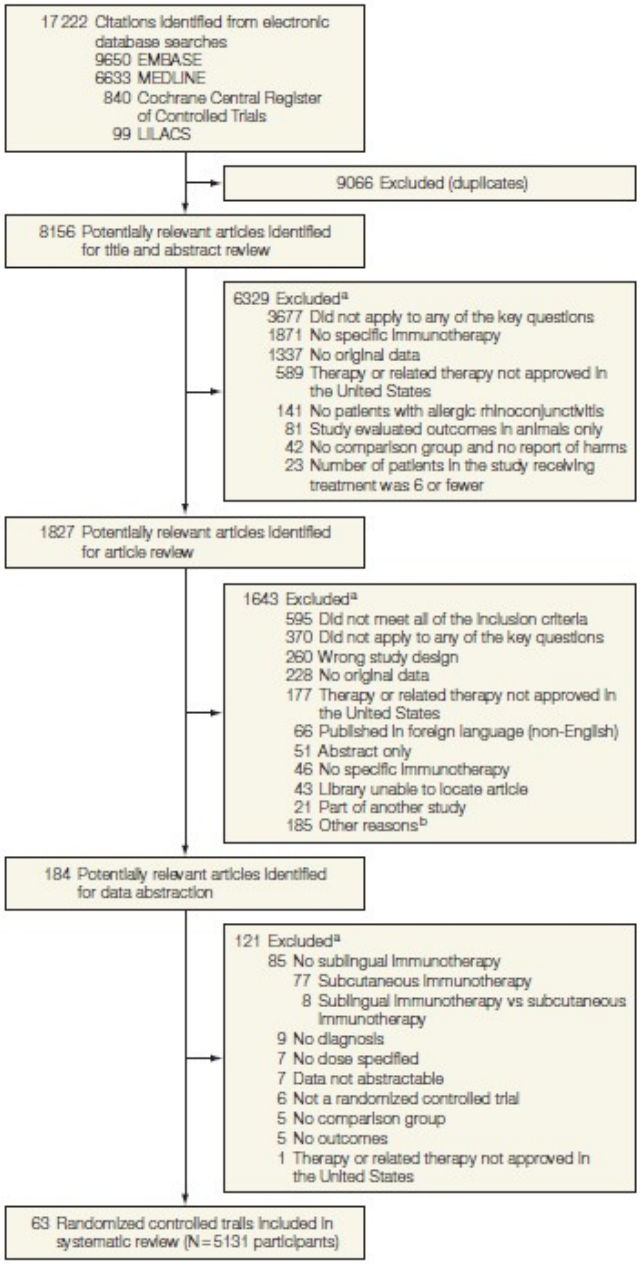
JAMA, 2013

Results Sixty-three studies with 5131 participants met the inclusion criteria. Participants' ages ranged from 4 to 74 years. Twenty studies (n=1814 patients) enrolled only children. The risk of bias was medium in 43 studies (68%). Strong evidence supports that sublingual immunotherapy improves asthma symptoms, with 8 of 13 studies reporting greater than 40% improvement vs the comparator. Moderate evidence supports that sublingual immunotherapy use decreases rhinitis or rhinoconjunctivitis symptoms, with 9 of 36 studies demonstrating greater than 40% improvement vs the comparator. Medication use for asthma and allergies decreased by more than 40% in 16 of 41 studies of sublingual immunotherapy with moderate grade evidence. Moderate evidence supports that sublingual immunotherapy improves conjunctivitis symptoms (13 studies), combined symptom and medication scores (20 studies), and disease-specific quality of life (8 studies). Local reactions were frequent, but anaphylaxis was not reported.

Conclusions and Relevance The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review.

JAMA. 2013;309(12):1278-1288 www.jama.com

Figure. Flow Diagram of Sublingual Immunotherapy Studies



WORLD ALLERGY ORGANIZATION

Sub-lingual Immunotherapy: WAO Position Paper 2009

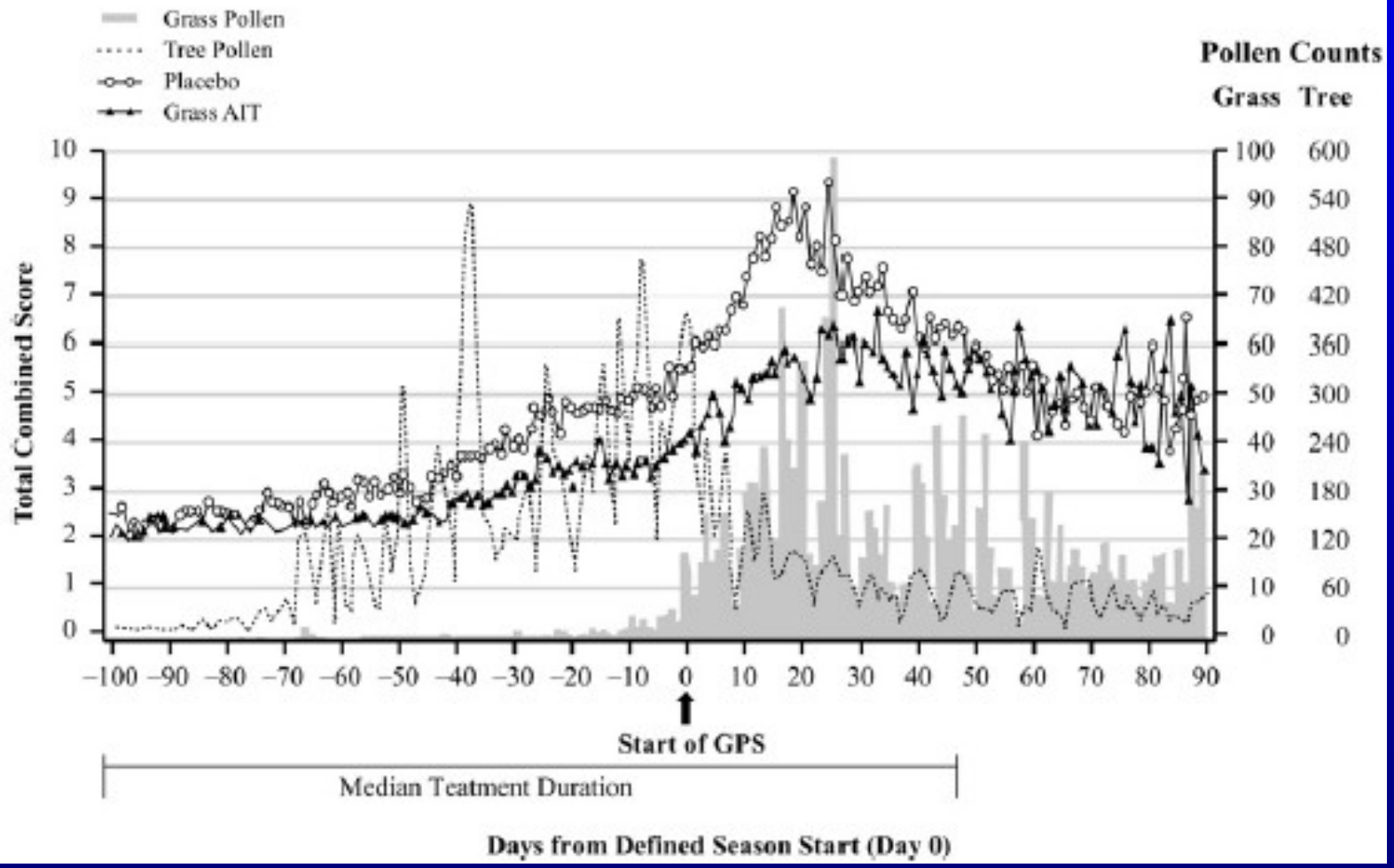
					Dura tion	Dose Administration	VS SCIT	Disease	Manufact.**	Main positive results	Negative results
					4 m	20 mcg Phl p 5/day. Tablets	NS	RC	STA	Significant reduction in RC score in Vienna challenge chamber at 4 mo in SLIT vs baseline and vs placebo. Reduction 29% vs plac Increase IgE and IgG4	Nasal airflow Weight of secretions Basophil activation
Skoner, 2010	18-50	39 med 36 high 40 plac	4/5/3	Ragweed	6 m	4.8 or 48 mcg Amb a 1/day Metered pump	NS	RC	GRE	Combined symptoms+drugs, and drug score versus placebo	Nasal challenge, IgE Symptom score during peak season
Cortellini 2010	16-44	15/12	0/1	Alternaria	10 m	60 mcg Alt a 1 cumul. 6 mcg/mo Drops	60	RCA	ANA	Significant reduction in combined score (-38%). Signif. reduction in skin reactivity	Specifcic IgE and IgG4
Panizo, 2010	18-65	52/26	2/1	Grass	5 mo	25 mcg Phl p 5/day. Tablets	NS	RC	ALK	Increase in IgE, IgG4 and IgE blocking activity only in active	
Yonekura, 2010	7-15	20/11	1/2	Mite	1 yr	0.5 mcg Der f 1 once a week	20	RC	TOR	Significant decrease in symptoms and combined score between wks 0-3 and 37-40 only in SLIT	Medication score
Blaiss 2011	5-17	349/358	33/30	Grass	6 m	450 g Phl p5/mo	NS	RC	STA	Significant reduction in combined score (-26%) QoL –38%	Asthma symptoms
Nelson 2011	18-63	213/225	33/33	Grass	10 m	450 mcg Phl p5/mo Tablets	NS	RCA	STA	Significant reduction in combined score (-20%) and medication score (-20%)	Daily medication score
Bush 2011	18-50	High 10 Low 10 Pla 11	2/3/5	Mite (Der f)	18 m	70 or 1 mcg Der f 1/dose. Drops	NS	RA	GRE	Signif reduction in specific bronch reactiv. Increase in IgG4	Symptoms and medication scores
Stelmach, 2012	6-18	Cont 20 Prec 20 Pla 20	3/1/2	Grass	2 yrs	Cumulative 7.3 and 3.6 mcg Phl p 5. Drops	NS	RCA	ALK	Significant improvement in drugs +symptoms with continuous and precos regimen. Reduction eNO.	Symptom score Medication score Pulmonary function
De Bot. 2012	6-18	126/125	15/17	Mite	2 yrs	4.06 mcg Der p 1/week Drops	NS	RC	ART		Symptom score, QoL Medication score, Well days
Cox 2012	18-65	233/240	26/17	Grass	6 m	20-25 mcg Phl p 5/day. Tablets	NS	RC	STA	Reduction in combined symptom+medication score 25% vs placebo. Improvement in QoL. Increase in IgG4	

WAO POS PAP 2013

Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents

JACI 2011

Michael Blaiss, MD,[a] Jennifer Maloney, MD,[b,c] Hendrik Nolte, MD, PhD,[b,d] Sandra Gawchik, DO,[e] Ruji Yao, PhD,[b] and David P. Skoner, MD[f,g] *Memphis, Tenn, Kenilworth, NJ, New York, NY, Copenhagen, Denmark, and Upland, Pittsburgh, and Philadelphia, Pa*



ORIGINAL ARTICLE AIRWAY DISEASES

European Academy of Allergy and Clinical Immunology task force report on 'dose–response relationship in allergen-specific immunotherapy'

M. A. Calderón[1], D. Larenas[2], J. Kleine-Tebbe[3], L. Jacobsen[4], G. Passalacqua[5], P. A. Eng[6], E. M. Varga[7], E. Valovirta[8], C. Moreno[9], H. J. Malling[10], E. Alvarez-Cuesta[11], S. Durham[1] & P. Demoly[12]

[1]National Heart and Lung Institute, Imperial College London, London, UK; [2]Hospital Médica Sur, Mexico City, Mexico; [3]Allergy & Asthma Center Westend, Berlin, Germany; [4]Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark; [5]Allergy and Respiratory Diseases, DIMI, Department of Internal Medicine, Genoa, Italy; [6]Section of Allergy and Pulmonology, Children's Hospital Aarau and Lucerne, Switzerland; [7]Department of Paediatrics, Respiratory and Allergic Disease Division, Medical University Graz, Graz, Austria; [8]Suomen Terveystalo Allergy Clinic, Turku, Finland; [9]Seccion de Alergia, Hospital Reina Sofia, Cordoba, Spain; [10]Allergy Unit, University Hospital, Copenhagen, Denmark; [11]Allergy Division, Ramon & Cajal University Hospital, Alcala de Henares University, Madrid, Spain; [12]University Hospital of Montpellier, Montpellier, France

Results: Fifteen dose-ranging studies fulfilled the inclusion criteria and twelve reported a dose-response relationship for clinical efficacy. Several studies also reported a dose-response relationship for immunological and safety endpoints. Due to the use of different reference materials and methodologies for the determination of allergen content, variations in study design, and choice of endpoints, no comparisons could be made between studies and, as a consequence, no general dosing recommendations can be made.

Allergy 2009: 64: 1570–1579

DOI: 10.1111/j.1398-9995.2009.021

Review article

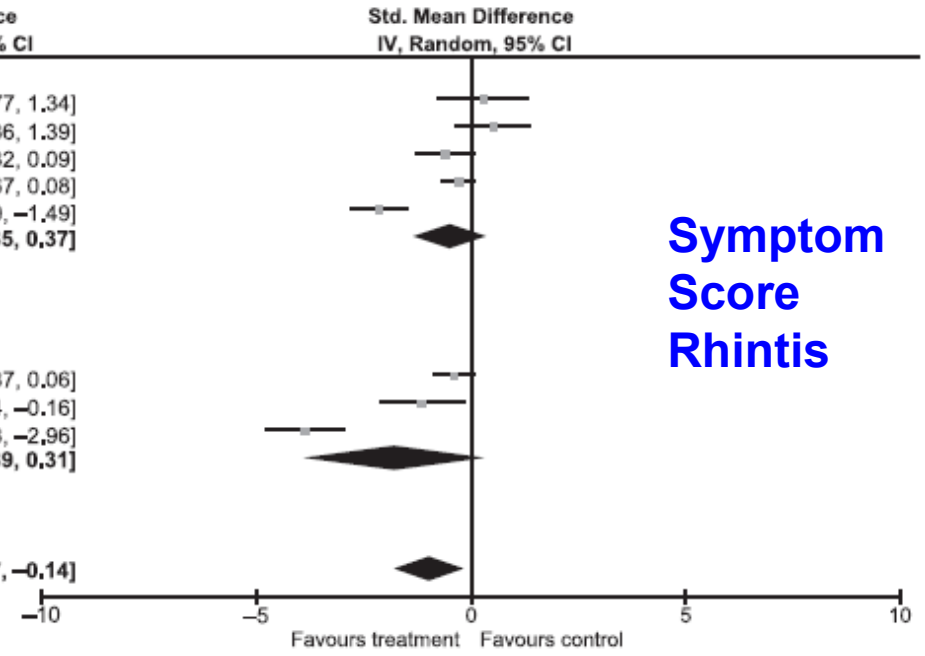
The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA²LEN meta-analysis

Recent meta-analyses documented the efficacy and safety of sublingual immunotherapy (SLIT) in patients with allergic rhinitis (AR) and asthma (AA).

