SUBLINGUAL IMMUNOTHERAPY PRESENT AND FUTURE

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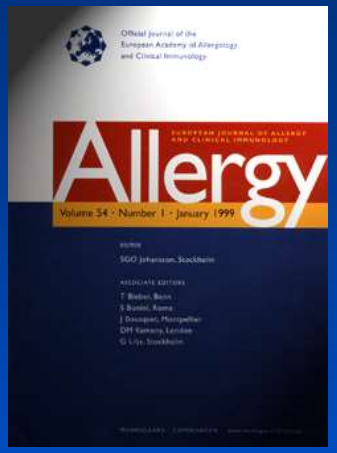
MOSCOW, FEBRUARY 19th 2015

WHO Pos Pap. Therapeutical vaccines for allergic diseases
Allergy 1998

Standards for practical allergen-specific immunotherapy.
Allergy 2006



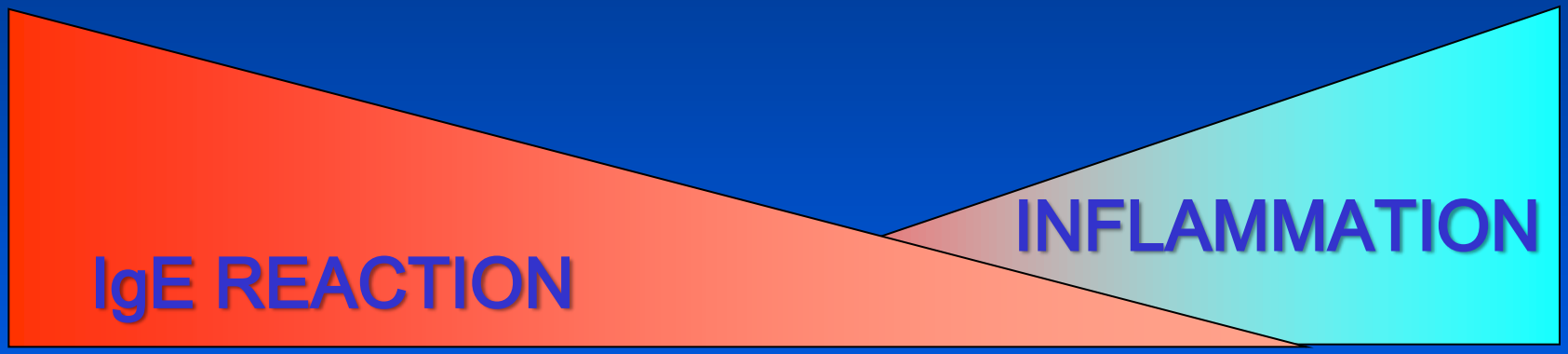
Allergen immunotherapy: A practice parameter third update
JACI 2011

WORLD ALLERGY ORGANIZATION

WORLD ALLERGY ORGANIZATION
A World Federation of Allergy, Asthma & Clinical Immunology Societies

Sublingual immunotherapy: WAO UPDATE 2013

Where does IT preferentially works?



Hymenoptera Allergy

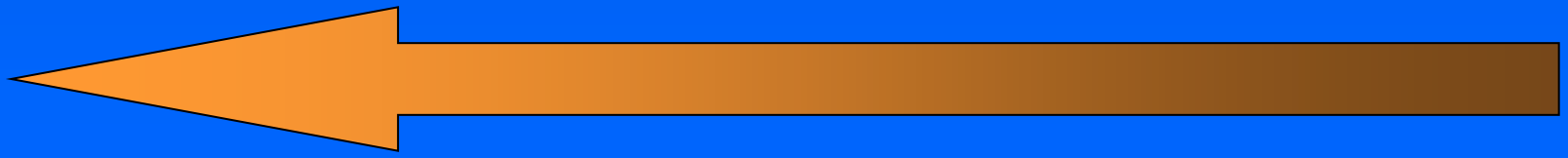
Food Allergy

Seasonal rhinitis

Perennial rhinitis

Atopic dermatitis

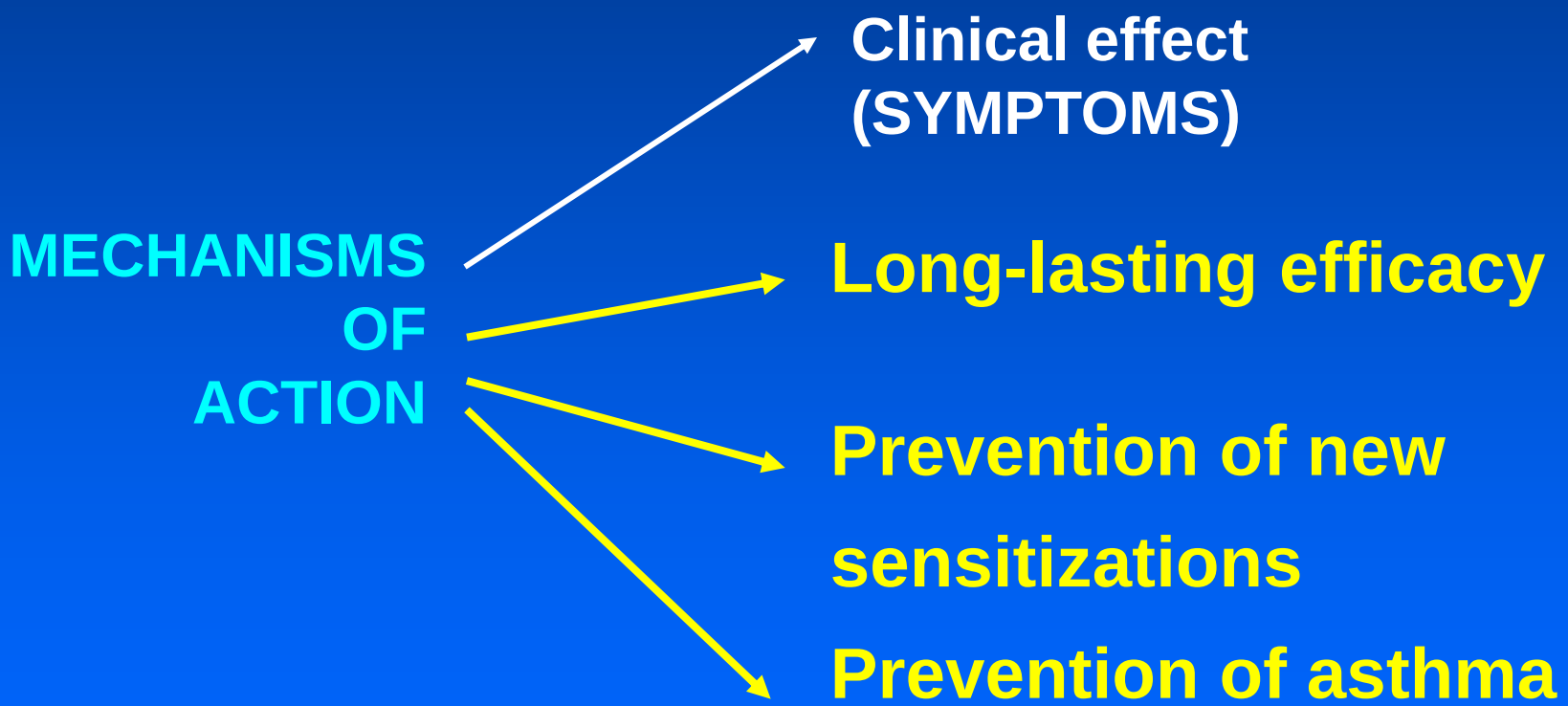
Asthma



Mechanisms of immunotherapy to aeroallergens

M. H. Shamji and S. R. Durham

Specific immunotherapy



SIT: carry-over EFFECT

Author, yr (ref)	Allergen	Patients enrolled	Sit	Design of original trial	Duration Sit	Patients reevaluated	Outcomes at follow-up	Main results at follow-up
Mosbech, 1988 (26)	Grass	39	SCIT	R-DB-C with 2 active arms. Open FU 6 yrs	2.5 yrs	32	Symptoms and drug intake in pollen season	The clinical benefit of SCIT was maintained at 6 yrs in both groups
Grammer, 1984 (28)	Ragweed	63	SCIT	R-DB-PC, 2 arms + untreated group Open FU 2 yrs	4 mo	63	Symptoms and drug intake in pollen season	Patients receiving placebo in the 2nd season maintained a clinical benefit similar to those receiving SCIT. Both groups better than untreated
Hedlin, 1995 (27)	Cat/dog	32	SCIT	Open, prospective Open FU 5 yrs	3 yrs	30	Specific and nonspecific bronchial challenge; subjective evaluation	Persisting clinical benefit reported 5 yrs after stopping SCIT. Bronchial responsiveness returned almost to baseline values.
Des Roches, 1996 (29)	Mite	40	SCIT	Prospective controlled Open FU 3 yrs	1–8 yrs	40	Appearance of asthma symptoms	Most subjects remained asymptomatic after 3 yrs. The long-lasting effect is related to the duration of SCIT
Durham 1999 (30)	Grass	40	SCIT	R-DB-C 3 or 4 yrs SCIT. One group continued for 3 years more	3–4 yrs	32	Symptoms and medication scores	After 3 years, symptoms and medication scores remained low in the group who discontinued and in the group who continued to receive maintenance SCIT
Di Rienzo 2006 (34)	Mite	60	SLIT	Open, non R, control led. Open FU 5 yrs	5 yrs	60	Clinical evaluation of asthma symptoms	The effect of SLIT on asthma symptoms persisted up to 5 yrs after stopping.
Eng 2002 (31)	Grass	28	SCIT	R-DB-PC Open FU 6 yrs	3 yrs	23	Symptom + drug score, individual symptoms, drug intake.	6 Years after discontinuation, the total score remained lower in the formerly SCIT group. No difference in drug intake between groups.
Taharmiler 2007 (35)	Mite	137	SLIT	R-DB-C 2 or 3 years SLIT. Open FU 3 yrs	2-3 yrs	137	Symptom + drug score, individual symptoms, nasal resistance	3 Years after discontinuation both groups maintained improvement in all parameters versus baseline, with better improvement in the 3-year SLIT group.
Durham 2010 (36)	Grass	308	SLIT	R-DB-PC. Open FU 1 yr	3 yrs	257	Rhinoconjunctivitis score; drug intake	1 Year after discontinuation, the difference remained in favour of the former SLIT group
Marogna 2010 (37)	Mite	78	SLIT	Open, controlled, non R. Open FU up to 15 yrs	3 yrs 4 yrs 5 yrs	59	Symptoms, drug intake, nasal eosinophils, bronchial challenge	The 3 groups receiving SLIT improved significantly vs controls. Clinical benefit maintained for 7 years in groups treated for 4 or 5 years and for 5 years in group treated for 3 years
Musarra 2010 (33)	parietaria	57	SCIT	Open, controlled, nonrandomized. Open FU 5 yrs	3 yrs	57	Visual analog scale for symptoms. Severity of asthma/rhinitis	The clinical improvement persisted for 5 years after stopping SIT in the active group, according to VAS and severity of asthma/rhinitis

Abbreviations: R, randomised; DB, double blind; PC, placebo controlled; FU, follow-up.

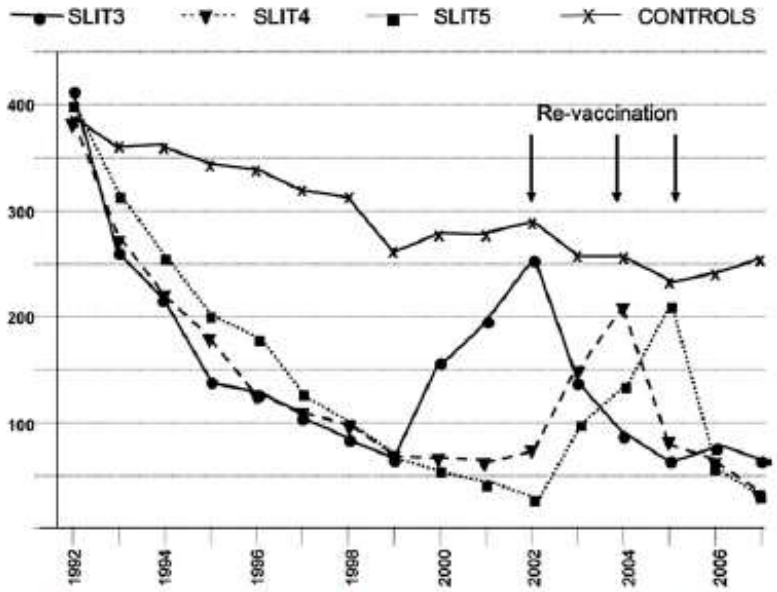


Figure 2. Symptom + medication scores year by year in 4 groups receiving mite SLIT for 3, 4, or 5 years or medications only. The arrows indicate the start of the new course of SLIT when the clinical benefit had vanished (from Marogna et al[37]).