E. Compalati, G. Passalacqua, M. Bonini, G. W. Canonica

A

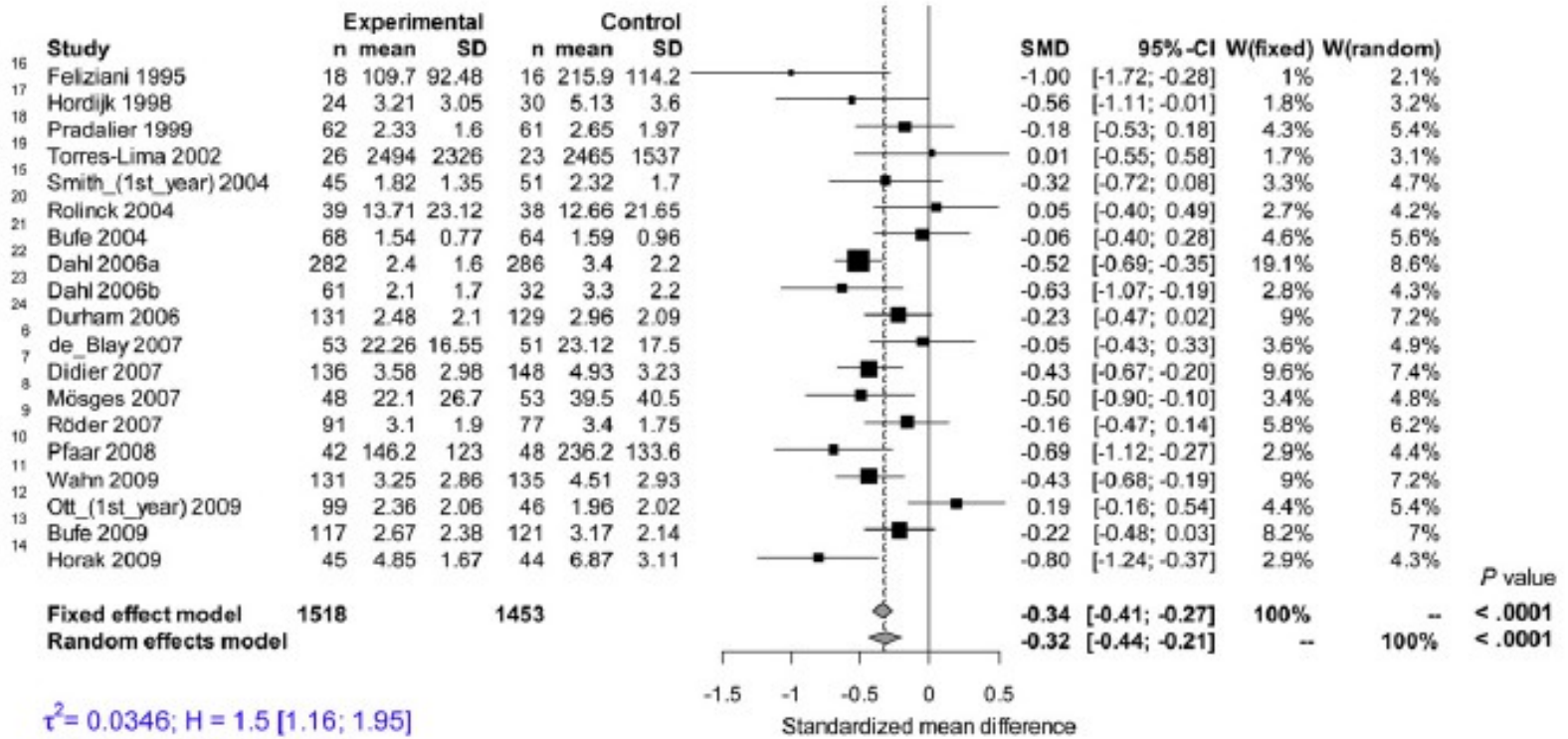
Study or Subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Pediatric population								
Bahecilier	0.53	0.4	7	0.41	0.39	7	11.4%	0.28 [–0.77, 1.34]
Hirsch	0.99	1.13	11	0.52	0.47	10	12.1%	0.51 [–0.36, 1.39]
Ippoliti	0.39	0.71	18	0.82	0.65	15	12.8%	–0.61 [–1.32, 0.09]
Pham-Ti	0.12	0.14	54	0.17	0.19	55	13.7%	–0.30 [–1.67, 0.08]
Tari	8	1.56	30	12	2.1	28	12.9%	–2.14 [–2.80, –1.49]
Subtotal (95% CI)			**120**			**115**	**62.9%**	**–0.49 [–1.35, 0.37]**
Heterogeneity: $\tau^2 = 0.82$; $\chi^2 = 32.62$, df = 4 ($P < 0.00001$); $I^2 = 88\%$								
Test for overall effect: $Z = 1.11$ ($P = 0.27$)								
1.1.2 Adult population								
Guez	2.6	1.5	36	3.3	1.9	36	13.5%	–0.40 [–0.87, 0.06]
Passalacqua 1998	75.5	30.7	10	125.6	51	9	11.7%	–1.15 [–2.14, –0.16]
Passalacqua 2006	1.73	0.14	28	2.28	0.14	28	12.0%	–3.87 [–4.78, –2.96]
Subtotal (95% CI)			**74**			**73**	**37.1%**	**–1.79 [–3.89, 0.31]**
Heterogeneity: $\tau^2 = 3.27$; $\chi^2 = 44.20$, df = 2 ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 1.67$ ($P = 0.09$)								
Total (95% CI)			**194**			**188**	**100.0%**	**–0.95 [–1.77, –0.14]**
Heterogeneity: $\tau^2 = 1.22$; $\chi^2 = 82.81$, df = 7 ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: $Z = 2.31$ ($P = 0.02$)								



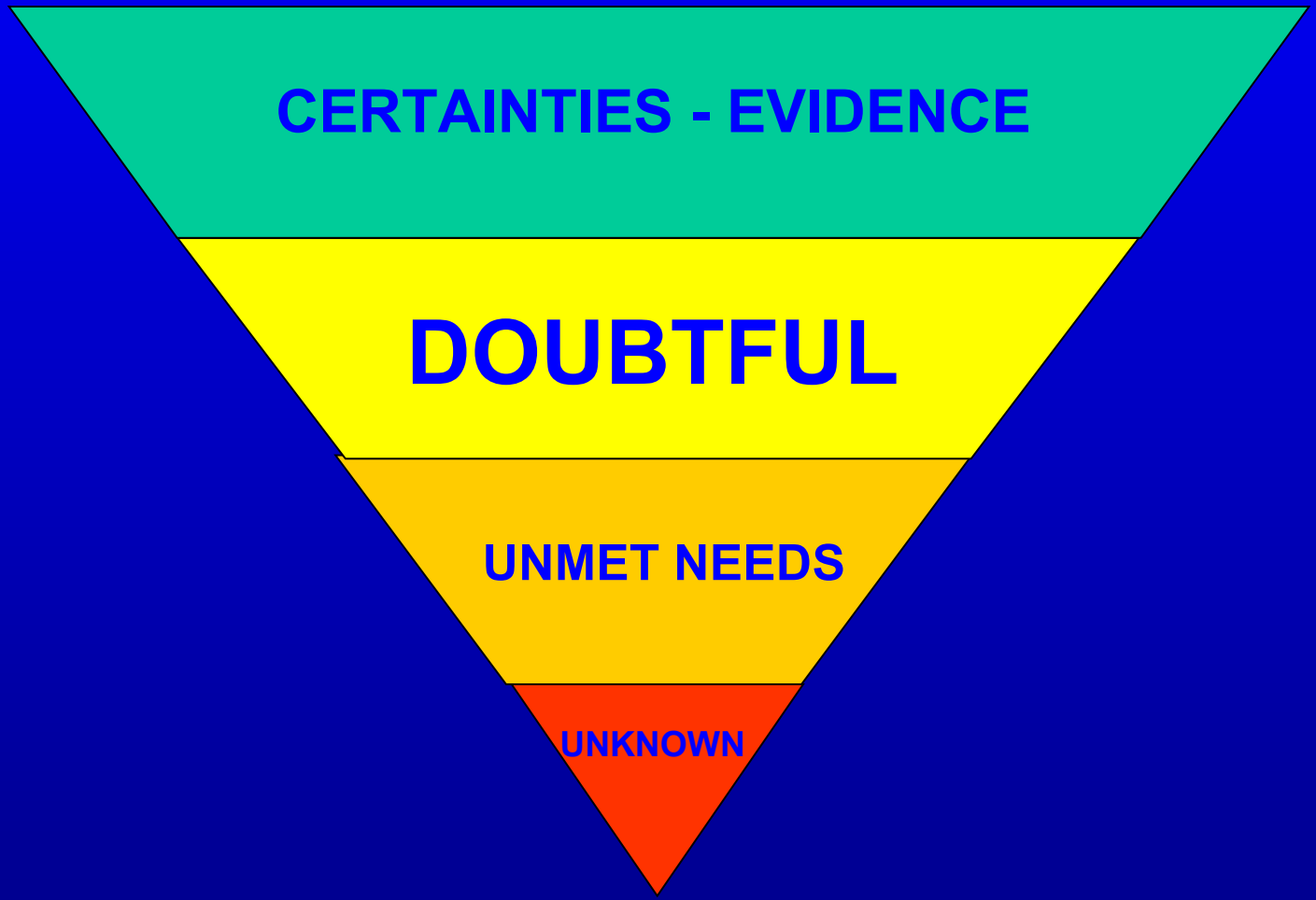
Symptom Score Rhintis

Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A systematic review and meta-analysis

Danilo Di Bona, MD, PhD,[a,e] Antonella Plaia, PhD,[b] Valeria Scafidi, PhD,[a,c] Maria Stefania Leto-Barone, MD,[d] and Gabriele Di Lorenzo, MD[d] *Palermo, Italy*



JACI 2010


CERTAINTIES - EVIDENCE
DOUBTFUL
UNMET NEEDS
UNKNOWN

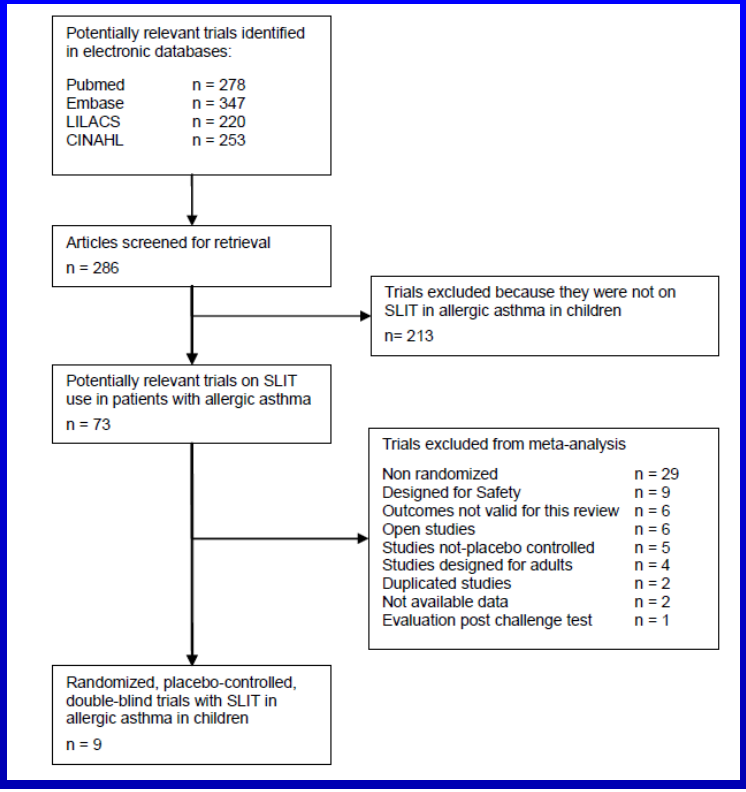
CHEST®

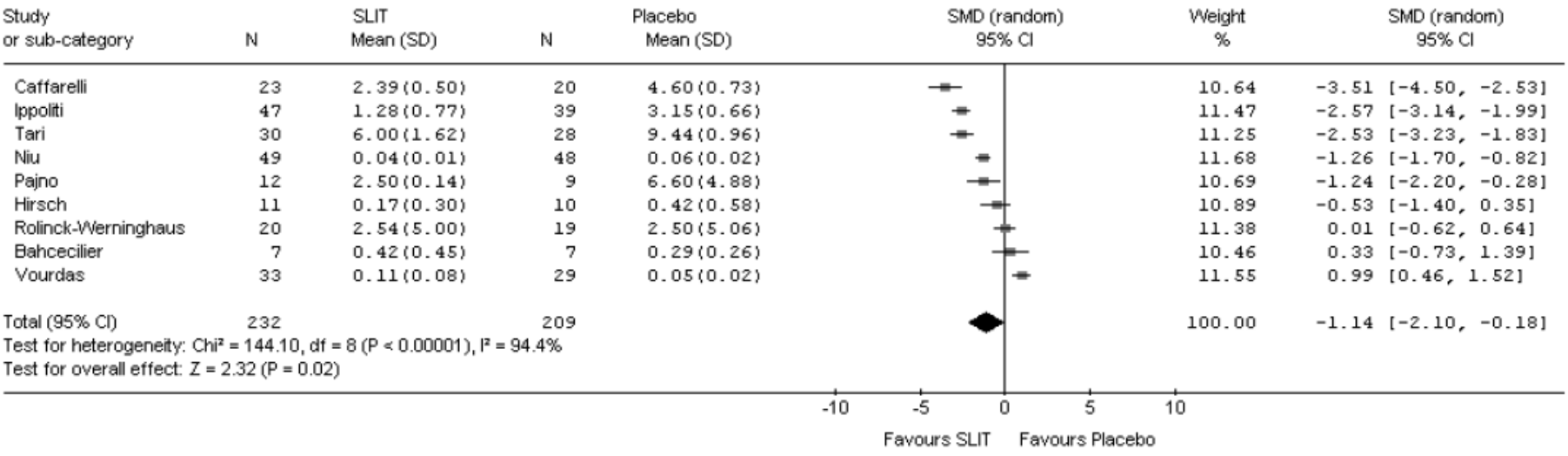
Official publication of the American College of Chest Physicians

Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age.

Martin Penagos, Giovanni Passalacqua, Enrico Compalati, Carlos E. Baena-Cagnani, Socorro Orozco, Alvaro Pedroza and Giorgio Walter Canonica

Chest published online October 20, 2007;





CHEST

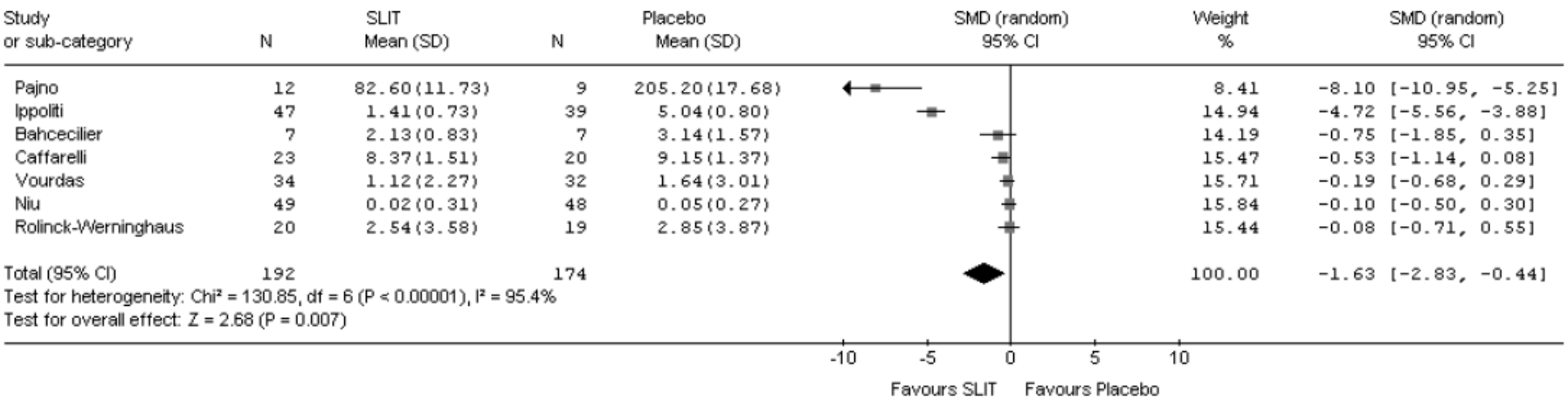
Official publication of the American College of Chest Physicians

Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age.

Martin Penagos, Giovanni Passalacqua, Enrico Compalati, Carlos E. Baena-Cagnani, Socorro Orozco, Alvaro Pedroza and Giorgio Walter Canonica

Chest published online October 20, 2007;

FIGURE 3. OUTCOME: MEDICATION SCORE.



GRADE:
Grading of Recommendation Assessment, Developing and Evaluation

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision

Should subcutaneous specific immunotherapy be used for treatment of AR in adults without concomitant ASTHMA?

Recommendation
We suggest subcutaneous allergen specific immunotherapy in adults with seasonal AR (conditional recommendation | moderate-quality evidence) and persistent AR caused by mites (conditional recommendation | low-quality evidence).

Should subcutaneous specific immunotherapy be used for treatment of in children without concomitant ASTHMA?

Recommendation
In children with , we suggest subcutaneous specific immunotherapy (conditional recommendation | low-quality evidence).

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision

Should subcutaneous allergen-specific immunotherapy be used in patients with AR and concomitant asthma?

Recommendation
In patients with AR and asthma , we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate-quality evidence).

Should sublingual allergen-specific immunotherapy be used in patients with AR and concomitant asthma ?

Recommendation
In patients with AR and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation | low-quality evidence).

Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report

A. Wesley Burks, MD,[a] Moises A. Calderon, MD, PhD,[b] Thomas Casale, MD,[c] Linda Cox, MD,[d] Pascal Demoly, MD, PhD,[e] Marek Jutel, MD,[f] Harold Nelson, MD,[g] and Cezmi A. Akdis, MD[h] *Chapel Hill, NC, London, United Kingdom, Omaha, Neb, Davie, Fla, Montpellier, France, Wroclaw, Poland, Denver, Colo, and Davos, Switzerland*

JACI 2013

TABLE E1. Symptom scores

Disease	Author	Studies (no.)	Population	Participants: Active (no.)	Participants: Placebo (no.)	Effect size, SMD (95% CI)*	Heterogeneity I^2†
SCIT							
Rhinitis	Calderon,[E1] 2007	15	Adults	597	466	−0.73 (−0.97 to −0.50)	63%
Asthma	Abramson,[E2] 2010	34	Adults and children	727	557	−0.59 (−0.83 to −0.35)	73%
SLIT							
Rhinitis	Wilson,[E3] 2003	21	Adults and children	484	475	−0.42 (−0.69 to −0.15)	73%
Rhinitis	Penagos,[E4] 2006	10	Children	245	239	−0.56 (−1.01 to −0.10)	81%
Rhinitis	Radulovic,[E5] 2011	49	Adults and children	2333	2256	−0.49 (−0.64 to −0.34)	81%
Asthma	Calamita,[E6] 2006	9	Adults and children	150	153	−0.38 (−0.79 to 0.03)	64%
Asthma	Penagos,[E7] 2008	9	Children	232	209	−1.14 (−2.10 to −0.18)	94%
Conjunctivitis	Calderon,[E8] 2011	36	Adults and children	1725	1674	−0.41 (−0.53 to −0.28)	59%
House dust mites	Compalati,[E9] 2009	8	Adults and children	194	188	−0.95 (−1.77 to −0.14)	92%
Grass allergens	Di Bona,[E10] 2010	19	Adults and children	1518	1453	−0.32 (−0.44 to −0.21)	56%

*Effect size (SMD): poor, <−0.20; medium, −0.50; high, >−0.80.

†Heterogeneity (I^2) = 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.

Comparing subcutaneous and sublingual immunotherapy: what do we know?

Nerin N. Bahceciler and Nilufer Galip

Curr Opin Allergy Clin Immunol 2012

Reference	Design	Patient number	Allergen	Duration (month)	Clinical results	Immunological results
Adults						
Quirino *et al.* [59]	RPC-DBDD	10 SLIT; 10 SCIT	Grass	12	SS↓ MS↓ in SLIT and SCIT	↑sp IgG, IgG4↓ in SPT reactivity in SCIT
Mungan *et al.* [58]	R-Open-SLITc	15 SLIT; 10SCIT; 11SL PLAC	HDM	12	Rhinitis SS↓, MS↓ in SCIT and SLIT asthma SS↓ in SCIT	↓SPT reactivity in SCIT
Khinchi *et al.* [56]	RPC-DBDD	21 SCIT; 18 SLIT; 19 PLAC	Birch	24	Rhinitis MS↓ in SCIT and SLIT	NE
Bernardis *et al.* [57]	Open	23 total	Alternaria	24	↓SS, ↓MS, ↑NP threshold in SCIT and SLIT	↓sp IgE, ↑IgG, ↓SPT reactivity in SCIT
Children						
Antúnez *et al.* [60]	R-open	12 SCIT; 11SLIT	HDM	24	NE	↓sp IgE, ↑IgG4 in SCIT, ↑sp IgE/IgG4, ↓$CD8^+$ $CD25^+$ in SCIT
Yukselen *et al.* [61]	RPC-DBDD	30 total	HDM	12	↓SS, MS, VAS in SCIT↓ MS and VAS in SLIT↑ NP threshold in SCIT and SLIT	↑sp IgG4 in SCIT ↑ IL-10↑, ↓ SPT reactivity, ↓sp IgE in SCIT and SLIT
Eifan *et al.* [62]	R-Open-C	16 SLIT; 16 SCIT; 16 PHARM	HDM	12	↓SS, MS, VAS, ↓nasal threshold in SLIT and SCIT	↓sp IgE, ↓SPT reactivity in SCIT and SLIT ↑ IL-10 in SLIT
Keles *et al.* [63▪▪]	R-Open-C	15 SCIT; 15 SLIT; 15 SCIT + SLIT; 15 PHARM	HDM	18	↓SS, MS, ICS dose, asthma attack no in SCIT, SLIT and SCIT-plus-SLIT, ↓NP threshold in SCIT, SLIT and SCIT-plus-SLIT	↑ Il-10, TGFβ, IFNγ in SCIT, SLIT and SCIT-plus-SLIT ↑sp IgG4 in SCIT and SCIT-plus-SLIT

HDM, house dust mite; MS, medication scores; NE, not evaluated; NP, nasal provocation; PHARM, pharmacotherapy; R-Open, randomized open; R-Open-C, randomized open controlled; R-Open-SLITc, randomized open placebo sublingual immunotherapy (SLIT) controlled; RPC-DBDD, randomized, placebo-controlled, double-blinded double dummy; SCIT, subcutaneous immunotherapy; sp, specific; SPT, skin prick test; SS, symptom scores; VAS, visual analogue score.

Assessment of sublingual imr efficacy in children with hous mite-induced allergic asthma controlled by pharmacologic and mite-avoidance measures

Pham Ti, PAI 2007

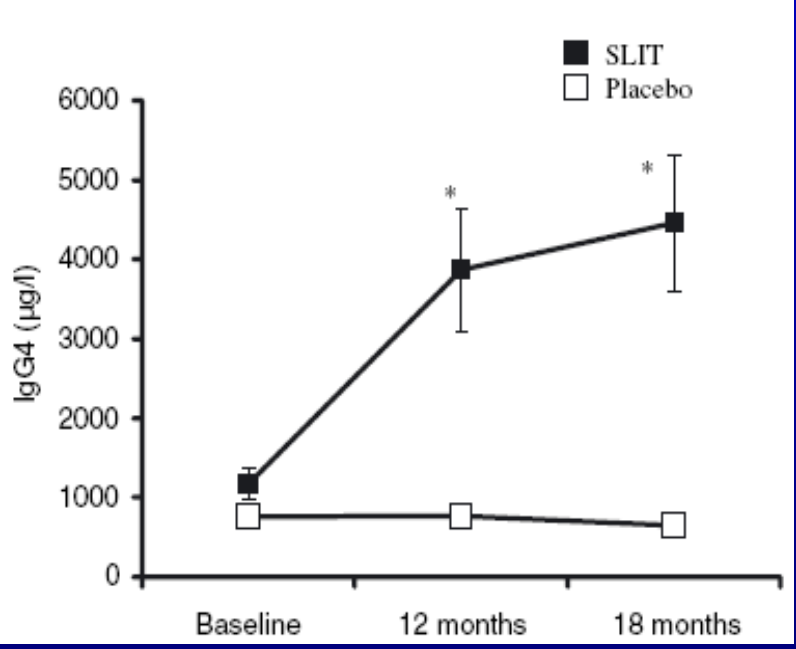


Table 2. Symptoms scores, medication intake and lung function parameters at baseline and at SLIT endpoint

	SLIT (n = 54), mean ± s.d.	Placebo (n = 55), mean ± s.d.	p-value*
Diumal asthma			
Baseline	0.19 ± 0.30	0.17 ± 0.24	
Endpoint	0.15 ± 0.26	0.08 ± 0.17	NS
Nocturnal asthma			
Baseline	0.17 ± 0.30	0.11 ± 0.18	
Endpoint	0.10 ± 0.19	0.07 ± 0.16	NS
% asthma-free days			
Baseline	78.5 ± 27.4	80.8 ± 23.8	
Endpoint	85.8 ± 23.8	91.1 ± 15.4	NS
Use of inhaled steroids (µg budesonide/day)			
Baseline	548 ± 220	534 ± 237	
Endpoint	257 ± 232	223 ± 270	NS
Use of inhaled β_2-agonists (terbutaline puffs/day)			
Baseline	0.87 ± 0.5	0.90 ± 0.8	
Endpoint	0.55 ± 0.6	0.47 ± 0.5	NS
Rhinitis daily score			
Baseline	0.71 ± 0.76	0.50 ± 0.58	
Endpoint	0.12 ± 0.14	0.17 ± 0.19	NS
PEFR variability (%)			
Baseline	8.03 ± 7.21	7.48 ± 6.14	
Endpoint	6.06 ± 5.45	6.36 ± 5.65	NS
FEV_1 (% predicted value)			
Baseline	91.9 ± 13.4	95.1 ± 15.1	
Endpoint	88.5 ± 13.4	94.5 ± 14.6	NS

Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis

Background: The best way to prevent allergy symptoms is to treat the allergic

R. Dahl[1], A. Stender[2], S. Rak[3]

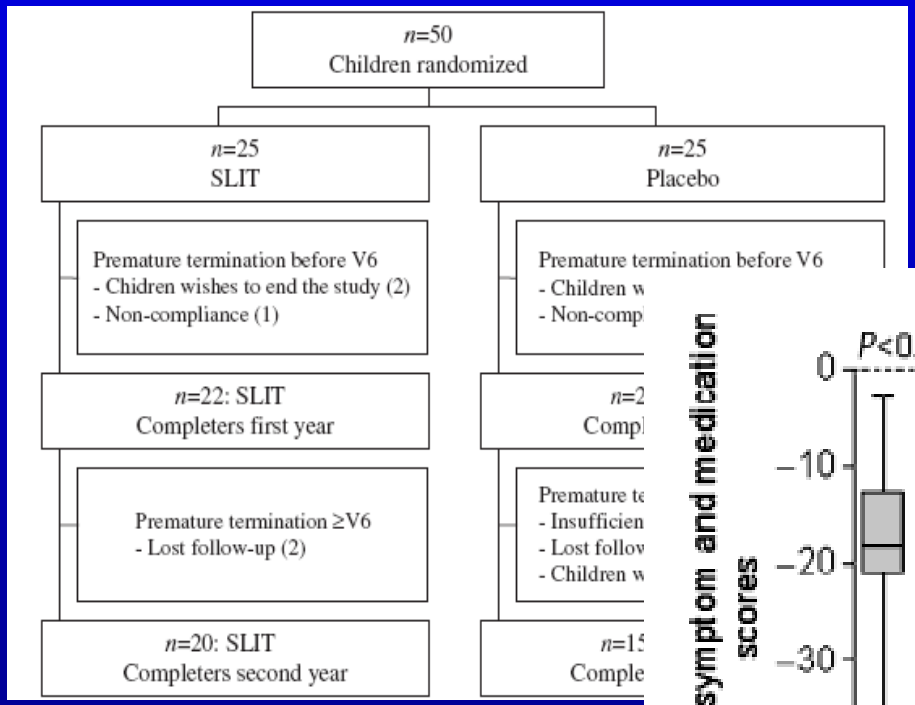
Table 3. Average daily asthma medication and symptom score

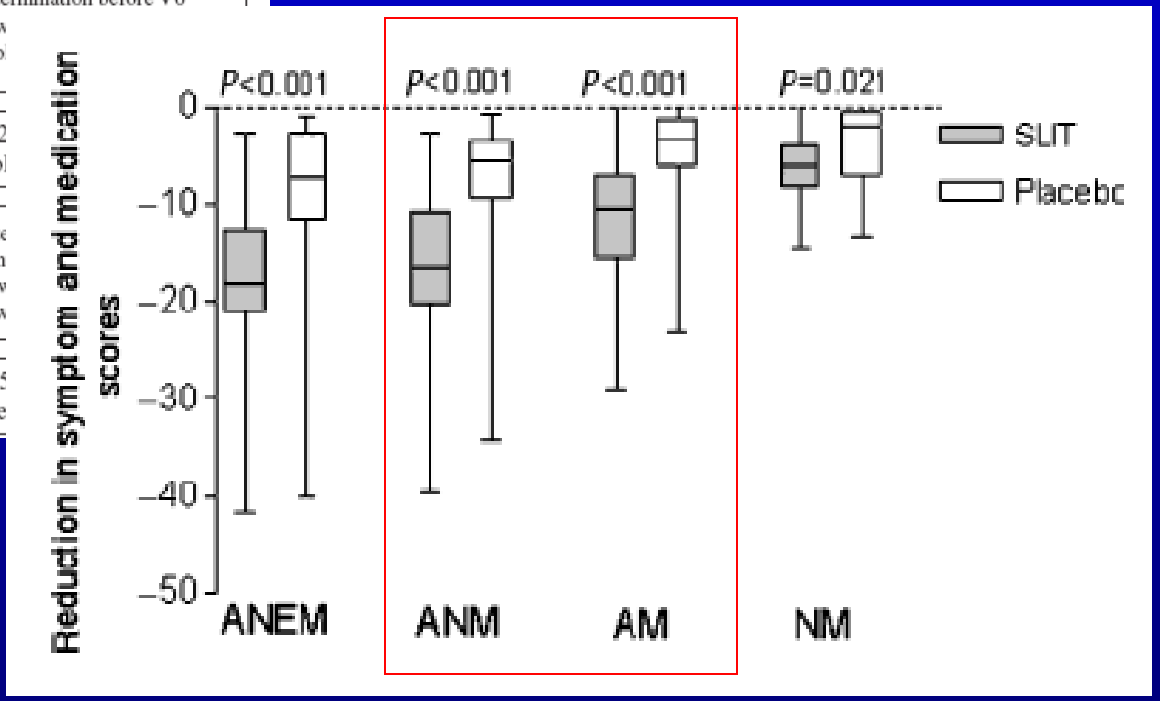
	Preseason		Grass pollen season	
Treatment group analysis set	Placebo FAS ($N = 40$)	75 000 SQ-T FAS ($N = 73$)	Placebo FAS ($N = 39$)*	75 000 SQ-T FAS ($N = 68$)*
Asthma medication score				
Mean (SD)	0.09 (0.14)	0.09 (0.23)	0.66 (1.08)	0.71 (1.28)
Median	0.00	0.00	0.07	0.00
Minimum–maximum	0.00–0.49	0.00–1.35	0.00–4.00	0.00–5.33
Asthma symptom score				
Mean (SD)	0.33 (0.33)	0.23 (0.34)	0.74 (0.92)	0.44 (0.68)
Median	0.23	0.10	0.36	0.18
Minimum–maximum	0.00–1.05	0.00–2.00	0.00–3.60	0.00–3.67

Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen

I. Stelmach, J. Kaczmarek-Woźniak, P. Majak, M. Olszowiec-Chlebna and J. Jerzynska
Department of Pediatrics and Allergy, N Copernicus Hospital, Lodz, Poland

March 2009





PROBLEMS:

The majority of the trials were not designed and sized for asthma as primary outcome

Heterogeneity of study designs, duration, dose and evaluation parameters.