Passalacqua G. Ann Allergy Asthma Immunol. 2011;107:401– 406.

Specific immunotherapy: beyond the clinical scores

Giovanni Passalacqua, MD*

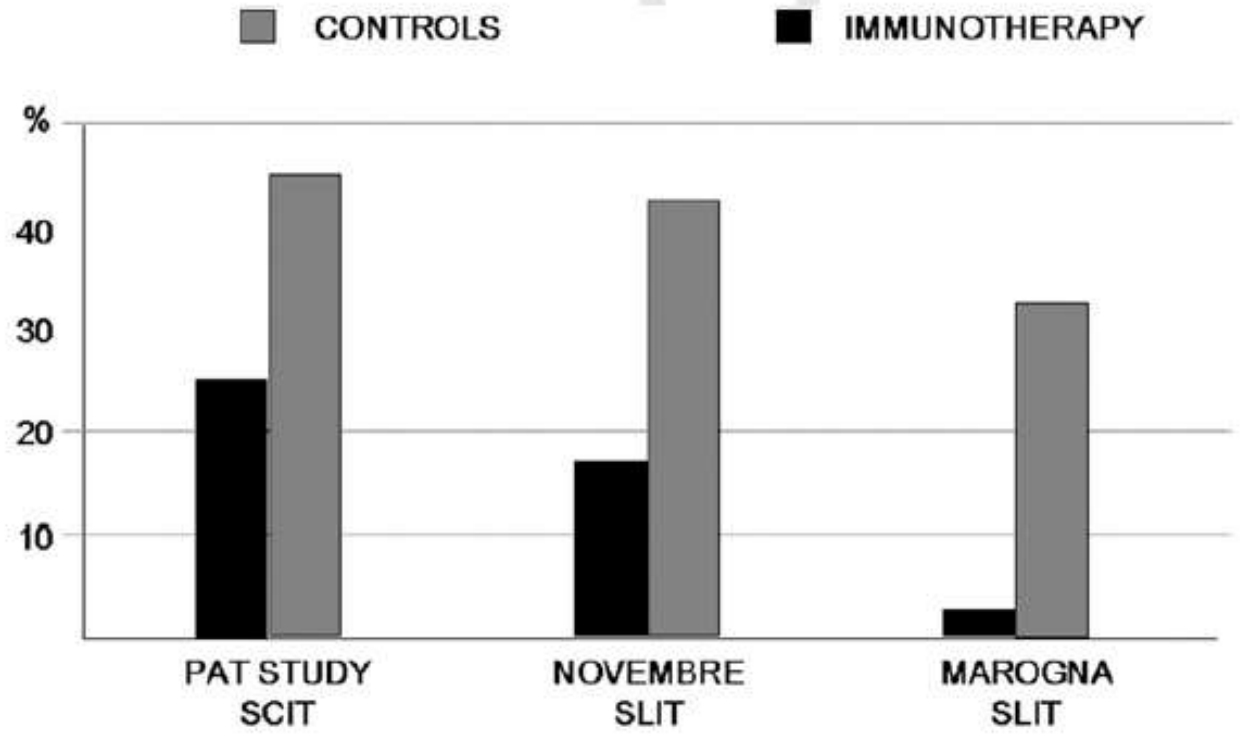


Figure 1. Percentage of children in the immunotherapy and control groups who developed asthma after 3 years, in the 3 available trials. In the study by Marogna et al,[37] the development of persistent asthma was assessed.

AAAI 2011

1986
Scalding et al.
1st DBPC trial

1997
Tari et al.
1st pediatric trial

Bagnasco et al
Absorption and kinetics of radiolabelled allergen

1998
Passalacqua et al.
1st study with tablets

1998
Lombardi et al., DiRienzo et al.
Postmarketing studies on SLIT safety in adults and children

1998
WHO accepts SLIT for adults

World Health Organization

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

2004
Wilson et al.
1° METANALYSIS

2004
Novembre et al.
Preventative effect

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

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

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

2006
Cox et al.
1° USA review

American Academy of Allergy Asthma & Immunology

2006-2009 Large EU RCT SLIT grass tablets and EU Registration

lacebo-controlled trials of SLIT performed since 2009

Age	Pts	t	Allergen	Duration	Dose and Administration	Disease	Manu-facturer	Main positive results	Negative results
Horak, 2009	18-50	45/44	3/4	Grass	4 mo	20 mcg Phl p 5/day Tablets	RC	STA	Significant reduction in RC score in Vienna challenge chamber at 4 mo in SLIT vs baseline and vs placebo. Reduction 29% vs placebo Increased 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 mo	4.8 or 48 mcg Amb a 1/day Metered pump	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 mo	60 mcg Alt a 1 cumul. 6 mcg/mo Drops	RCA	ANA	Significant reduction in combined score (–38% VS placebo). Significant 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	RC	ALK	Increase in IgE, IgG4, and IgE blocking activity only in active	
Yonekura, 2010	7-15	20/11	1/2	Mite	1 y	0.5 mcg Der f 1 once a week	RC	TOR	Significant decrease in symptoms and combined score in wk 0–3 and 37–40 only in SLIT	Medication score
Blaiss, 2011	5-17	349/358	33/30	Grass	6 mo	450 g Phl p 5/mo	RC	STA	Significant reduction in combined score (–26%) VS placebo. Quality of Life 38% improvement vs placebo	Asthma symptoms
Nelson, 2011	18-63	213/225	33/33	Grass	10 mo	450 mcg Phl p 5/mo Tablets	RCA	STA	Significant reduction in combined score (–20%and medication score (–20%) vs placebo	Daily medication score
Bush, 2011	18-50	High 10 Low 10 Pla 11	2 3 5	Mite (Der f)	18 mo	70 or 1 mcg Der f 1 per dose. Drops	RA	GRE	Signif.reduction in specific bronchial reactivity Increase in IgG4	Symptoms and medication scores
Stelmach, 2012	6-18	Cont 20 Prec 20 Pla 20	3 1 2	Grass	2 y	Cumulative 7.3 and 3.6 mcg Phl p 5. Drops	RCA	ALK	Significant improvement in drugs +symptoms with both continuous and precoseasonal regimen. Reduction in FeNO	Symptom score Medication score Pulmonary function

	Age	Pts								
				Mite	2 y	4.06 mcg Der p 1/week Drops	RC	ART		Symptom score, QoL Medication score, Well days
Ahmadiasfshar 2012	5-18	12/12	2/2	Grass	6 mo	Cumulative: about 6,000 IR Spray	RC	STA	Significant improvement in symptom and medication scores; reduction of skin wheal diameter	
Wahn, 2012	4-12	158/49	26/2	Grass	8 mo	Cumulative: 7.2 – 8.4 mg group 5 Drops	RC	ALL	Significant reduction VS placebo in combined symptom/medication and individual scores	
Cox, 2012	18-65	233/240	26/17	Grass	6 mo	Cumulative: approx 3.6 mg group 5 allergen. Tablets	RC	STA	Significant reduction of combined symptom + medication score (-28% VS placebo) and overall quality of life	Itchy nose symptom score VS placebo
Bozek, 2013]	60-75	51/57	7/9	Mite	3 y	NS	RC	STA	Total nasal scores decreased by 44% VS baseline in SLIT and by 6% in placebo. Medication score decreased vs baseline 35% in SLIT group.	Symptoms after specific nasal provocation VS placebo
Wang, 2013	4-65	60/60	12/23	Mite	6 mo	NS	RC	ZHE	Significant decrease in each individual rhinitis symptom VS placebo starting from week 14.	No change VS placebo in medication intake
Nolte 2013	19-50	High 187 Low 188 Pla 190	142 overall	Ragweed	1 y	6 or 12 mcg Amb A 1 Daily tablet	RCA	MSD	Significant decrease in combined symptom +medication score for both active groups vs placebo (27% and 21%)	
Creticos, 2013	18-50	Low 197 Med 195 High 194 Pla 198	40/ 43/ 57/ 38	Ragweed	1 y	Cumulative dose 4.38 mg Amb a 1 Tablets	RCA	MSD	Only the high dose decreased daily symptom-medication- and combimed-score during peak pollen season and whole season VS placebo.	Low dose overalll less effective than the 2 other doses on symptoms/medications in peak pollen and whole season
Aydogan 2013	5-10	10/18	2 active	Mite	1 y	Cumulative dose 11.7 mcg Der p 1, 28 mcg Der f	RC	STA	Significant decrease in wheal skin test to mite only in the active group vs	No change in symptoms, medications and

		High 150 PLA 163	High 34 PLA 17	Mite	1 y + 1 follow-up	Cumulative : High Der p 1 11 mg ; Low Der p 1 5.8 mg. Tablet	RC	STA	Adjusted symptom-medication score decreased in both active groups vs placebo (17 and 20%). Decrease in wheal diameter	No significant change in IgE, but sigmificant increase in IgG4 in active.
Creticos 2014	18-55	ACT 218 PLA 211	Act 27 Pla 21	Ragweed	3 m	Not specified	RCA	GRE	Significant reduction in combined score versus placebo (43%). Increase in IgG4	
Maloney 2014	5-65			Grass	5 m	Not specified	RCA	ALK	Reduction in symptom score 29% peak season, 21% entire season	

Abbreviations: A/P= active/placebo; NS= not stated; RC=rhinoconjunctivitis; RCA= rhinoconjuntivitis/asthma: STA= Stallergenes; GRE= Greer, ANA= Anallergo, ALL= Allergopharma; ALK=ALK-Abellò; MSD= Merck Sharp and Dome; TOR=Torii Pharmaceuticals ;.ZHE= Zheng Wolwo Bio Pharm;.

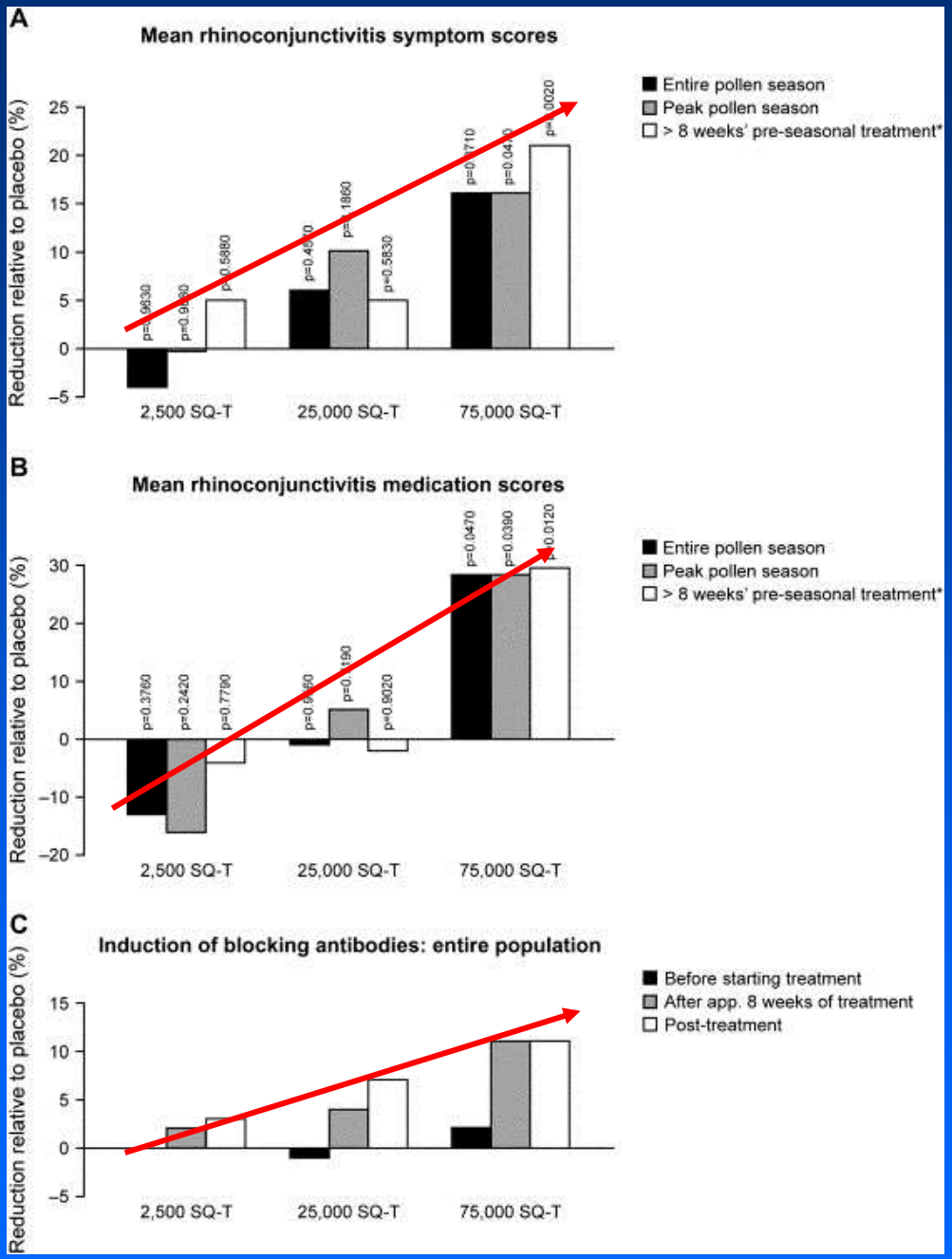
1st WAO pos pap (2009): 60 trials
2nd WAO pos pap (2013): 77 trials
After 2013: 82 trials