Few studies had functional parameters evaluated

Implications for clinical trials:

If asthma is investigated, the trial should consider asthma as primary outcome

Functional parameters (FEV1, VEMS, oscillometry) should be evaluated

Patients should be symptomatic, or therapeutic control should be evaluated.

doi: 10.1111/j.1365-2222.2009.03448.x

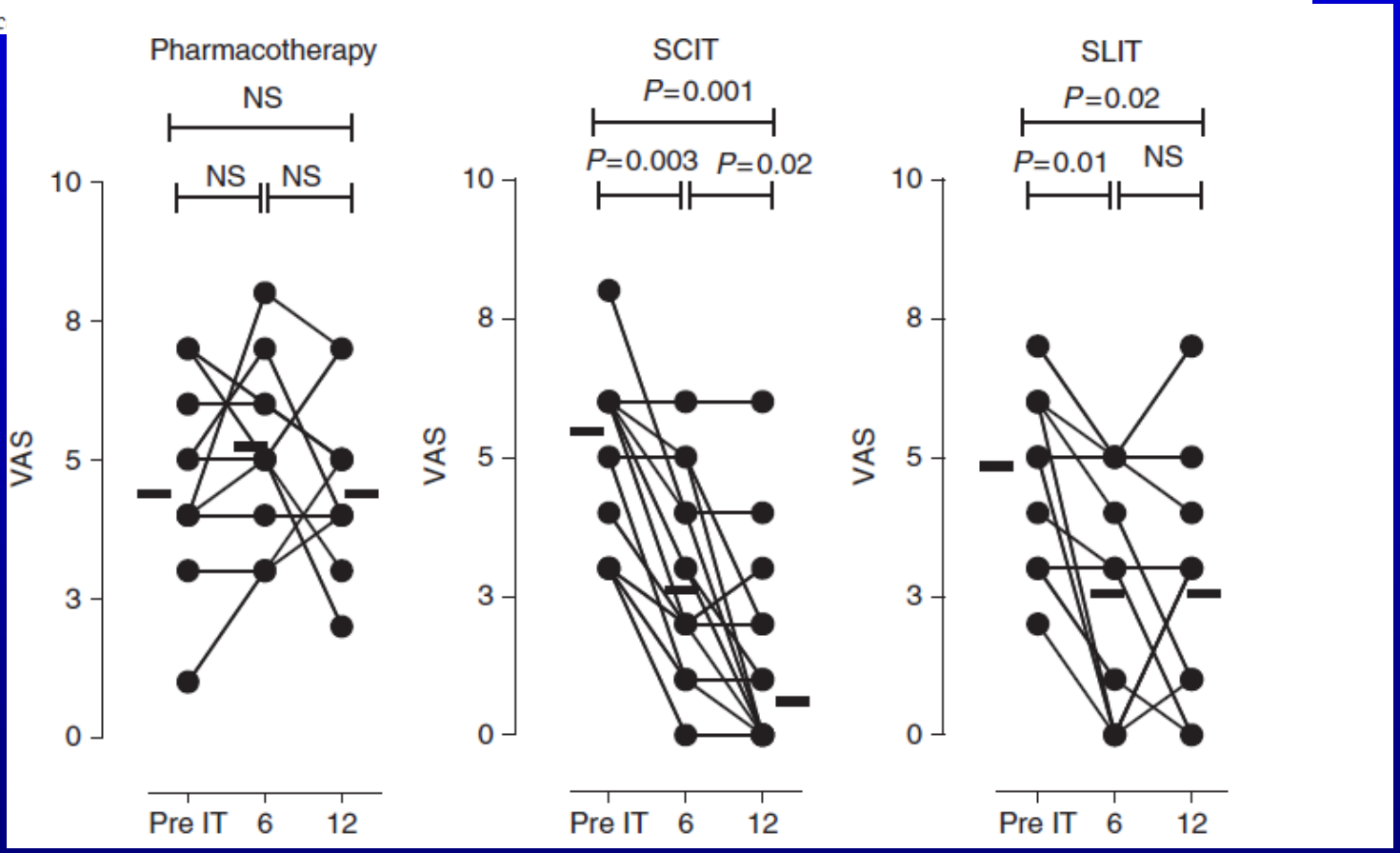
Clinical & Experimental Allergy, **40**, 922–932

ORIGINAL ARTICLE Clinical Allergy

Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial

A. O. Eifan[1,2], T. Akkoc[1], A. Yildiz[1], S. Keles[1], C. Ozdemir[1], N. N. Bahceciler[1] and I. B. Barlan[1]

[1]*Division of Pediatric Allergy and Immunology, Marmara University Medical Faculty, Istanbul, Turkey and* [2]*Allergy & Clinical Immunology Section, NHLI, Imperial College, Fac*



REVIEW ARTICLE

Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile

M. A. Calderón[1], F. E. R. Simons[2], H.-J. Malling[3], R. F. Lockey[4], P. Moingeon[5] & P. Demoly[6]

Table 1 Clinical efficacy of SLIT and SCIT in comparative studies

Authors	Year	Study design	Patients (*n*)	Patient age range	Allergen extract	Treatment duration	SLIT allergen dose (-fold the SCIT dose)	Conclusion in terms of efficacy
Bernardis et al. (9)	1996	Open, controlled, no placebo	23	5–26	*Alternaria tenuis*	2 years	×3.6	SLIT > SCIT
Quirino et al. (10)	1996	RCT, double-dummy, no placebo	20	13–39	Five grasses	1 year	×2.4	SLIT = SCIT
Mungan et al. (11)	1999	RCT, single-blind, placebo	36	18–46	Der p, Der f	1 year	×80	SLIT = SCIT
Khinchi et al. (12)	2004	RCT double-dummy, placebo	58	20–58	Birch	2 years	×210	SLIT = SCIT
Herrscher (13)	2006	Patient survey	328	3–71	Multi-allergen extracts	Typically 9–18 months	×5–10	SLIT = SCIT
Mauro et al. (14)	2007	RCT, no placebo	47	18–59	Alder, birch, and hazel	*Not stated*	×92	SLIT = SCIT

Implications for clinical trials:

The optimal study design to compare SLIT and SCIT is the DB DD RPC fashion

This is not currently feasible, due to economic limitations.

Changing the route of immunotherapy administration: An 18-year survey in pediatric patients with allergic rhinitis and asthma

Giovanni Pajno, M.D.,[1] Lucia Caminiti, M.D.,[1] and Giovanni Passalacqua, M.D.[2]

Table 2 **Changing SLIT to SCIT and *vice versa***

	SCIT TO SLIT (n = 54/648)	SLIT TO SCIT (n = 340/4285)	$p\chi^2$
%	8.3	7.9	NS
Nonadherence	5 (9.25%)	48 (14.12%)	NS
Side effects	49 (90.75%)	0	<0.001
Inefficacy	0	292 (85.88%)	<0.001
Parietaria	29 (4.47%)*	184 (4.29%)*	NS
Grass	18 (2.77%)*	110 (2.56%)*	NS
Dust mite	5 (0.77%)	41 (0.95%)	NS
Olive	2 (0.30)	5 (0.11%)	NS

Numbers, percentages, and reasons for shifting the regimen.
**SCIT for single allergen:* Parietaria, *10.62%, and grass, 8.32%.*
**SLIT for single allergen:* Parietaria *11.73%, and grass, 8.95%.*
NS = not significant; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

ANAPHYLAXES DUE TO SLIT

AUTHOR	SEX	AGE	ALLERG	EPINEPH
Antico	M	36	Latex	?
Dunsky	F	31	Mix	N
Eifan	F	11	Mix	N
Blazowski	F	16	Mite	Y
Rodriguez	M	11	Mite	N
De Groot	M	13	Grass	Y
De Groot	F	27	Grass	Y
Buyukozurk	M	28	Latex	Y
Buyukozurk	M	35	Latex	Y
Rodriguez	M	27	Mite	Y
Rodriguez	F	7	Mite	Y

Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

Linda Cox, MD,[a] Desiree Larenas-Linnemann, MD,[b] Richard F. Lockey, MD,[c] and Giovanni Passalacqua, MD,[d] Editors

Davie and Tampa, Fla, M

TABLE I. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

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

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis; eg, becoming very quiet or irritable and cranky.

Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to onset of symptom(s)/sign(s) of the SR:a, ≤ 5 minutes; b, >5 minutes-to ≤10 minutes; c: >10 to ≤20 minutes; d:>20 minutes; z, epinephrine not administered.

The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection*** and a suffix reflecting if and when epinephrine was or was not administered, **eg, Grade 2a; rhinitis:10 minutes.**

Final Report: Grade a-d, or z_____ First symptom(s)/sign(s)_____ Time of onset of first symptom_____

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*

From [a]Allergy and Respiratory Diseases, University of Genoa; [b]Catholic University of Cordoba; [c]University Hospital, Hopital A. de Villeneuve, Department of Respiratory Diseases, Montpellier; [d]the Creighton University School of Medicine, Omaha; [e]Nova Southeastern University, Ft Lauderdale; [f]the National Heart and Lung Institute, Imperial College, London; [g]the Allergy Department, Hospital Medica Sur, Mexico City; [h]the University of South Florida, Tampa; [i]Nippon Medical School, Tokyo; [j]the University of Cape Town, Groote Schuur; [k]the Federal University of Parana, Curitiba; and [l]the American College of Allergy Asthma and Immunology, Arlington Heights.

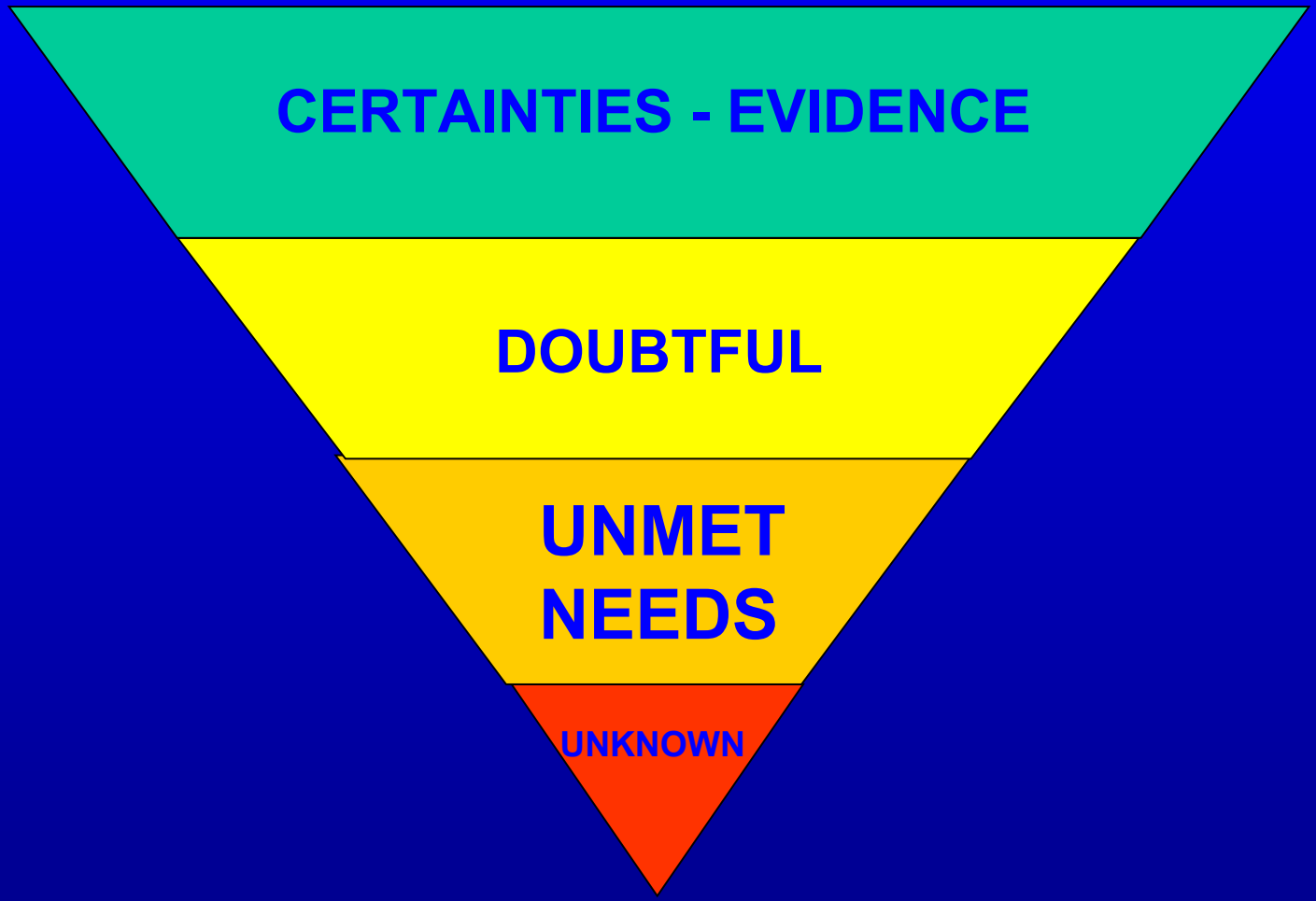
This document has been officially endorsed by the American Academy of Allergy, Asthma & Immunology (AAAAI); the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAACI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Latin American Society for Allergy and Immunology (SLAAI).

JACI 2013

Implications for clinical trials:

Adverse events should be described, graded and classified in a standardized fashion

Adverse events should be notified promptly, to monitoring authorities or manufacuturers


CERTAINTIES - EVIDENCE
DOUBTFUL
UNMET NEEDS
UNKNOWN

UNSOLVED QUESTIONS

Optimal maintenance regimen (continuous VS pre-coseasonal)

Dose and extract standardization?

Better drugs or SIT?

Polysensitized?

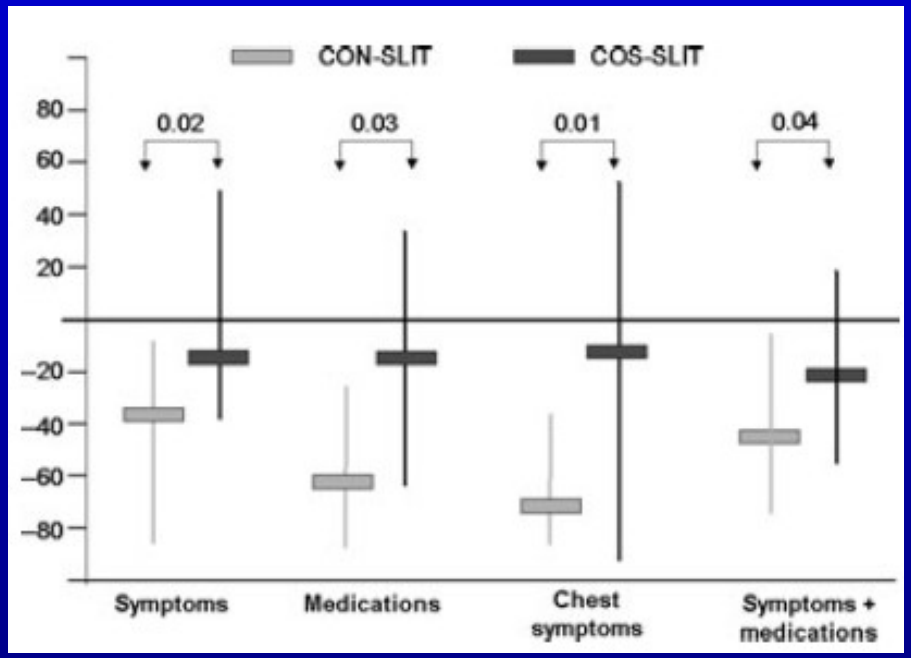
Optimal maintenance SLIT dose for other allergens

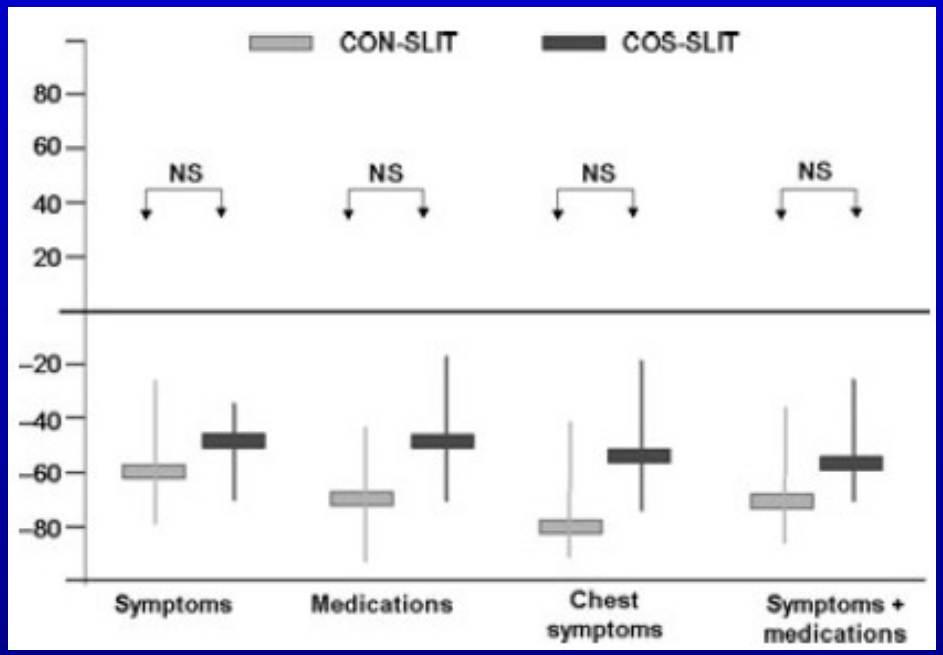
Pediatric Allergy and Immunology

SHORT REPORT

Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: A randomized controlled study