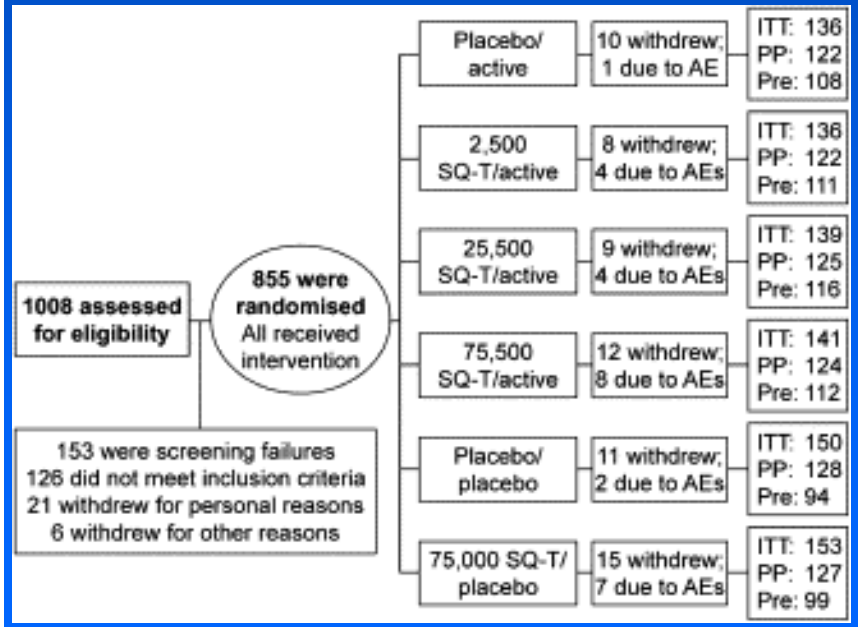
9/22 big trials conducted in the USA

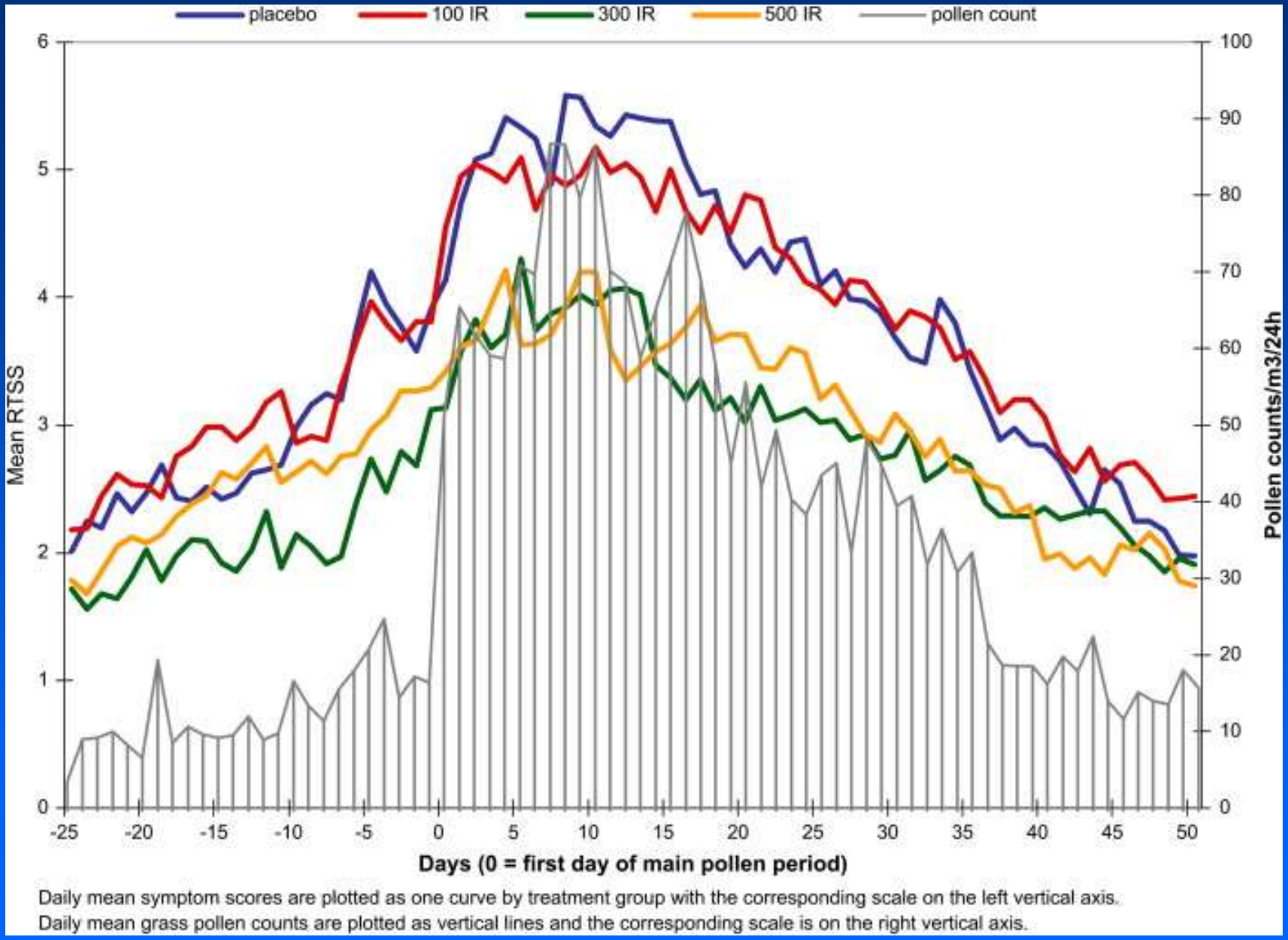
IMPROVEMENT VS PLACEBO IN THE SLIT BIG TRIALS

AUTHOR	PTS	ALLER	SYMPT	DRUGS
Frew 2005	350	Grass	-29%	-32%
Dahl 2006	634	Grass	-30%	-38%
Durham 2006	855	Grass	-21%	-28%
Didier 2007	628	Grass	-28%	-32%
Ott 2008	211	Grass	-33%	
Wahn 2009	278	Grass	-28%	-24%
Bufe 2009	253	Grass	-24%	-34%
Blaiss 2011	707	Grass	-26 %	
Nelson 2011	438	Grass	-20%	-20%
Wahn 2012	207	Grass	-24%	-26%
Cox 2012	273	Grass	-28%	
Nolte 2013	565	Mite	-27%	
Creticos 2013	784	Ragweed	-22%	-18%
Bergmann 2014	509	Mite	-21%	
Creticos 2014	429	Ragweed	-40%	

Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis Durham SR, JACI 2006







Daily mean symptom scores are plotted as one curve by treatment group with the corresponding scale on the left vertical axis.
Daily mean grass pollen counts are plotted as vertical lines and the corresponding scale is on the right vertical axis.

TABLE I. Baseline characteristics (FAS_{Year1})

	Placebo (n = 163)	300IR (n = 153)	500IR (n = 150)
Age (y)	30.0 (8.96)	29.0 (8.52)	30.1 (8.43)
Female sex, no. (%)	80 (49.1)	85 (55.6)	77 (51.3)
Duration of AR (y)	10.5 (8.49)	10.1 (8.62)	10.6 (8.57)
FEV_1 (% predicted)	99.3 (13.04)	100.3 (11.01)	97.9 (13.44)
ARTSS*	6.79 (1.456)	6.94 (1.491)	7.26 (1.655)
Asthma	47 (28.8%)	49 (32.0%)	43 (28.7%)
Polysensitization†	88 (54.0%)	74 (48.4%)	82 (54.7%)

Results describing continuous variables are expressed as means (SDs). Results describing categorical variables are expressed as the number of participants and percentage relative to the number of participants in the FAS with nonmissing data.
*ARTSS at baseline based on a 7-day daily record of the 4 rhinitis symptoms; no rescue medications were allowed.
†Sensitized to HDM allergen(s) and at least 1 other allergen tested.

TABLE II. AAdSS during the year 1 primary period (FAS_{Year1})

Treatment	No.*	LS mean (SE)
Placebo	153	3.87 (0.217)
300IR	141	3.18 (0.224)
500IR	136	3.09 (0.230)

	Difference in LS means			
Comparison	Point estimate	95% CI	*P* value	Relative difference (%)
500IR vs placebo	−0.78	−1.34 to −0.22	.0066	−20.2
300IR vs placebo	−0.69	−1.25 to −0.14	.0150	−17.9
500IR vs 300IR	−0.09	−0.66 to 0.49	.7638	—

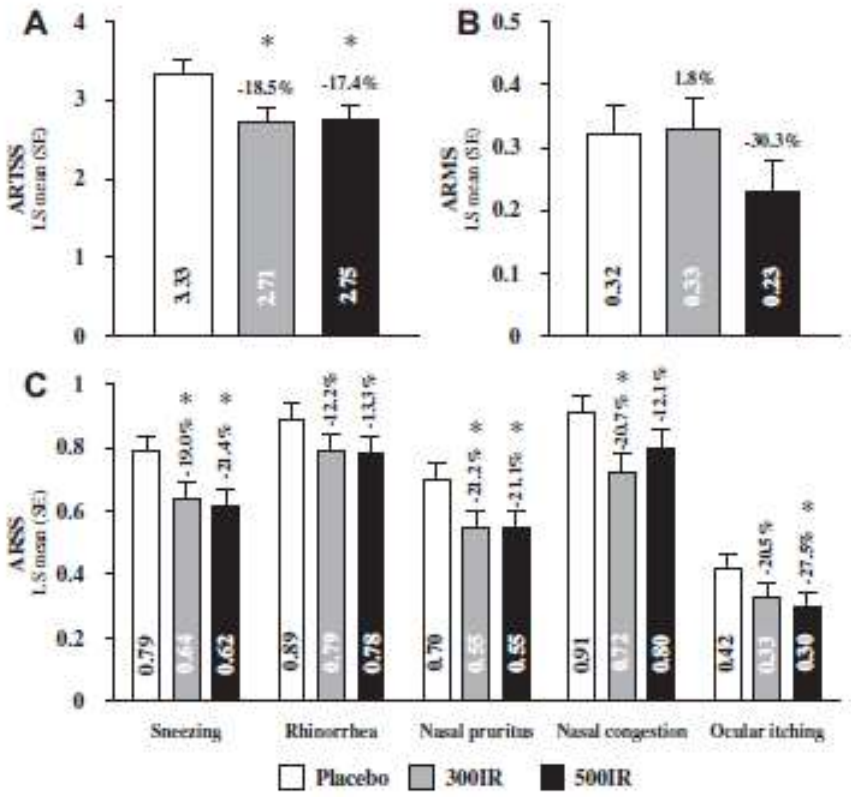


FIG 2. Symptom and rescue medication scores (FAS_{Year1}); ARTSS **(A)**, ARMS **(B)**, and ARSS **(C)**. Observations for all variables were available for 136 participants in the 500IR group, 141 participants in the 300IR group, and 153 participants in the placebo group, except for ocular itching (131, 139, and 148 participants, respectively). *$P < .05$ (analysis of covariance, each of the 2 active groups vs the placebo group).

Serum immunologic outcomes

JACI 2014

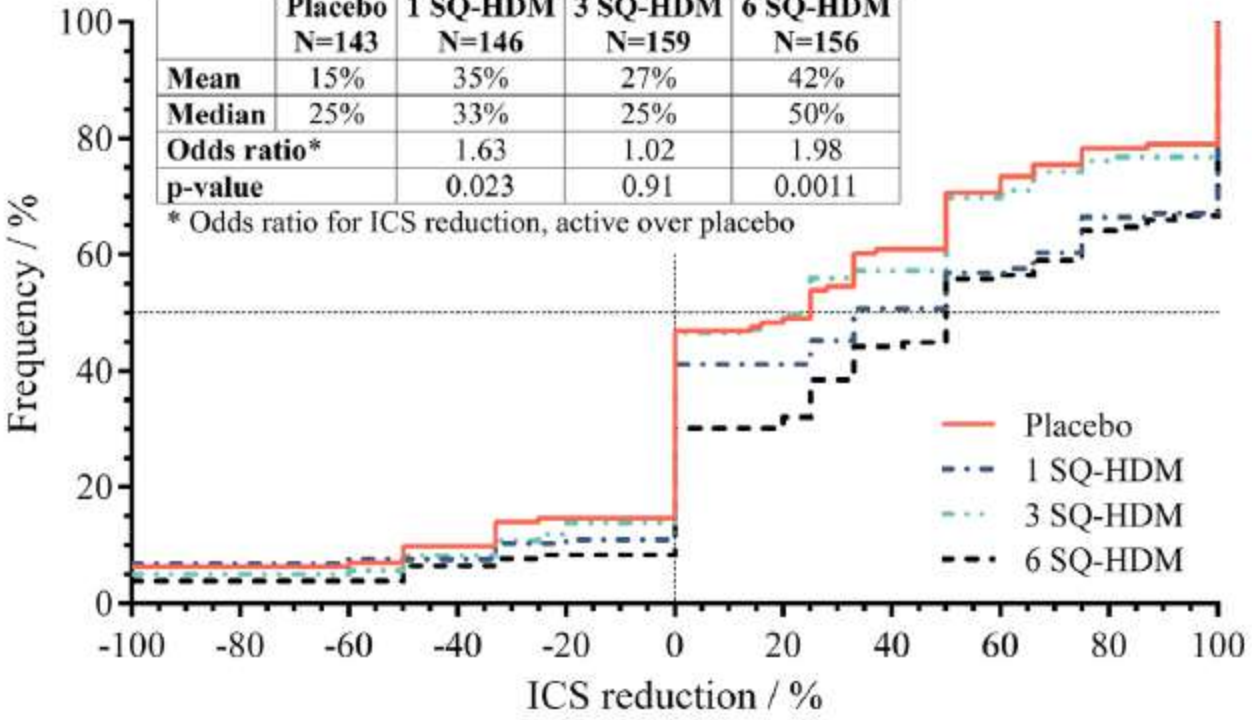
Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Holger Mosbech, MD,[a] Regina Deckelmann, MD,[b] Fréderic de Blay, MD,[c] Elide Anna Pastorello, MD,[d] Ewa Trebas-Pietras, MD,[e] Luis Prieto Andres, MD,[f] Inga Malcus, MD,[g] Christian Ljørring, MSc,[h] and Giorgio Walter Canonica, MD[i] *Gentofte, Denmark, Leipzig, Germany, Strasbourg, France, Milan and Genoa, Italy, Lublin, Poland, Valencia, Spain, Malmö, Sweden, and Hørsholm, Denmark*

604 patients
1 yr

	Placebo N=143	1 SQ-HDM N=146	3 SQ-HDM N=159	6 SQ-HDM N=156
Mean	15%	35%	27%	42%
Median	25%	33%	25%	50%
Odds ratio*		1.63	1.02	1.98
p-value		0.023	0.91	0.0011

* Odds ratio for ICS reduction, active over placebo



OPTIMAL DOSES (dose-finding studies)

DURHAM 2006: 15 mcg Phl p 5/day

DIDIER 2007: 20 mcg Group 5 /day

CRETICOS 2013: 12 mcg Amb a 1/day

BERGMANN 2014: 28/120 Der p 1/Der f 1/day

MOSBECH 2014: 6 SQ/day (70 mcg day?)

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.

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy 2013

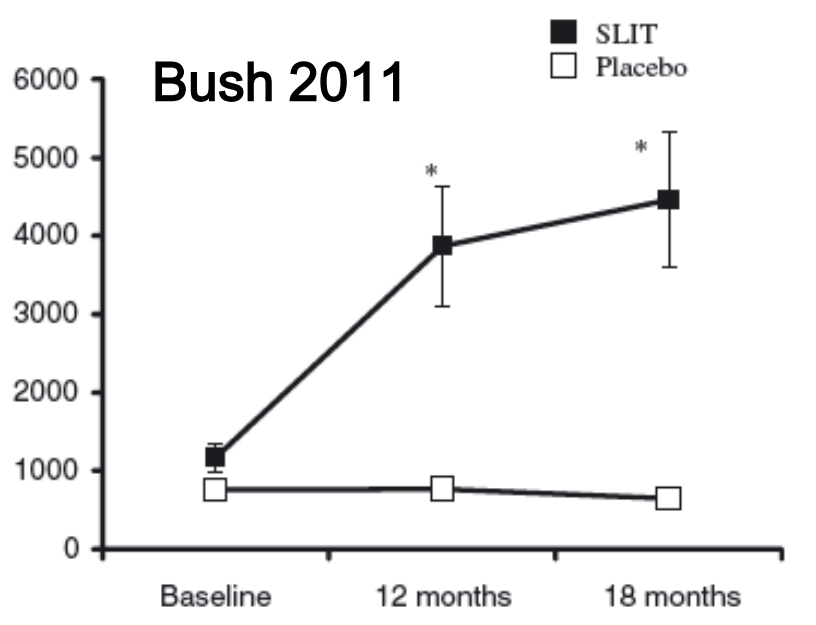
REVIEW ARTICLE

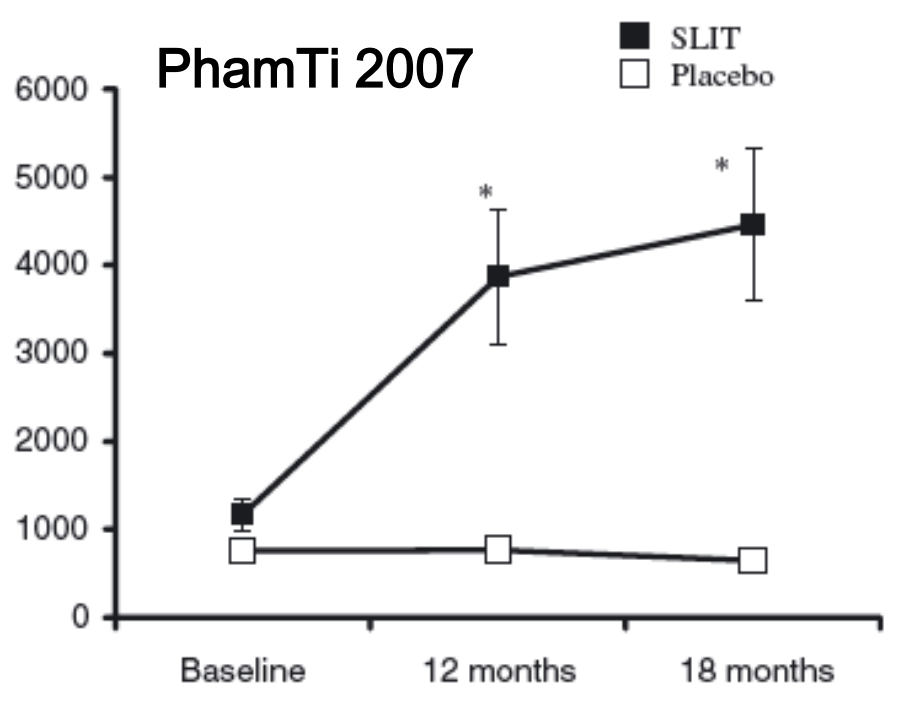
Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile

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

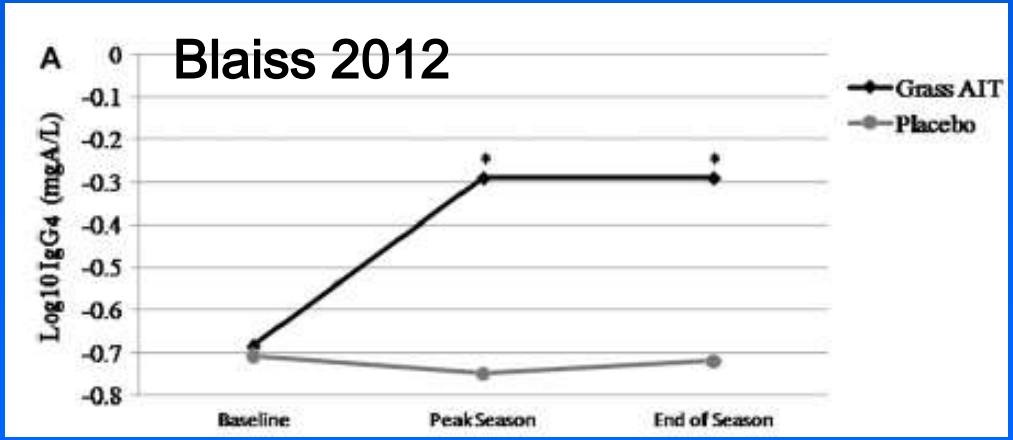
Table 1 Clinical efficacy of SLIT and SCIT in comparative studies

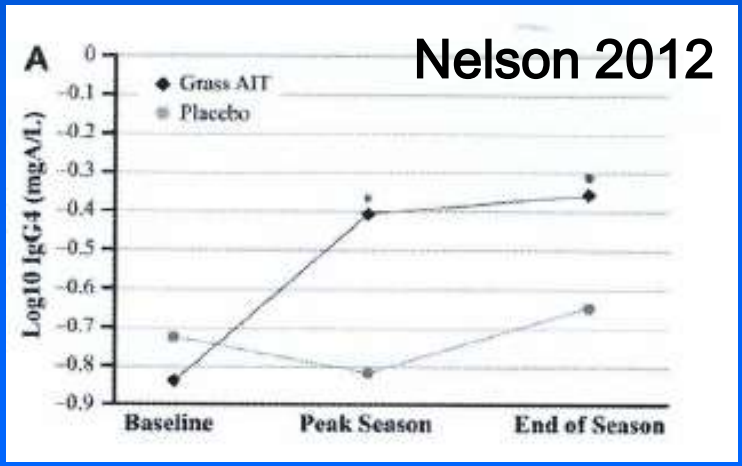
Authors	Year	Study design	Patients (*n*)	Patient age range	Allergen extract	Treatment duration	SLIT allergen dose (-fold the SCIT dose)	Conclusion in terms of efficacy
Bernardis et al. (9)	1996	Open, controlled, no placebo	23	5–26	*Alternaria tenuis*	2 years	×3.6	SLIT > SCIT
Quirino et al. (10)	1996	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