Giovanni B. Pajno[1], Lucia Caminiti[1], Giuseppe Crisafulli[1], Daniela Vita[1], Mariella Valenzise[1], Raffaele De Luca[1] & Giovanni Passalacqua[2]





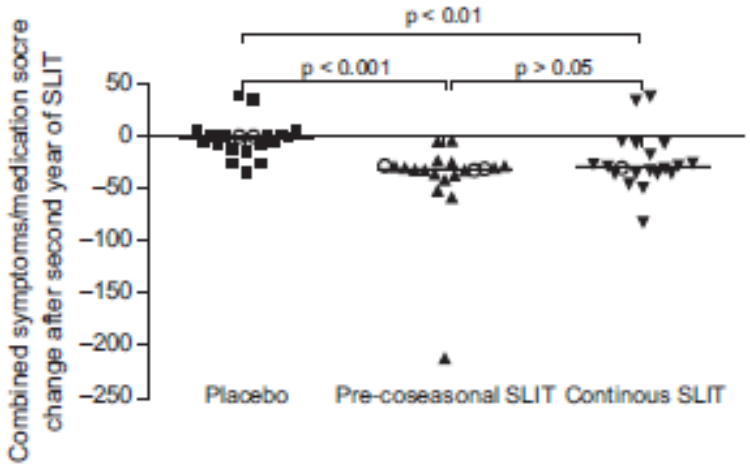
Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
Allergy

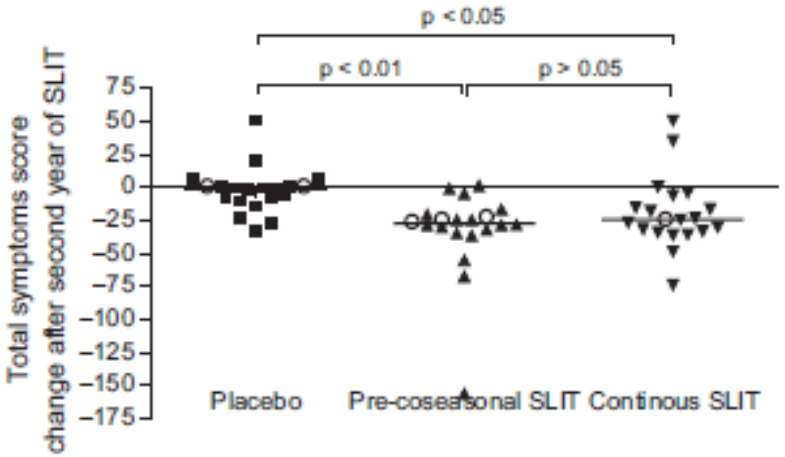
ORIGINAL ARTICLE

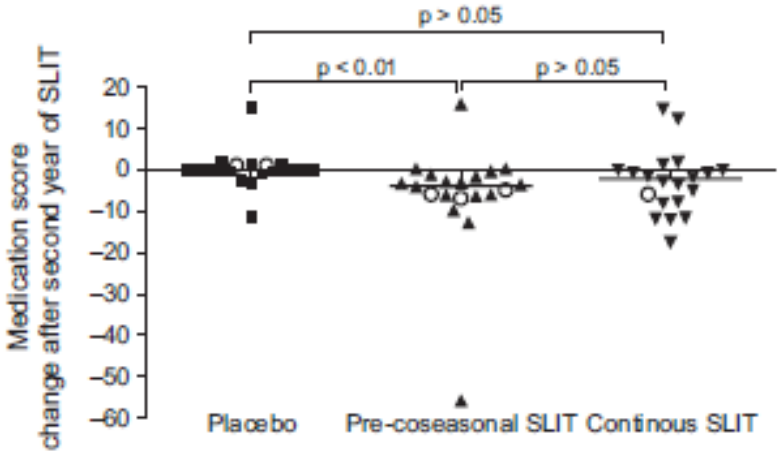
EXPERIMENTAL ALLERGY AND IMMUNOLOGY

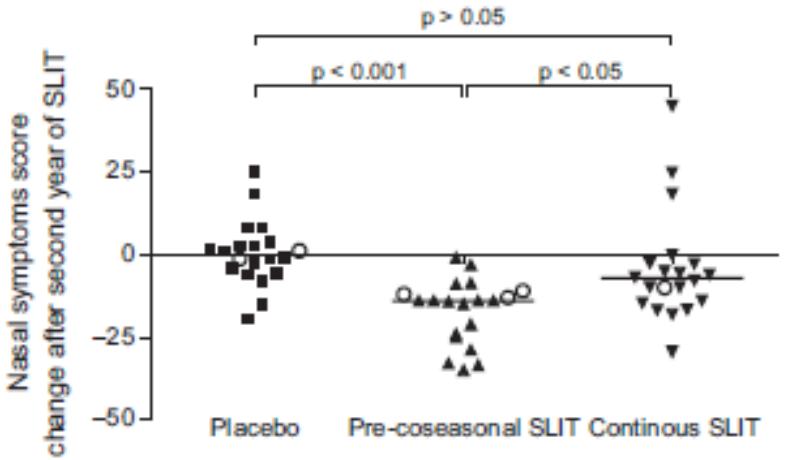
Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children

I. Stelmach[1], I. Kaluzińska-Parzyszek[1], J. Jerzynska[1], P. Stelmach[2], W. Stelmach[3] & P. Majak[1]









Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy

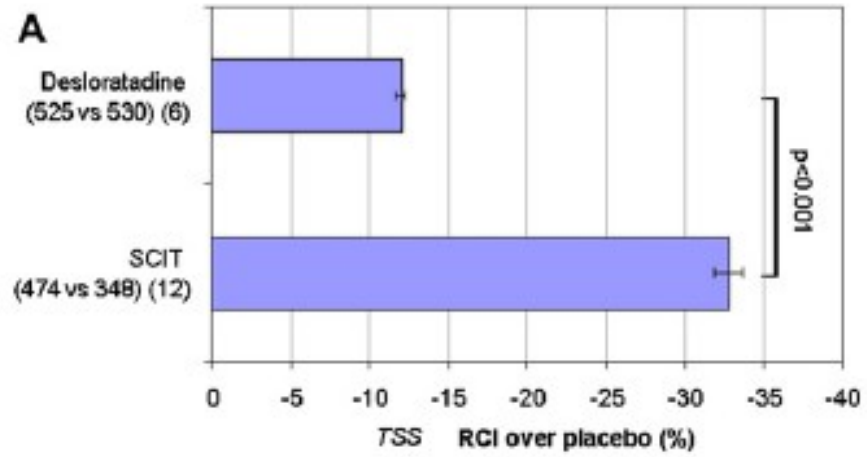
I. Sander, C. Fleischer, U. Meurer,

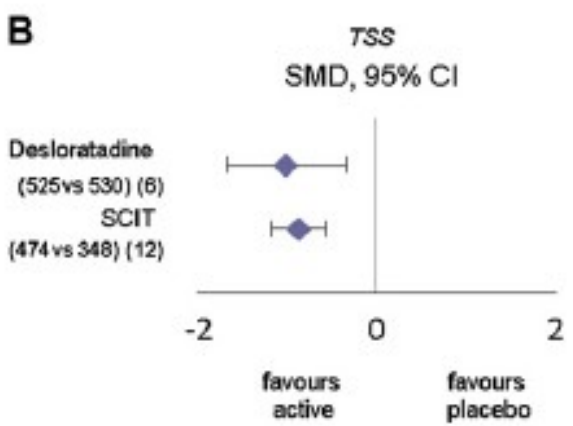
Background: The allergen content of diagnostics and immunotherapeutics is

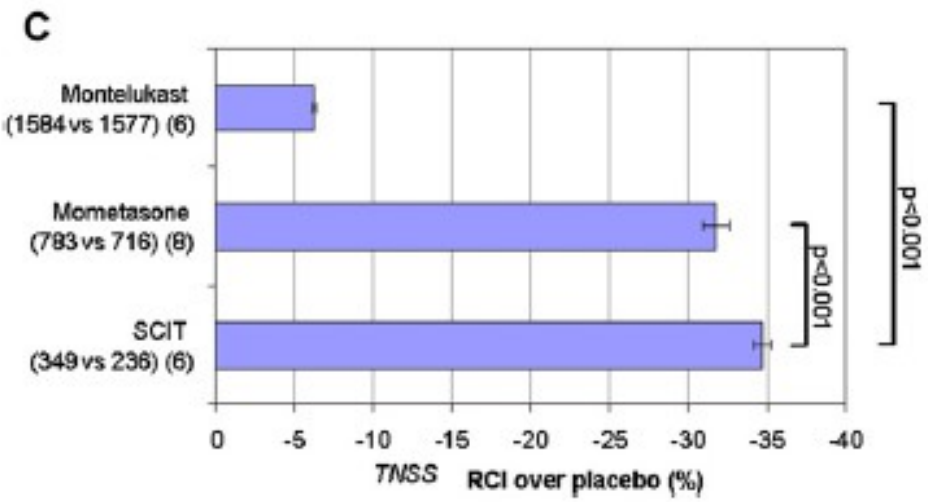
Manufacturer	Conc.	Protein (μg/ml)	Phl p 5 (μg/ml)
Allergopharma	50 000 SBE/ml	77	8.75
ALK-Abelló	10 HEP	84	4.19
Allergy Therapeutics	10 000 DU/ml	15	0.15
HAL Allergy	10 000 AU/ml	427	18.30
Stallergenes	100 RI	30	2.70

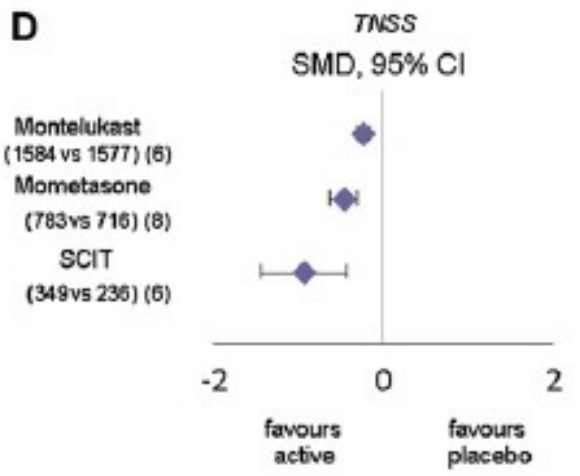
Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: A comparison based on meta-analyses

Paolo Maria Matricardi, MD,[a] Piotr Kuna, MD,[b] Valentina Panetta, MSc,[a] Ulrich Wahn, MD,[a] and Annemie Narkus, MD[c] *Berlin and Reinbeck, Germany, and Lodz, Poland*



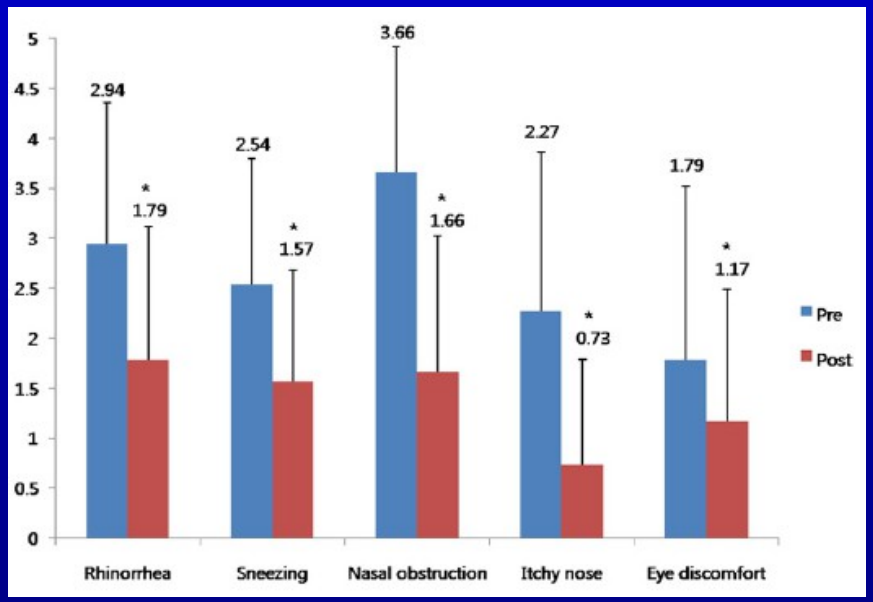


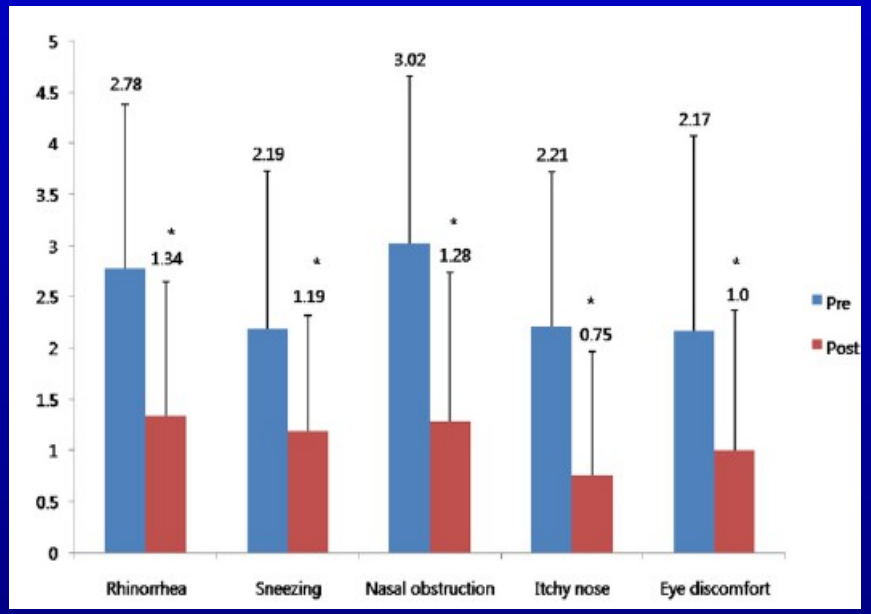




Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis

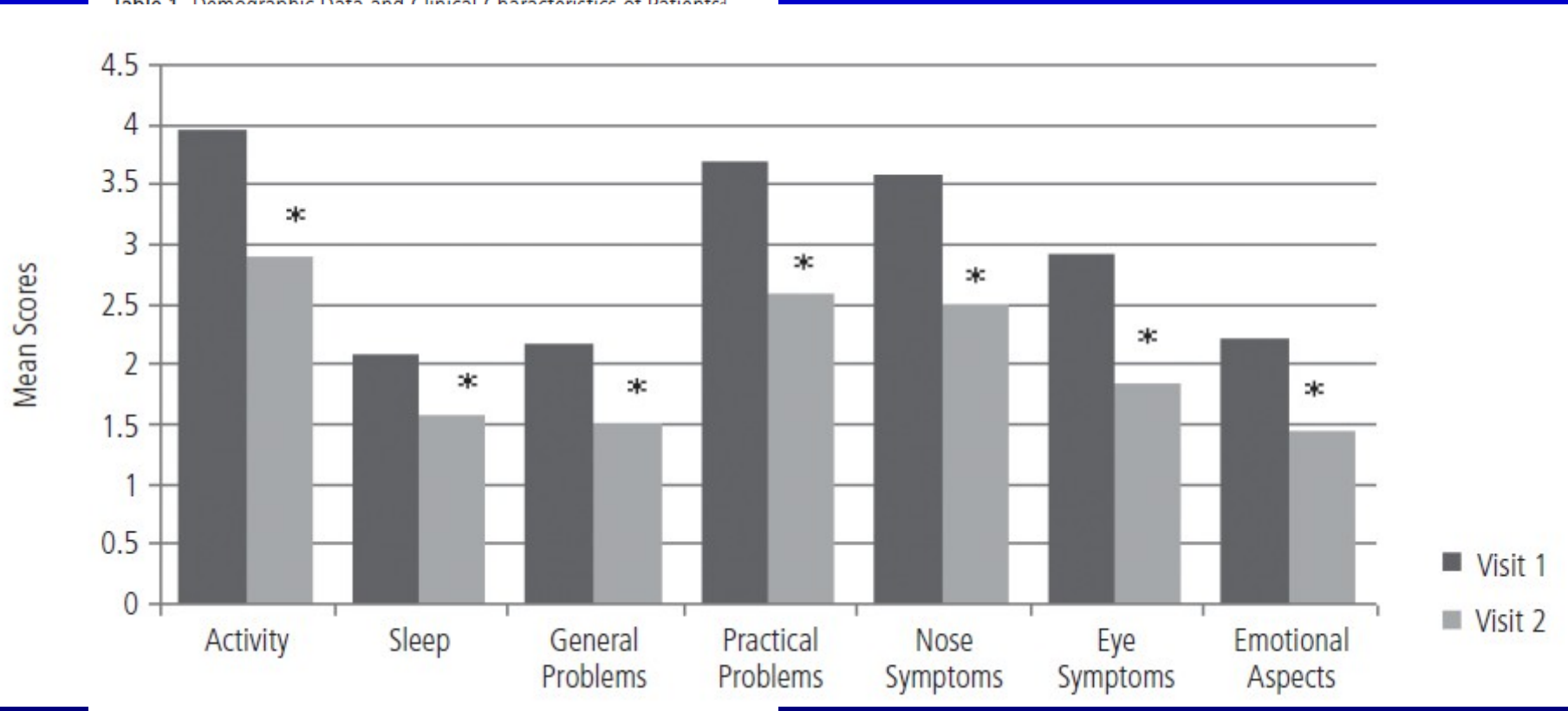
Ji-Eun Lee, MD*; Yoon-Seok Choi, MD*; Min-Su Kim, MD*; Doo Hee Han, MD*; Chae-Seo Rhee, MD*†; Chul Hee Lee, MD*†; and Dong-Young Kim, MD*†





Sublingual Immunotherapy in Polysensitized Patients: Effect on Quality of Life

G Ciprandi,[1] G Cadario,[2] C Valle,[3] E Ridolo,[4] M Verini,[5] M Di Gioacchino,[6] M Minelli,[7] S Gangemi,[8] V Sillano,[9] C Colangelo,[10] V Pravettoni,[11] R Pellegrino,[12] P Borrelli,[13] A Fiorina,[14] A Carosso,[15] A Gasparini,[16] GG Riario-Sforza,[17] C Incorvaia,[17] P Puccinelli,[18] S Scurati,[18] F Frati[18]



METHODOLOGICAL ISSUES

- HETEROGENEITY OF TRIALS

- DOSES

-PATIENTS' SELECTION

- PRIMARY OUTCOME/ANALYSIS

- SAMPLE SIZE CALCULATION

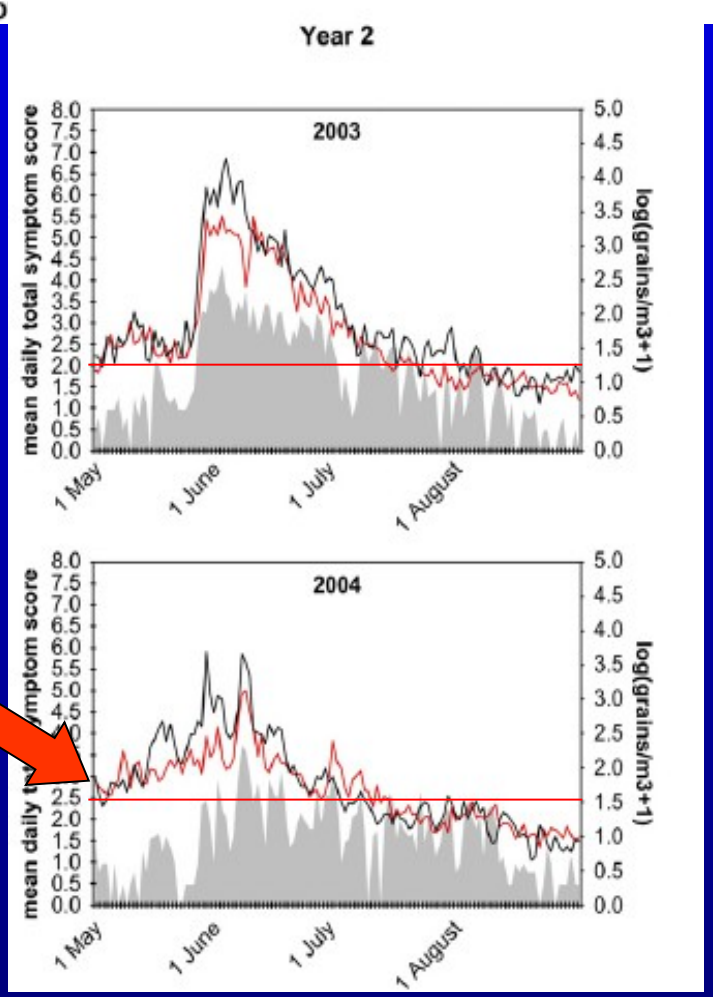
- ADHERENCE

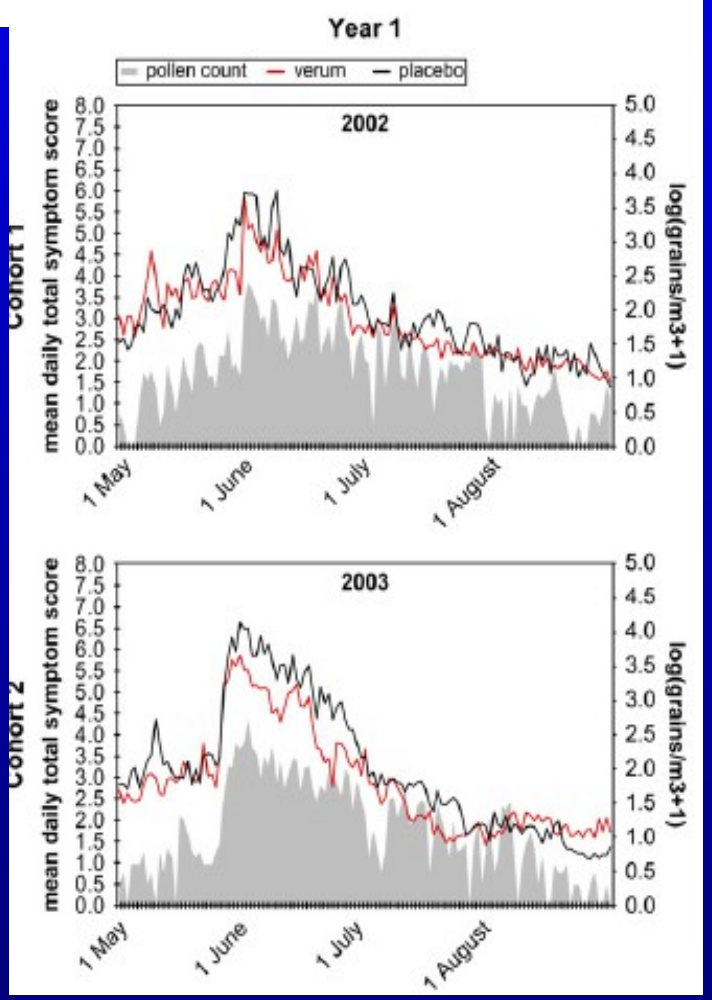
- REPORTING

Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care

Esther Röder, MD,[a,b] Marjolein Y. Berger, MD, PhD,[b] Wim C. J. Hop, PhD,[c] Roos M. D. Bernsen, PhD,[b] Hans de Groo

Patients with symptoms out of the season

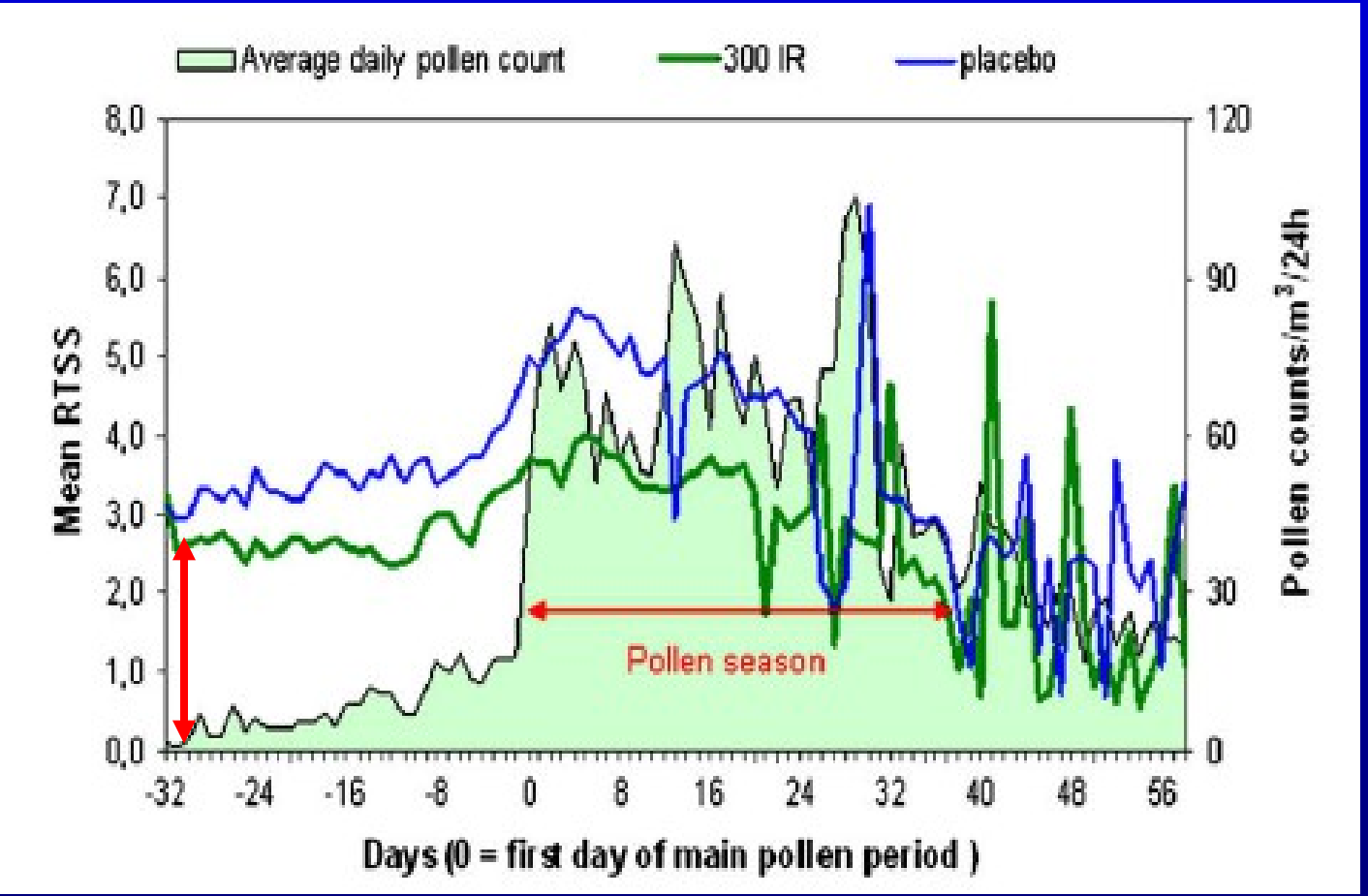


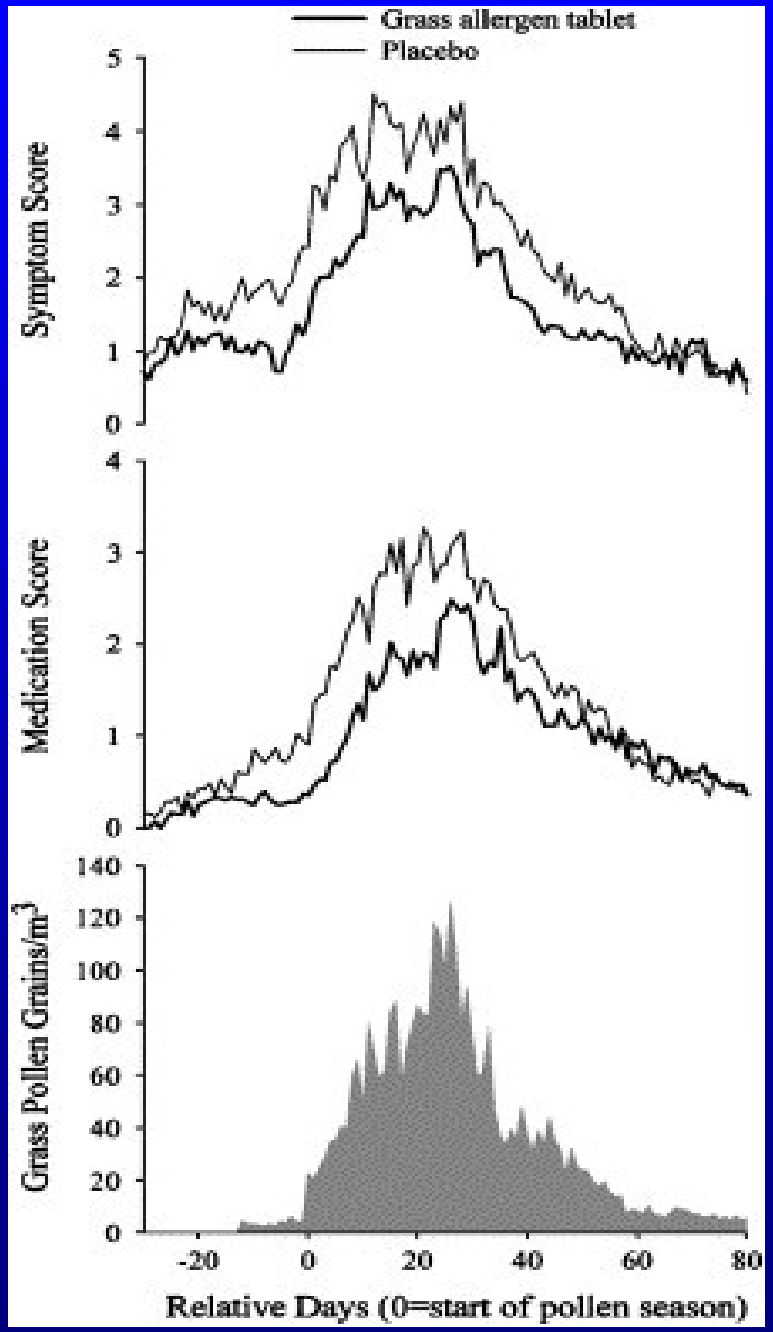


VS PLACEBO
Symptoms
-28% (-39%)
Medications
- 24% (-48%)

Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis

Wahn 2009





Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis.
Dahl et al, JACI 2006

VERSUS PLACEBO:

SYMPTOM REDUCTION
- 30%
MEDICATION REDUCTION
- 38%

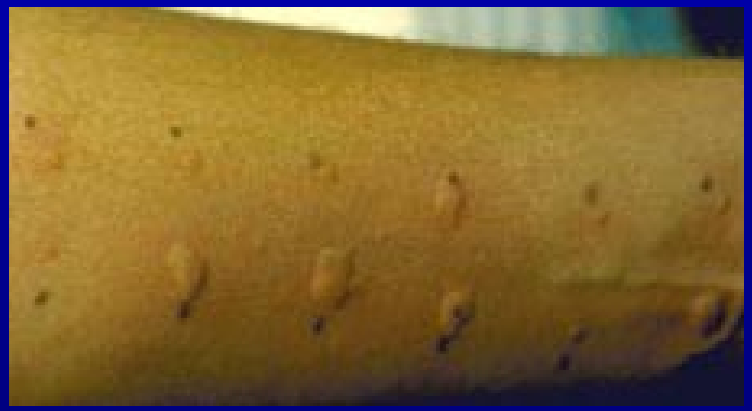
634 PATIENTS !!!