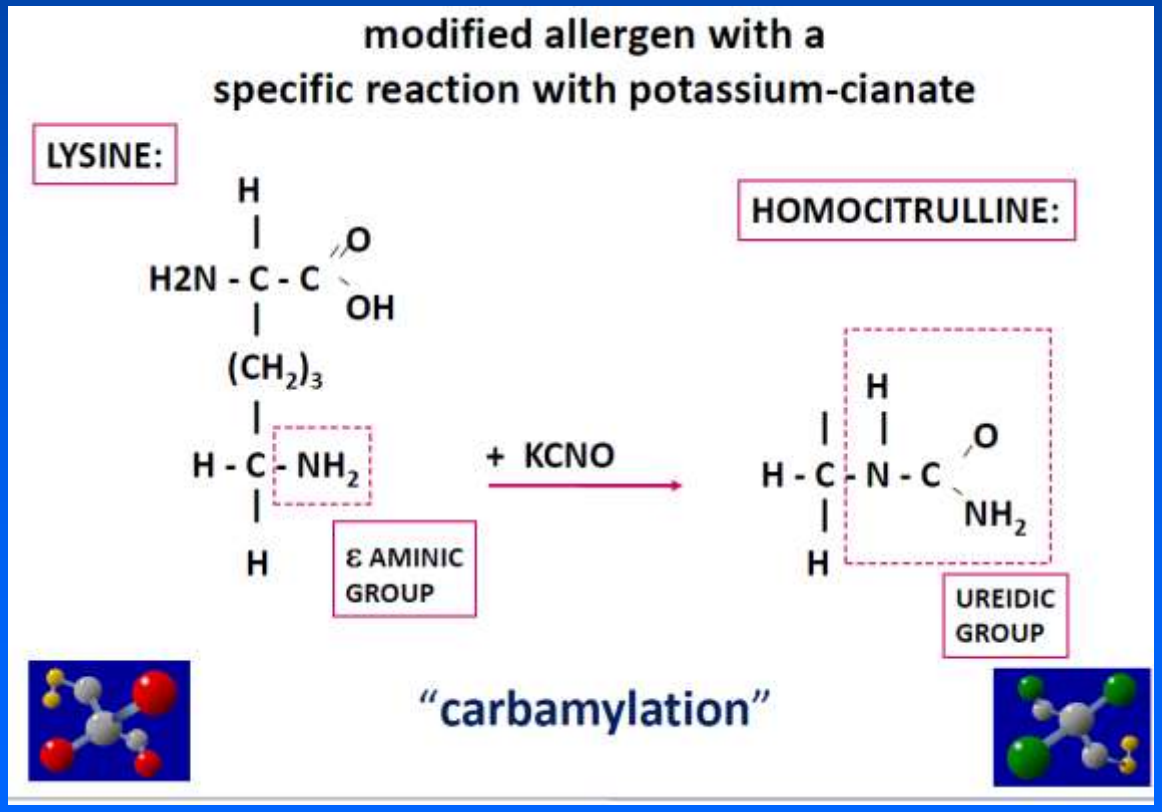
Allergen-specific IgG4



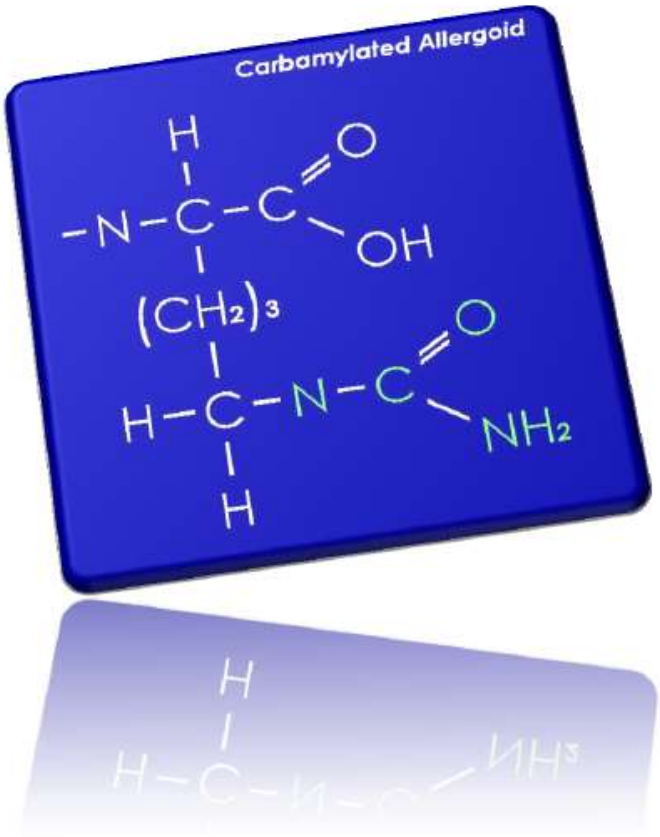


CAN SLIT BE IMPROVED?
BESIDES THE "TRADITIONAL" SLIT ?

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



Consequences of chemical modification



1. **PRESERVATION**
   of molecular sizes
   -monomericity-

2. **Dramatic REDUCTION**
   of specific IgE linking
   -reduced allergenicity-

3. **NO**
   alteration of T-epitopes
   -preserved immunogenicity-

4. **RESISTENCE**
   to enzymatic degradation
   -high bioavailability-

226

Allergen identification and characterisation of lysine modification in monomeric allergoids

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

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

liquid chromatography coupled to tandem mass spectrometry

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

Betula verrucosa and Alnus glutinosa

Bet v1, Aln g1, Bet v2, Bet v 6, Bet v7

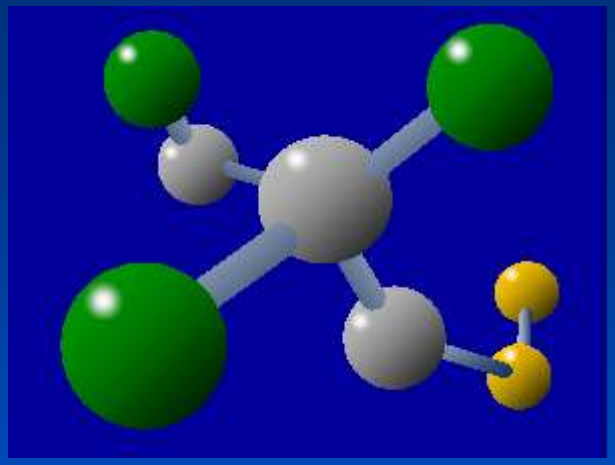
Phleum partense, Holcus lanatus and Poa pratense

Phl p1-2-4-5-6-7-11-12-13 Hol l 1-5; Poa p1-5

mix mite

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

Detected allergens after modification



Monomeric allergoid:

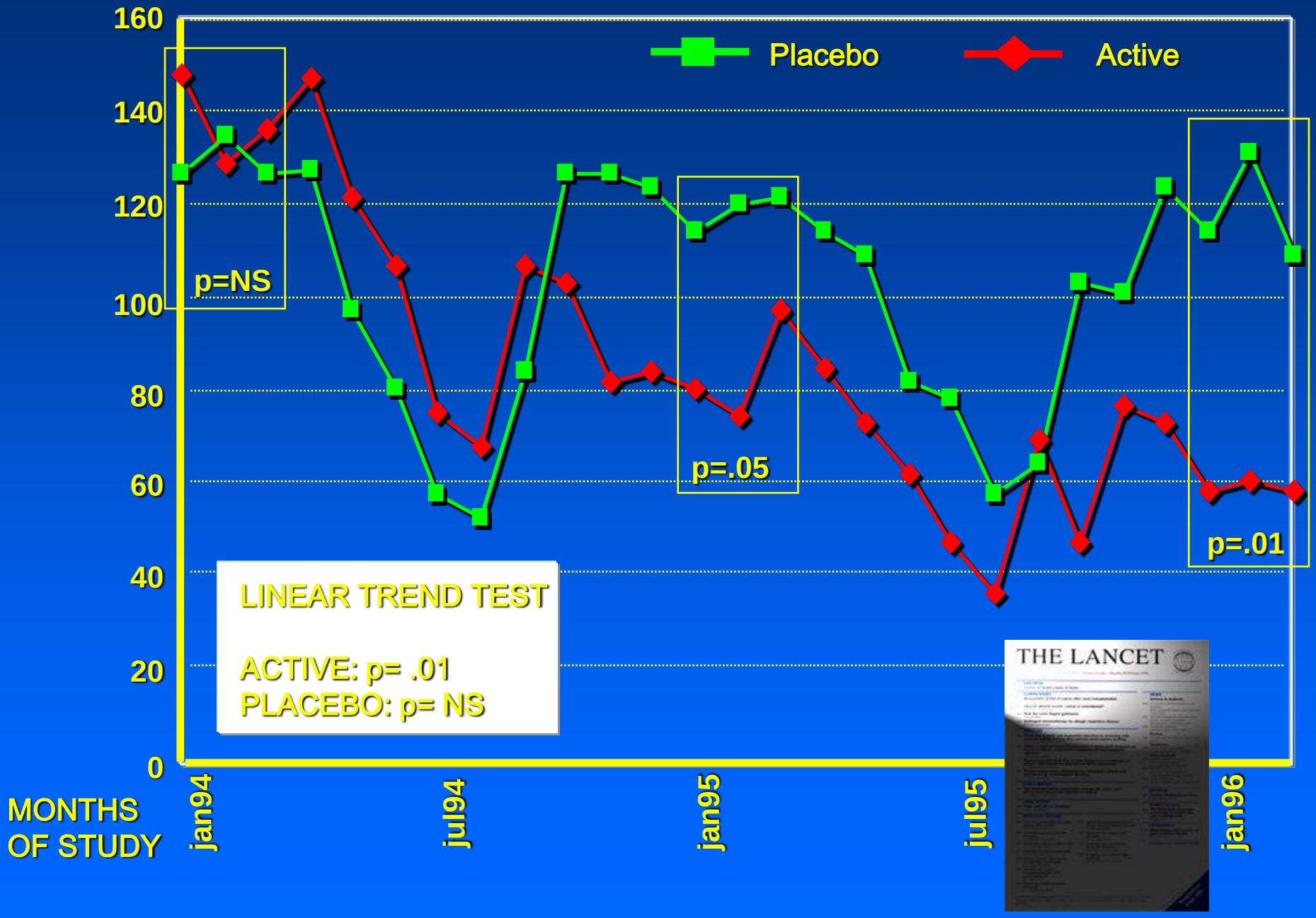
Retained immunological characteristics

The carbamylation, to obtain the allergoid, keeps intact the molecular weight and sizes of the native allergen.

(Mistrello et al, Allergy 1996)

EFFICACY

SYMPTOM/MED. SCORES



EVOLUTION OF THE TRADITIONAL SLIT

Lais THE ALLERGOID SLIT

Allergen	Study	Pathology	Patients	Medication score	Symptoms score	Publication
Grasses Bordignon 1994	DBPC	SAR	60 7 - 21 yrs	p<0.05	p<0.05	GIAIC
Grasses Caffarelli 2000	DBPC	SAR / AA	48 4 - 14 yrs	p<0.05	p<0.05	Allergy
Grasses Cavagni 1996	DBPC	SAR	51 4 - 14 yrs	--	p<0.01	Not.All.
Grasses Lombardi 2001	Open	AA	51 15 - 48 yrs	p<0.01	p=0.01 Mch BHR	J.Inv.All.
Grasses Palma Carlos 2006	DBPC	SAR / AA	33 19 - 43 yrs	p<0.02	p<0.03 Mch BHR	All.et Imm.
Pellitory (Parietaria) Ariano 1998	DBPC	SAR / AA	30 14 - 60 yrs	p<0.01	p<0.05	J.Inv.All.
Ragweed (Ambrosia) Mezei 1996	DBPC	SAR	60 6 - 60 yrs	p<0.01	p<0.05	Not.All.

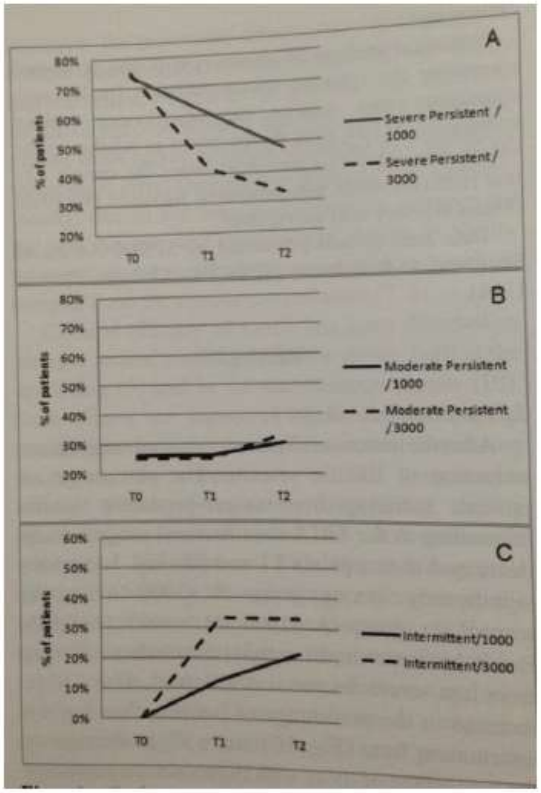
EVOLUTION OF THE TRADITIONAL SLIT

Lais THE ALLERGOID SLIT

Allergen	Study	Pathology	Patients	Medication score	Symptoms score	Publication
Mites Cosmi 2006	**Open**	**AR / AA**	**25** 20 - 45 yrs	**p<0.05**	**p<0.05**	**Clin.Exp.All.**
Mites La Rosa 1996	**Open** *vs* **SCIT**	**AA**	**57** 4 - 16 yrs	**ns** *vs* **SCIT**	**ns** *vs* **SCIT**	**Not.All.**
Mites Passalacqua 1998	**DBPC**	**AR / AA**	**20** 15 - 46 yrs	**--**	**p<0.05**	**THE LANCET**
Mites Passalacqua 2006	**DBPC**	**AR / AA**	**68** 15 - 48 yrs	**p<0.03**	**p<0.05**	**Allergy**
Mites / Pellitory La Grutta 2007	**Perspectiv e**	**AR**	**56** 6 - 26 yrs	**p<0.001**	**p<0.01**	**Eur.Ann.All.**

Dose-dependent clinical and immunological efficacy of sublingual immunotherapy with mite monomeric allergoid.