	Primary sensitization	Cross-reactivity
Pollens		
Ragweed	Amb a 1	
Mugwort	Art v 1, Art v 3	Art v 3
Parietaria	Par j 2	Par j 2
Russian thistle or saltwort	Sal k 1	
Goosefoot or Lambs quarters	Che a 1	
Plantain or Ribwort	Pla l 1	
Timothy	Phl p 1	Phl p 4
	Phl p 5	Phl p 7
	Phl p 6	Phl p 11
		Phl p 12
Bermuda grass	Cyn d 1	
Birch	Bet v 1	Bet v 1
	Bet v 6	Bet v 2
		Bet v 4
Alder	Aln g 1	Aln g 1
Oak	Que a 1	Que a 1
Olive	Ole e 1	Ole e 2
	Ole e 7	Ole e 7, Ole e 9
	Ole e 9	
Japanese cedar, Cypress	Cry j 1Z	
	Cup a 1	
Plane tree	Pla a 1	
	Pla a 2	
Latex	Hev b 1, Hev b 3, Hev b 5, Hev b 6	Hev b 5
		Hev b 6
		Hev b 8

	Primary sensitization	Cross-reactivity
House dust mite	Der p 1, Der p 2	Der p 10
pyroglyphidae	Der f 1, Der f 2	
Blomia tropicalis	Blo t 5	
Euroglyphus mannei	Eur m 2	
Lepidoglyphys destructor	Lep d 2	
Cat	Fel d 1, Fel d 4	Fel d 2
		Fel d 4
Dog	Can f 1, Can f 2,	Can f 3
	Can f 5	Can f 5
Horse	Equ c 1	Equ c 3
Alternaria alternata	Alt a 1, Alt a 6	Alt a 6
Aspergillus fumigatus	Asp f 1, Asp f 2, Asp f 3 Asp f 4, Asp f 6	Asp f 6

Sastre,
Clin Exp Allergy 2010

GRASS	BIRCH	PARIETARIA
Phl p 1	Bet v 1	Par j 1
Phl p 5		Par j 2
Phl p 6		
Phl p 7 (profilin)	Bet v 2 (profilin)	Par j 3 (profilin)
Phl p 12 (CBP)	Bet v 3 (CBP)	

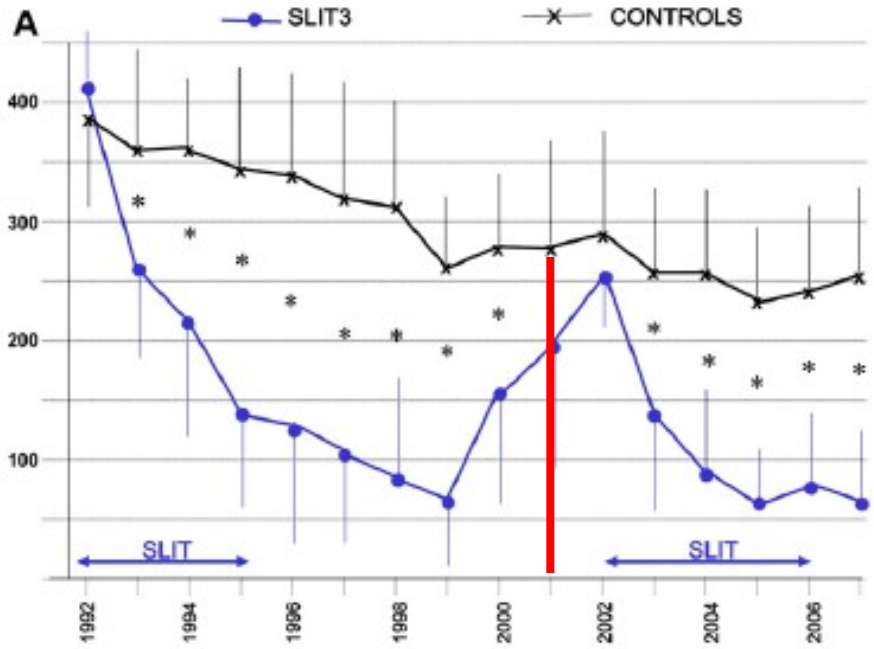


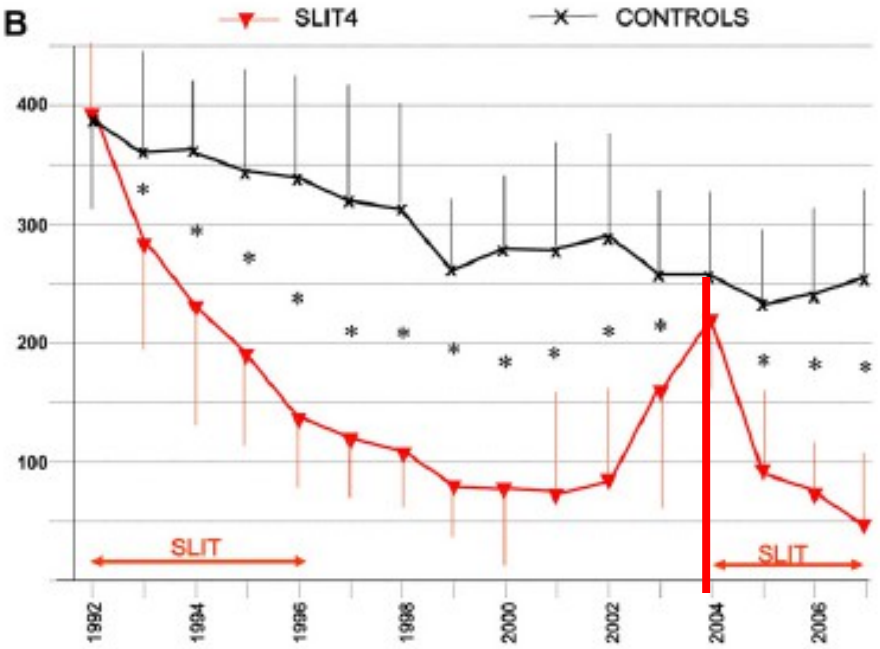
Original article

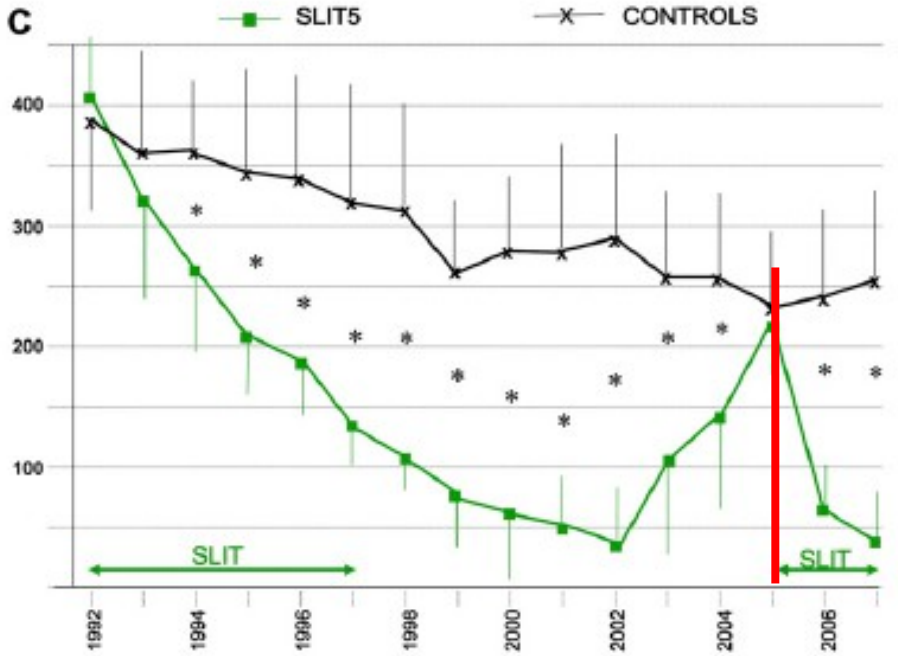
Molecular profiles of IgE to *Phleum pratense* in children with grass pollen allergy: Implications for specific immunotherapy

Salvatore Tripodi, MD,[a] Tullio Frediani, MD,[b] Sandra Lucarelli, MD,[b] Francesco Macrì, MD,[b] Giuseppe Pingitore, MD,[c] Andrea Di Rienzo Businco, MD,[a] Arianna Dondi, MD,[d] Paola Pansa, MD,[b] Giovanni Ragusa, MD,[b] Riccardo Asero, MD,[e] Diego Faggian, MSc,[f] Mario Plebani, MD,[f] and Paolo Maria Matricardi, MD[g] *Rome, Bologna, Paderno Dugnano, and Padua, Italy, and Berlin, Germany*

	Allergic rhinitis (n = 175)		Asthma (n = 103)		All (n = 200)*	
	No.	Percent	No.	Percent	No.	Percent
Age (y), mean ± SD	11.1	3.4	10.7	3.3	11.0	3.3
Male sex (no./total [%])	111	63.4	65	63.1	126	63.0
Atopic sensitization (SPT ≥3 mm)						
Phleum pratense	158	90.3	90	87.4	182	91.0
Wheal diameter 3-5 mm	44	27.8	29	32.2	20	11.0
Wheal diameter 6-10 mm	61	38.6	31	34.4	102	56.0
Wheal diameter >10 mm	70	44.3	43	47.8	60	33.0
Cynodon dactylon	126	72.0	67	65.0	141	70.5
Betula verrucosa	43	24.6	26	25.2	51	25.5
Cupressus arizonica	88	50.3	53	51.5	98	49.0
Platanus orientalis	53	30.3	33	32.0	63	31.5
Olea europaea	113	64.6	63	61.2	128	64.0
Parietaria judaica	75	42.9	44	42.7	83	41.5
Artemisia vulgaris	27	15.4	18	17.5	33	16.5
Plantago lanceolata	67	38.3	31	30.1	76	38.0
≥3 Pollens	103	58.8	59	57.3	117	58.5
Dermatophagoides pteronyssinus	87	49.7	57	55.3	100	50.0
Dermatophagoides farinae	92	52.6	62	60.2	106	53.0
Blattella germanica	20	11.4	15	14.6	26	13.0
Cat	42	24.0	27	26.2	48	24.0
Dog	48	27.4	31	30.1	58	29.0
Alternaria tenuis	57	32.6	38	36.9	63	31.5
Cladosporium herbarum	15	8.6	13	12.6	17	8.5
≥3 Indoor allergens	67	38.3	42	40.8	77	38.5


A
SLIT3
CONTROLS
400
300
200
100
SLIT
SLIT
1992
1994
1996
1998
2000
2002
2004
2006


B
SLIT4
CONTROLS
400
300
200
100
SLIT
SLIT
1992
1994
1996
1998
2000
2002
2004
2006


C
SLIT5
CONTROLS
400
300
200
100
SLIT
SLIT
1992
1994
1996
1998
2000
2002
2004
2006

Evidence of adherence to allergen-specific immunotherapy

Gianenrico Senna[a], Erminia Ridolo[b], Moises Calderon[c], Carlo Lombardi[d], Giorgio W. Canonica[e] and Giovanni Passalacqua[e]

Table 3 Studies on compliance with sublingual immunotherapy

Reference	No. of patients	Age	Compliance (%)
Marogna *et al.* [25]	319	Adults	80
Lombardi *et al.* [26]	86	Adults	75–97
Pajno *et al.* [24]	806	Children	79
Passalacqua *et al.* [27]	443	Adults/adolescents	76
Passalacqua *et al.* [28]	71	Children	85
Roder *et al.* [29••]	154	Adolescents	77

Current Opinion in Allergy and Clinical Immunology 2009, 9:544–548

How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint

To the Editor:

Adherence to prescriptions is crucial for all long-term treatments,[1] and this is true also for sublingual immunotherapy (SLIT), which is self-managed at home by the patients themselves. In fact, in the case of SLIT, medical supervision is usually limited to control visits or to prescription renewals. Available postmarketing studies indicate that the compliance with SLIT ranges from 50% to 95%, depending on age and on duration of treatment.[2] Nonetheless, the postmarketing surveys on compliance have an inherent limitation in that the observation itself can distort the results to some extent. In other words, when patients are aware that their compliance with treatment is recorded, they tend to be more adherent. Moreover, those studies assessed the adherence over limited periods, whereas SLIT should be continued for at least 3 years, according to recommendations. In everyday clinical practice, the general perception is that a large proportion of patients discontinues the prescribed SLIT, and this usually happens within the first year.

To address this latter aspect better, and to quantify the rate of discontinuations in real life, we collected the Italian sales figures from 2 large manufacturers (Stallergenes Italy, Milan, and ALK-Abelló Italy, Lainate, Milan), who kindly provided their data subdivided as per the 20 Italian administrative regions. It is to be noted that these manufactures account for more than 60% of the Italian immunotherapy market. To assess the discontinuation rates

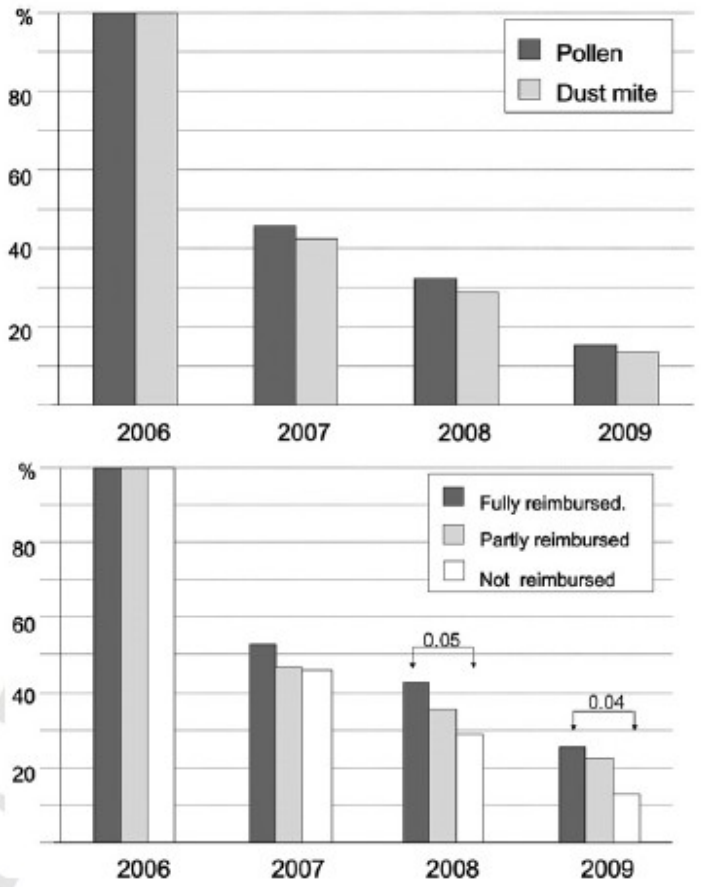


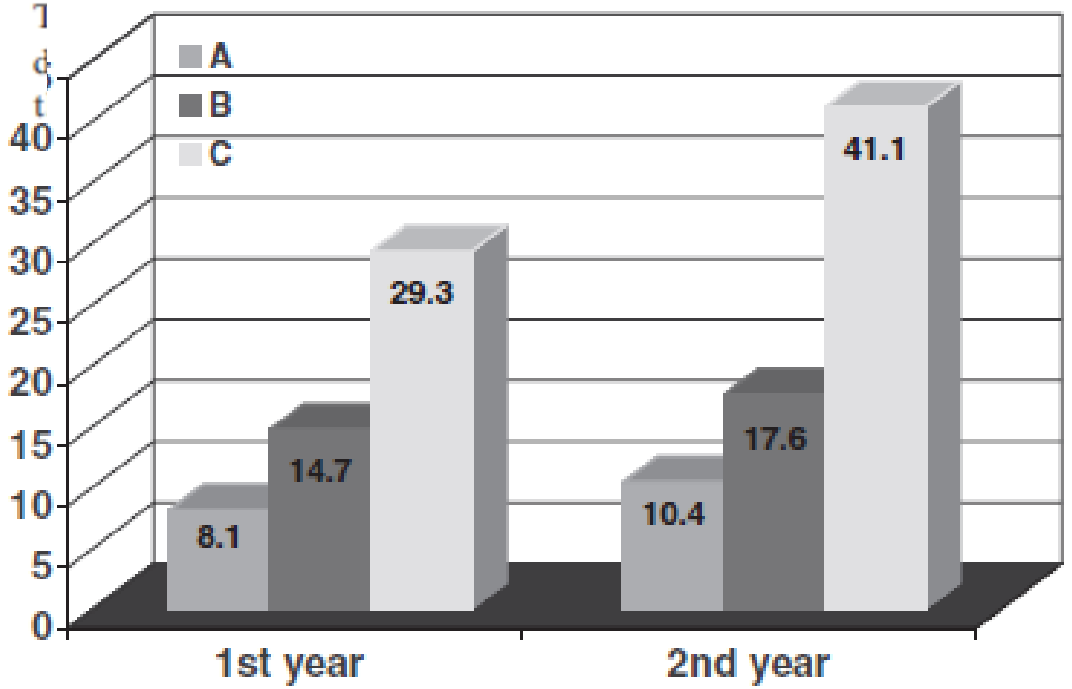
FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. *Upper panel,* Percentages for pollens and house dust mite SLITs. *Lower panel,* Percentages according to the reimbursement modality.

Senna GE, Lomabrdi C, Passalacqua G. JACI 2010

ALLERGY Net

Sublingual immunotherapy: adherence based on timing and monitoring control visits

D. Vita, L. Caminiti, P. Ruggeri, G. B. Pajno*



Original article

The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: A Global Allergy and Asthma European Network (GA^{2}LEN) article

Philippe J. Bousquet, MD, PhD,[a*] Moises A. Calderon, MD, PhD,[b*] Pascal Demoly, MD, PhD,[a,c*] Désirée Larenas, MD,[d] Giovanni Passalacqua, MD,[e*] Claus Bachert, MD, PhD,[f*] Jan Brozek, MD, PhD,[g*] G. Walter Canonica, MD,[e*] Thomas Casale, MD,[h] Joao Fonseca, MD, PhD,[i*] Ronald Dahl, MD, DrMedSci,[j*] Stephen R. Durham, MD,[b*] Hans Merk, MD,[k*] Margitta Worm, MD,[l*] Ulrich Wahn, MD,[m*] Torsten Zuberbier, MD, PhD,[l*] Holger J. Schünemann, MD, PhD, MSc,[g*] and Jean Bousquet, MD, PhD[a,n*] *Montpellier and Villejuif, France, London, United*

SCIT: 46 trials

CONSORT: 1 trial
Flowchart: 16 trials
Dropouts: 12 trials
Randomization: 16 trials

SLIT: 48 trials

CONSORT: 3 trial
Flowchart: 20 trials
Dropouts: 16 trials
Randomization: 12 trials

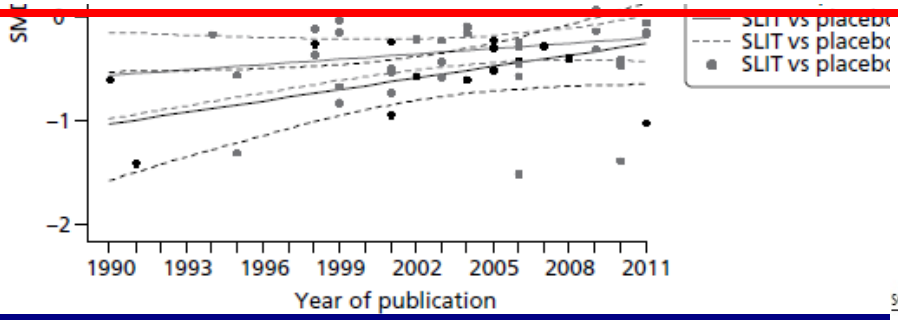
HEALTH TECHNOLOGY ASSESSMENT

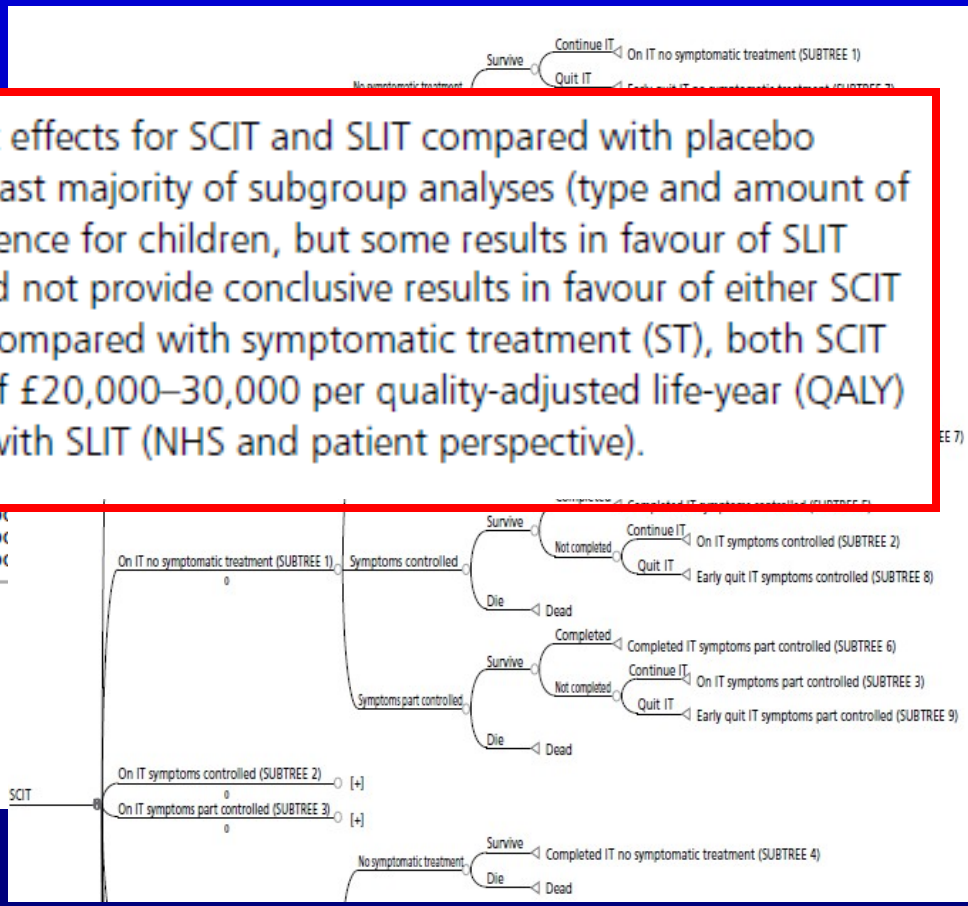
VOLUME 17 ISSUE 27 JULY 2013
ISSN 1366-5278

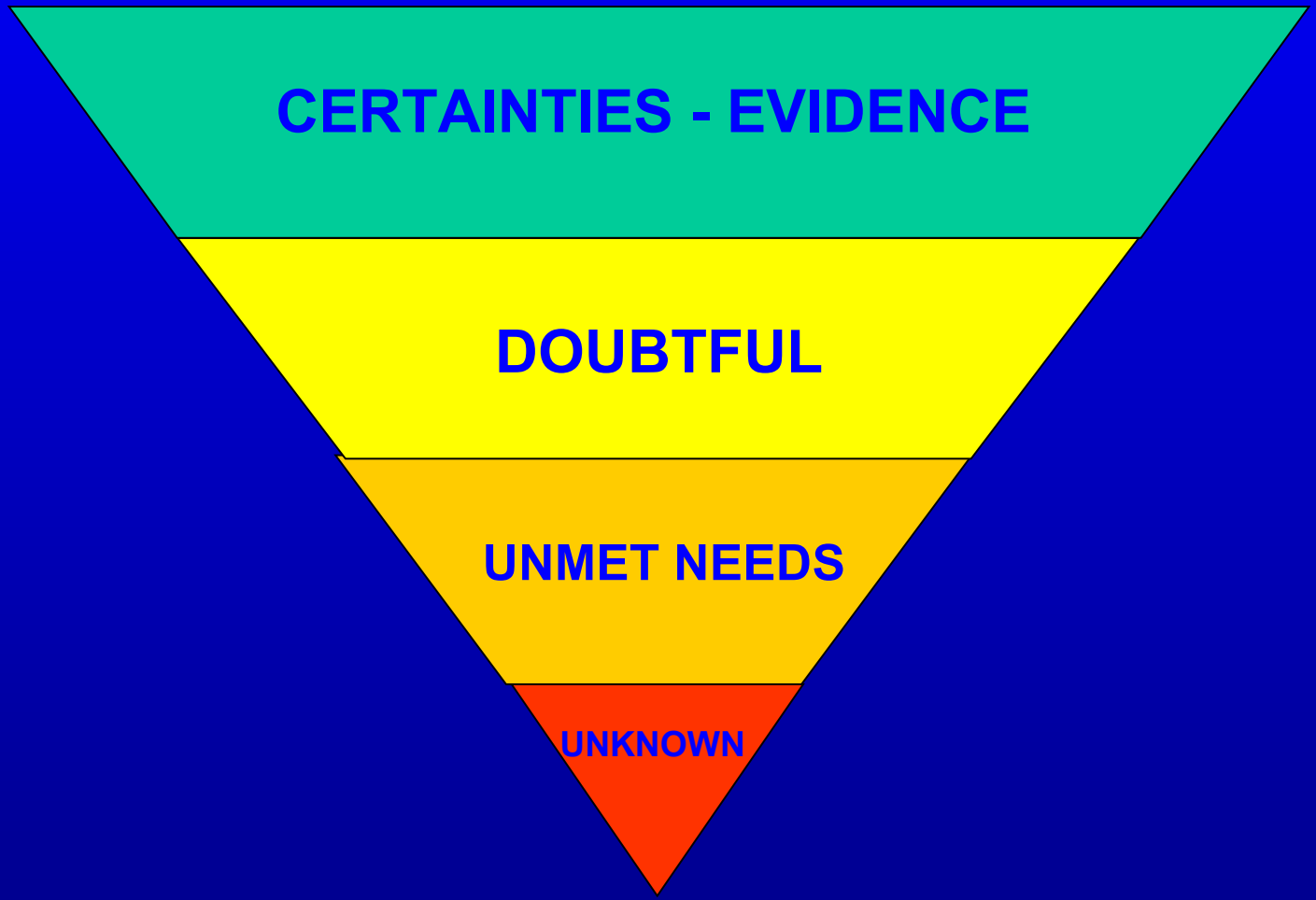
A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis

A Meadows, B Kaambwa, N Novielli, A Huissoon, A Fry-Smith, C Meads, P Barton and J Dretzke

Results: Meta-analyses found statistically significant effects for SCIT and SLIT compared with placebo across a number of outcome measures and for the vast majority of subgroup analyses (type and amount of allergen, duration of treatment). There was less evidence for children, but some results in favour of SLIT were statistically significant. Indirect comparisons did not provide conclusive results in favour of either SCIT or SLIT. Economic modelling suggested that, when compared with symptomatic treatment (ST), both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per quality-adjusted life-year (QALY) from around 6 years, or 5 years for SCIT compared with SLIT (NHS and patient perspective).






CERTAINTIES - EVIDENCE
DOUBTFUL
UNMET NEEDS
UNKNOWN

BIOMARKERS

FOR RESPONDER (NON RESPONDER) ?

Recommendations for appropriate sublingual immunotherapy clinical trials

Thomas B. Casale, MD,[a] G. Walter Canonica, MD,[b] Jean Bousquet, MD,[c] Linda Cox, MD,[d] Richard Lockey, MD,[e] Harold S. Nelson, MD,[f] and Giovanni Passalacqua, MD[b] *Omaha, Neb, Genoa, Italy, Montpellier, France, Davie and Tampa, Fla, and Denver, Colo*

TABLE III. Points to consider for randomized controlled trials in SLIT

Allergen vaccine	
Composition	Single allergen or mixtures
If mixture	Compatible allergens in liquid form with proven stability
Standardization	Defined based on major allergen content
Updosing regimen	Not required
Dose	~5 μg major allergen/d recommended
Patient selection	
Assess all sensitizations (monosensitization or polysensitization)	Panel of allergens using skin prick tests
Prove concordance of sensitization and symptoms because not all sensitizations are clinically relevant	Skin prick tests and serum-specific IgE Optional: allergen challenge
Assess severity of symptoms before SLIT	● Historical: moderate to severe symptoms with exposure in previous year ● Run-in (difficult to do for seasonal allergens) with low pretreatment symptoms
Report comorbidities	May be used in the analysis
Exclude patients who received SIT within 5 y	
Study design	
● Randomized ● Double-blind ● Placebo-controlled: appropriate predefined minimal symptom increase during pollen season	

JACI, Oct 09

Rescue medication	● Standardized list ● Weighted medication score
Primary outcome	● Total symptom score ● Combined symptom-medication score (preferred) ● For asthma: coprimary, FEV_1 or peak expiratory flow
Secondary outcomes	● Rescue medications ● Individual symptoms ● Visual analog scale ● QOL ● Asthma control ● Symptom-free days ● Physician and patient rated clinical global improvement

Pediatric Allergy and Immunology

REVIEW ARTICLE

Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement

M. A. Calderon[1], R. Gerth van Wijk[2], I. Eichler[3], P. M. Matricardi[4], E. M. Varga[5], M. V. Kopp[6], P. Eng[7], B. Niggemann[8], A. Nieto[9], E. Valovirta[10], P. A. Eigenmann[11], G. Pajno[12], A. Bufe[13], S. Halken[14], K. Beyer[4] & U. Wahn[4]

[1]Department of Allergy and Respiratory Medicine, Royal Brompton Hospital, Imperial Erasmus MC-University Medical Center, Rotterdam, The Netherlands; [3]European Me Pneumology and Immunology, Charité Medical University, Berlin, Germany; [5]Departn Division, Medical University Graz, Graz, Austria; [6]Department of Allergology and Pne Germany; [7]Allergy Unit, Children's Hospital, Kantonsspital Aarau, Switzerland; [9]Depa Cross Hospital Westend, Berlin, Germany; [9]Pediatric Allergy and Pneumology Unit, C Clinic, Suomen Terveystalo AllergyClinic, Turku, Finland; [11]Division of Immunology an of Geneva, Geneva, Switzerland; [12]Department of Pediatrics, Allergy Unit, University Experimental Pneumology, Ruhr-University Bochum, Bochum, Germany; [14]Hans Chri Hospital, Odense, Denmark

To cite this article: Calderon MA, Gerth van Wijk R, Eichler I, Matricardi PM, Varga EM, Kopp Pajno G, Bufe A, Halken S, Beyer K, Wahn U. Perspectives on allergen-specific immunothera Immunol 2012; 23: 309–306

Unmet needs of allergen-specific immunotherapy in children

- Optimal dose and dosing frequency of administration
- Frequency of side effects and safety
- Efficacy and safety in patients unresponsive to pharmacotherapy
- For SLIT: Drops vs. tablets
- Duration of treatment
- Long-term efficacy and safety
- Preventive capacity (asthma, new sensitizations)
- Identification of immunological biomarkers
- Definition of duration of disease before starting treatment (minimal age)
- Development of generally accepted primary outcome measures (i.e. symptom medication scores)
- Studies targeting children with moderate asthma
- Evaluating the effectiveness of allergen-specific immunotherapy in real life in allergic rhinitics with concomitant asthma, especially in terms of a steroid-sparing effect.
- Cost-effectiveness studies and pharmaco-economic aspects
- Developing strategies to enhance adherence

THANK YOU !

Contact us at
canonica@unige.it
passalacqua@unige.it

WAO, Chicago, Dec 2013