Di Gioacchino M, Cavallucci E, Ballone E, Cervone M, Di Rocco P, Piunti E, Filardo GS, Turi MC, Mangifesta R, Quecchia C, Mistrello G, Braga M, Petrarca C.

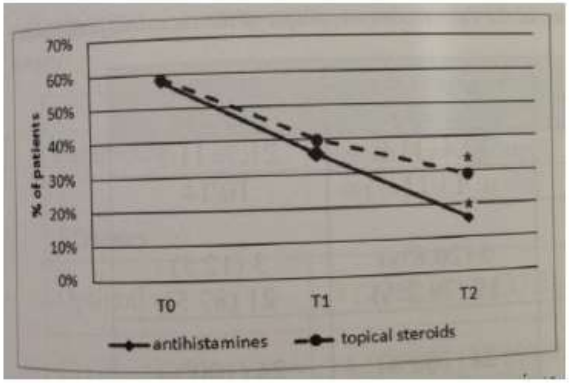


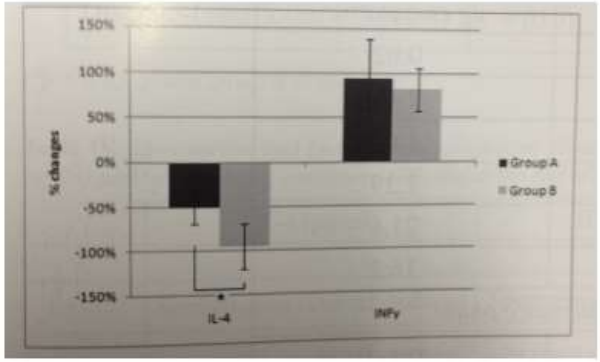
Randomized to
group A (n=24):1000 AU

group B (n=24): 3000 AU

weekly during one-year maintenance phase

T1= 6 months
T2= 12 months





Int J Immunopathol Pharmacol. 2012 Jul-Sep;25(3):671-9.

Sublingual immunotherapy with a carbamylated monomeric allergoid in cat-allergic patients suffering from rhinoconjunctivitis and/or allergic asthma.

A multicenter, cross-sectional survey.

Hauswald B.[1], Nguyen T.N.[2], Shah-Hosseini K.[2], Zadoyan G.[2], Eberle P.[3], Mösges R.[2]

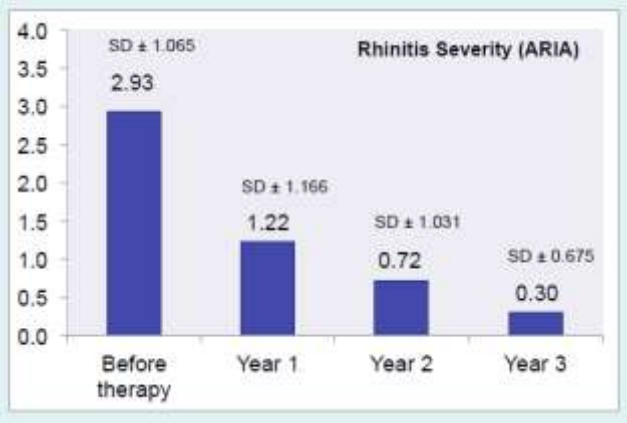
[1]Clinic and Polyclinic for Ear, Nose and Throat Medicine, University Hospital Carl Gustav Carus Dresden, Germany

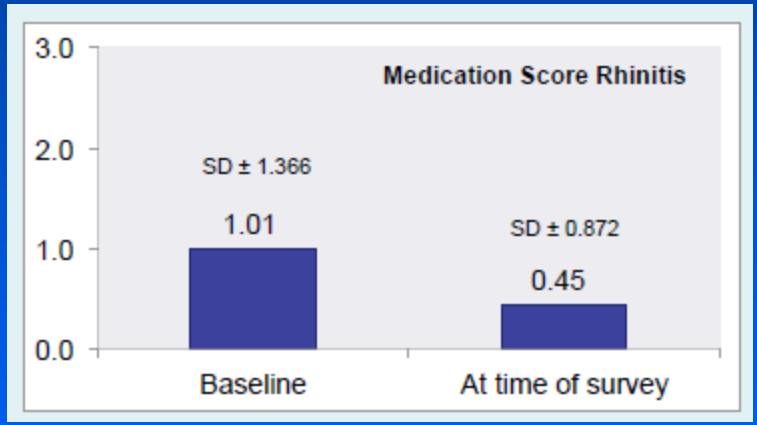
[2]Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University Hospital of Cologne, Germany

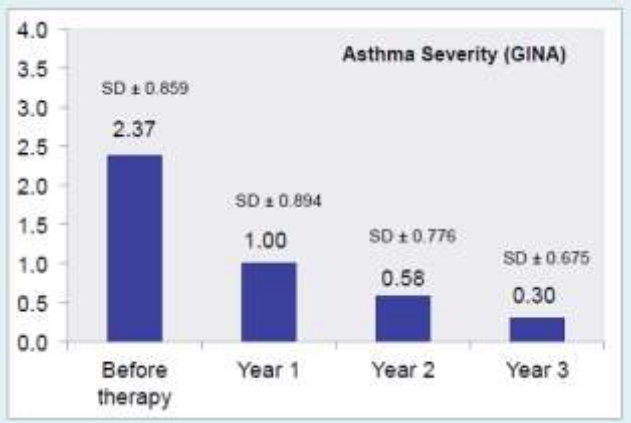
[3] MD Pediatrician, Allergist, Kassel Germany

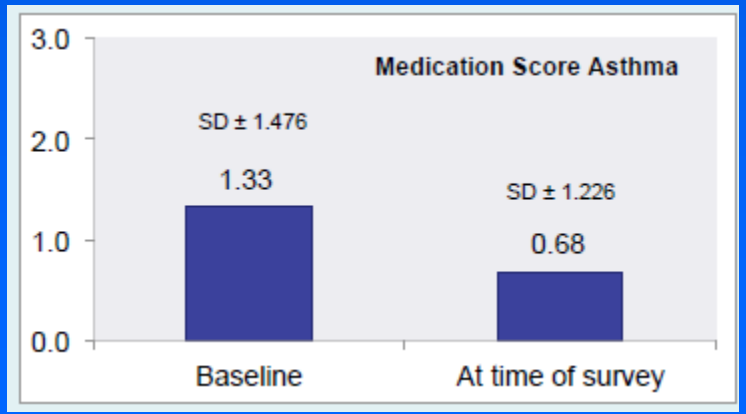
University Hospital of Cologne | Institute of Medical Statistics, Informatics and Epidemiology (IMSIE)

Retrospective, multicenter, observational, cross-sectional survey on 70 cat--allergic patients in 20 German centers from November 2006 to December 2013





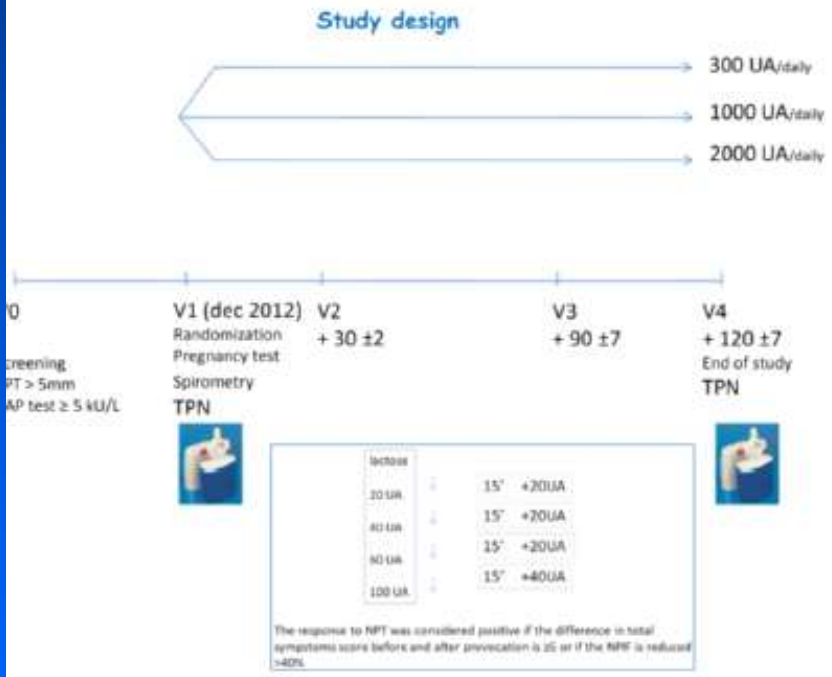


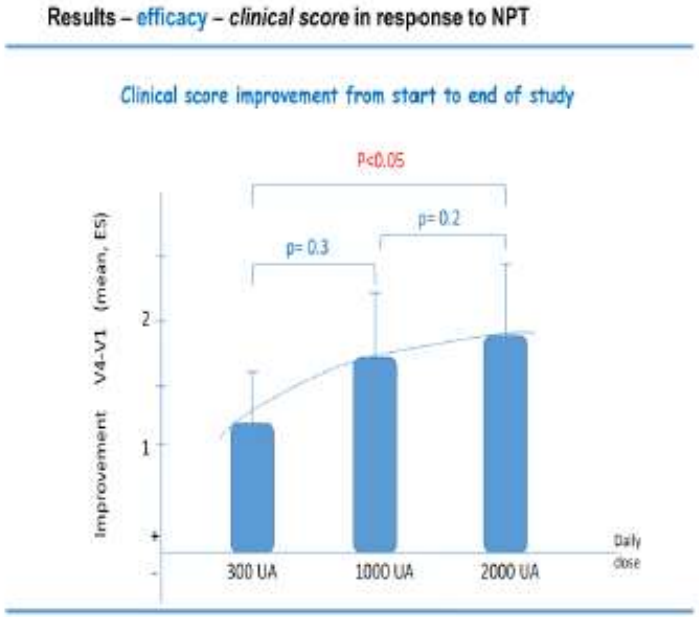


No fatalities, no anaphylaxis,
No use of epinephrine,
No systemic adverse reactions
7 Local adverse reactions

EFFICACY AND SAFETY OF SPECIFIC SUBLINGUAL IMMUNOTHERAPY WITH CARBAMYLATED ALLERGOID TABLETS OF RAGWEED POLLEN: a dose-ranging study

Pastorello E, Moscato G, Berra D, Tosi A, Mauro M, Compalati E, Ortolani C





WAO Immunotherapy and Biologics Symposium 2013 - Chicago

Clinical Development of Lais®
- Registrative trials -

2011 — adults — children — 2024

	adults		children
Grass pollen tablet 	concluded Phase II	Concluded (Under analysis) Phase III	planned Phase III
Tree pollen tablet 	concluded Phase II	Concluded (Under analysis) Phase III	planned Phase III
Ambrosia pollen tablet 	concluded Phase II	starting Phase III	planned Phase III
HDM tablet 	concluded Phase II	starting Phase III	planned Phase III
Parietaria pollen tablet 	planned Phase II	planned Phase III	planned Phase III

SLIT

No fatal event
reported since 1986
(14 anaphylaxes)

Characteristics of reported systemic side-effects

298 pts, 1 to 3 years of SLIT

SIDE EFFECT	EPISODES	% OF PATIENTS	GRADE	TIME OF ONSET
Conjunctivitis	1	0.5	Moderate	45 min
G.I. complaints	3	1.5	Mild	30-120 min
Rhinitis	7	3.5	Mild	< 60 min
Urticaria	3	1.5	2 mild 1 moderate	> 30, <60 min
Oral itching	3	1.5	Mild	< 30 min
Angioedema	0	-	-	-
Asthma	0	-	-	-
Anaphylaxis	0	-	-	-
TOTAL	17	8.6	15 mild 2 moderate	-

Lombardi et al. Allergy 2001

SLIT: Post Marketing surveys

Author	N pats	Age range	Follow-Up	Total AE % of patients	Total AE/1000 doses	Local AE% of patients
Di Rienzo	268	2-15	3 years	3 %	0.083	7%
Lombardi	198	18-65	3 years	5.5 %	0.5	1.5%
Pajno	354	5-15	3-4 years	6 %	0.15	Not stated
Fiocchi	65	3-7	1 year	15%	Not stated	6%
Drachenberg	159	6-60	< 1 year	6.3%	Not stated	5%
Agostinis	36	3-5	2 years	5 %	0.07	Not stated
Di Rienzo	128	3-5	2 years	5. 6%	0.2	1.5%
Rodriguez	43	8-20	1 year	11.6%	0.3	46%
Agostinis	433	3-18	1 year	41%	4.4	32%
Lombardi	159	16-59	1 year	63%	6.5	41%

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.

Allergy Asthma Proceedings 2013

Treatment-related adverse events

AEs are usually brief in duration and resolve soon after initiation

	Duration[a] (minutes) median (P25%-P75%)	Resolution[b] (days) median (P25%-P75%)
Oral pruritus	**8.5 min** (3.0 - 29.0)	**5.5 days** (2.0 - 16.0)
Mouth oedema	**46.0 min** (25.0 - 60.0)	**1.0 days** (0.0 - 7.0)
Ear pruritus	**8.5 min** (3.0 - 29.0)	**5.5 days** (2.0 - 16.0)
Throat irritation	**10.0 min** (5.0 - 20.5)	**13.5 days** (0.5 - 22.0)

a. Duration of episode post administration
b. Resolution defined as days from first intake until AE no longer occurred

Ibanez et al. Pediatr Allergy Immunol 2007;18:516-22

SAFETY:

No fatal event have been reported over about 20 years

Side effects are mostly local, transient and subsiding after the first doses

The safety of SLIT is overall superior to that of SCIT

An uniform grading system is required to describe and grade systemic and local side effects.

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
VanDyken	F	21	Mite	Y

Rostrum

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

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

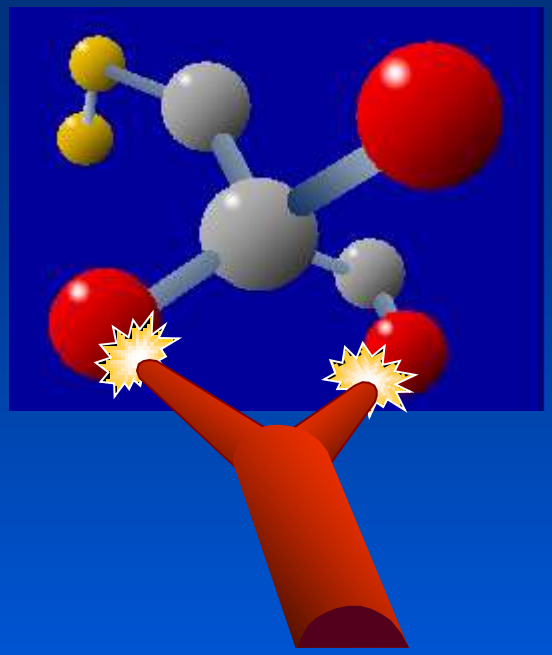
JACI 2013

TABLE IV. Grading system for SLIT local AEs*

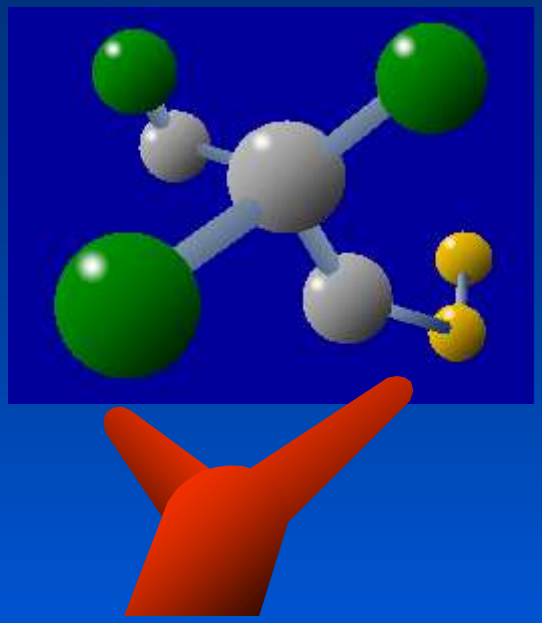
Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	• Not troublesome AND • No symptomatic treatment required AND • No discontinuation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

WORLD ALLERGY ORGANIZATION

A World Federation of Allergy, Asthma & Clinical Immunology Societies



The native Allergen
is recognized and bound
by specific IgE.



The Monomeric Allergoid is NOT
recognized by specific IgE:
the carbamylation strongly decreases
the capacity to react with IgE
antibodies.

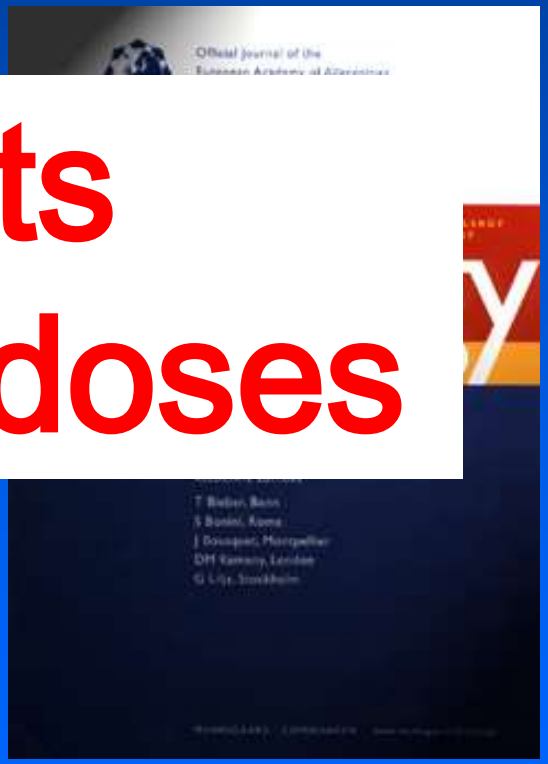
SAFETY

Safety of SLIT with a monomeric allergoid in very young children

F.Agostinis, L.Tellarini, G.W.Canonica, G.Passalacqua
Bergamo and Genoa

5% of patients

0.071 per 1,000 doses



Mean age: 3 years

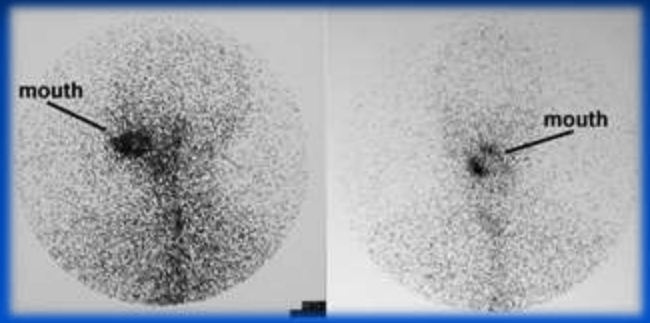
8 RC, 4 A, 26 RC+A

20 mite SLIT + 18 grass SLIT

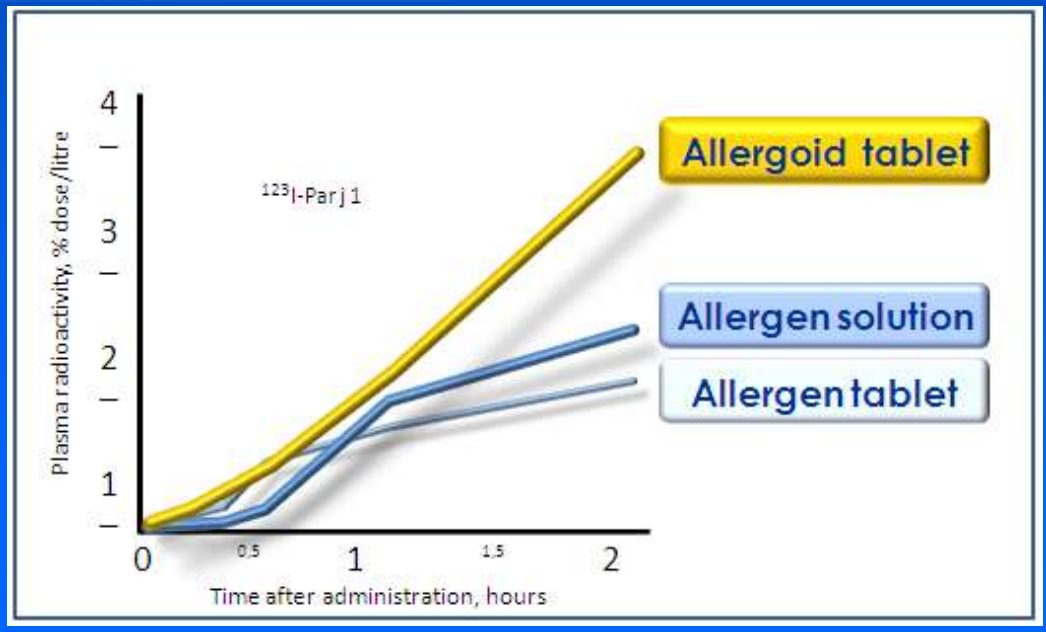
Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers.

Bagnasco M, Passalacqua G, Villa G, Augeri C, Flamigni G, Borini E, Falagiani P, Mistrello G, Canonica GW, Mariani G.
Allergy and Clinical Immunology, Department of Internal Medicine, Genoa, Italy.

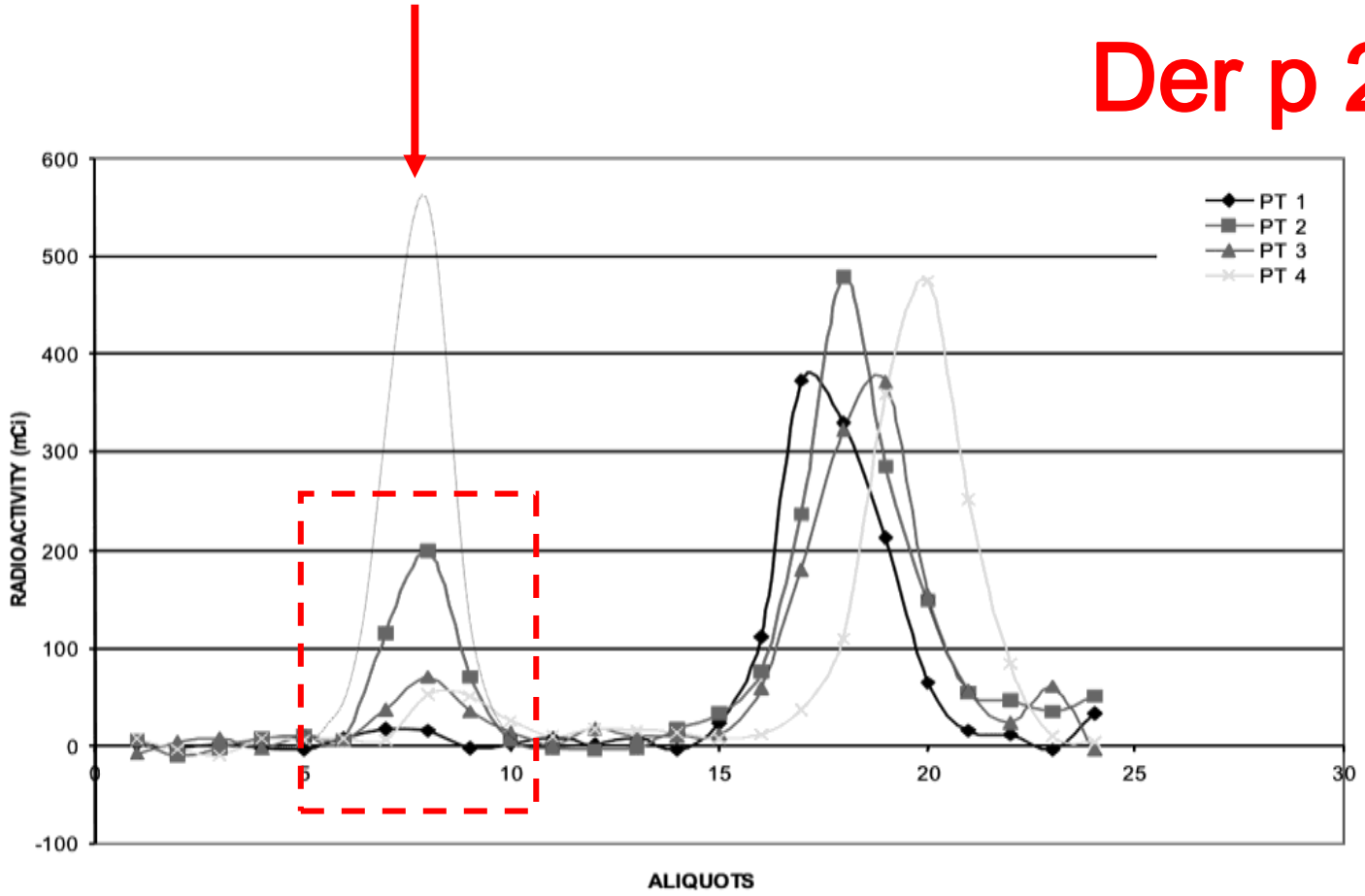
Comment in: Clin Exp Allergy. 2001 Jan;31(1):8-10.



Increased biodistribution



Gel chromatography at plasma peak



DECREASED G.I. BIODEGRADATION

Human Vaccines & Immunotherapeutics 8:10, 1492-1498; October 2012; © 2012 Landes Bioscience

Adjuvants for allergy vaccines

Philippe Moingeon

Table 1. Immunopotentiators for allergy vaccines

TLR ligands	Clinical (for CpGs and MPL), preclinical (others)	Subcutaneous, intradermal / sublingual	OVA, Amb a 1, grass pollen	Ligands for TLR2 (including lipopeptides, Pam3Csk4), TLR4 (MPL, RC 529, OM294-BA-MP), TLR7 (imidazoquinolines), TLR9 (CpGs) have some efficacy in murine asthma models (decrease of both airway inflammation and Th2 responses, with induction of Th1 and/or T Reg responses). Intradermal immunization with Amb a 1 fused to CpG oligonucleotides prevents allergen-induced hyperresponsiveness in mice. A conjugate Amb a 1-CpG vaccine has been tested in ragweed allergic humans through the subcutaneous route, with some level of clinical efficacy, and induction of Th1 responses and $CD25^+$ T Reg cells. In humans, the TLR4 ligand monophosphoryl lipid A (MPL) with or without tyrosine-absorbed grass pollen allergens induces a strong production of IgG1 and IgG4 antibodies through the subcutaneous route. Following SLIT in grass pollen allergic patients, MPL enhanced specific IgG responses and decreased reactivity to nasal allergen challenge.
Small synthetic molecules	Clinical (fluticasone), preclinical (others)	Systemic, sublingual	OVA, grass pollen	Dihydroxyvitamin D3 plus glucocorticoids, calcineurin inhibitors (cyclosporin A, FK 506), rapamycin, aspirin and mycophenolate mofetil enhance IL10 production by $CD4^+$ T cells. Dexamethasone plus dihydroxy vit D3 enhance SLIT efficacy in a murine asthma model. No synergy between fluticasone and SLIT was observed in humans when using distinct administration routes.

or asthma after intradermal administration.

A New Era of Targeting the Ancient Gatekeepers of the Immune System: Toll-Like Agonists in the Treatment of Allergic Rhinitis and

Zahra Aryan[a] Stephen T. Holgate[c] Danuta Radzioch

International Archives of Allergy and Immunology

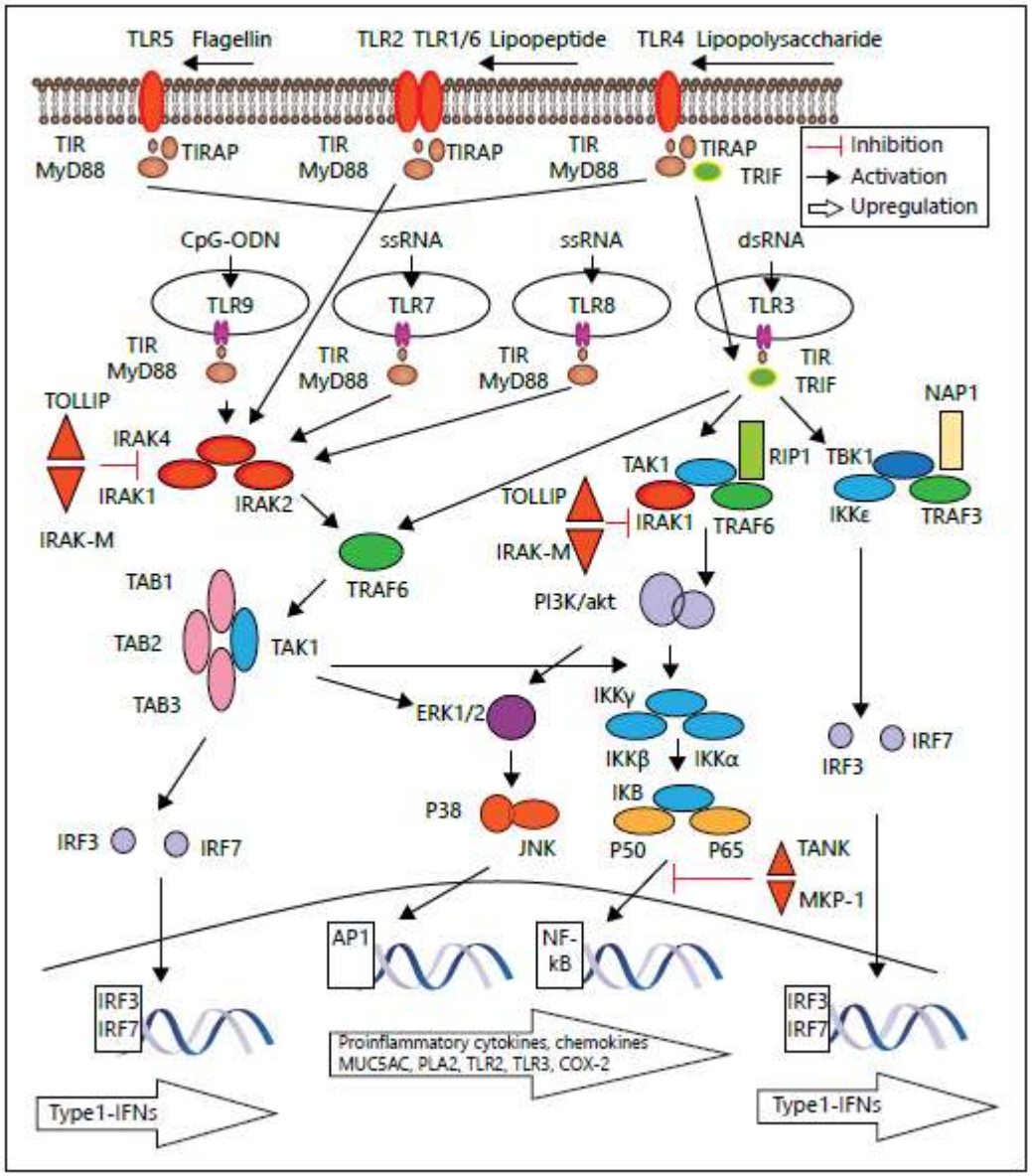


Table 2. Clinical efficacy of targeting TLRs

Targeting	Study	Design	Level of evidence	Compound	Dose of compound	Route	Participants (active:placebo)	Age, years	Symptom score (active vs. placebo)	Medication score (active vs. placebo)
TLR4 agonist	Dullaske et al. [135] 2011	Single-center RCTDB	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course	SCIT	AR patients sensitized to grass pollens, 514:514	NA	Significantly reduced	Significantly reduced
TLR4 agonist	Pfaar et al. [136] 2011	Single-center RCTDB	Level 2	Pollinex Quattro rPhl p + MPL	9.45 or 19.04 μg Phl p + 21 or 52.5 μg MPL/day for 8 weeks	SLIT	AR patients sensitized to grass pollen, 64:16	35.9 (18–64)	NA (combined symptom and medication score was reduced)	NA (combined symptom and medication score was reduced)
TLR4 agonist	Musarra et al. [64] 2010	Single-center open clinical trial	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course	SCIT	AR/asthma-sensitized patients to grass pollen, 29:28	33.7 (10–59)	Significantly reduced as assessed by VAS	NA
TLR4 agonist	Rosewich et al. [66] 2010	Post-marketing multi-center open trial (cohort)	Level 3	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course	SCIT	AR/asthma patients sensitized to grass pollen, 34 active	10.2 (6–18)	Significantly reduced	Significantly reduced
TLR4 agonist	Rosewich et al. [62] 2010	Post-marketing multi-center open trial (cohort)	Level 3	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course	SCIT	AR/asthma patients sensitized to	13.2 (6–18)	Significantly reduced	Significantly reduced
TLR4 agonist	Casale et al. [69] 2006	Single-center RCTDB	Level 2	CRX-675	2–20–100–200 μg/patient					
TLR4 agonist	Von Baehr et al. [65] 2005	Single-center RCT	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course					
TLR4 agonist	Drachenberg et al. [137] 2003	Multi-center open trial	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course					
TLR4 agonist	Mothes et al. [138] 2003	Single-center RCTDB	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course					
TLR4 agonist	Drachenberg et al. [139] 2001	Multi-center RCTDB	Level 2	Pollinex Quattro	300–2,000 SU/ml ×4 ultra-short course					
TLR7 agonist	Greiff et al. [106] 2012	Single-center RCTDB NCT00770003	Level 2	AZD8848	60 μg/week ×5					
TLR8 agonist	Horak et al. [107] 2011 (abstract)	Single-center RCTDB	Level 2	VTX-1463	0.25, 0.50, 0.75 and 1.0, or 62.5 μg/week ×4	Intranasal	Grass pollen-sensitized AR patients, 80:NA	NA	Significantly reduced	Significantly reduced
TLR9 agonist	Klimek et al. [132] 2011	Multi-center RCTDB	Level 2	CYT003-QbG10	0.5 or 1 mg/week ×6	SCIT	HDM-sensitized AR patients, 99:35	31.2 (18–64)	Significantly reduced	Significantly reduced
TLR9 agonist	Senti et al. [133] 2009	Single-center open-label	Level 3	QbG10	300 μg/week ×6	SCIT	HDM-sensitized AR patients, 20:0	34.0 (18–56)	Significantly reduced	Significantly reduced
TLR9 agonist	Creticos et al. [127] 2006	Single-center RCTDB	Level 2	Amb a1-1018 ISS (AIC)	0.06–12 μg/week ×6	SCIT	Ragweed-sensitized AR patients, 14:11	39.4 (23–60)	Significantly reduced	Significantly reduced
TLR9 agonist	Nayak et al. [130] 2006 (abstract)	Single-center RCT	Level 2	Amb a1-1018 ISS (AIC)	0.06–12 μg/week ×6	SCIT	Ragweed-sensitized asthmatic patients, 18:6	NA (6–17)	NS	NS
TLR9 agonist	Gauvreau et al. [131] 2006	Single-center RCTDB	Level 2	1018 ISS	36 mg/week ×4	Inhalation	Atopic asthmatics, 21:19	24.8 (18–55)	NS	NS
TLR9 agonist	Tulic et al. [129] 2004	Single-center RCTSB	Level 2	Amb a1-1018 ISS (AIC)	0.06–12 μg/week ×6	SCIT	Ragweed-sensitized AR patients, 28:29	39.9 (27–55)	Significantly reduced (second year)	Significantly reduced

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Sublingual Allergen-Specific Immunotherapy Adjuvanted with Monophosphoryl Lipid A: A Phase I/IIa Study

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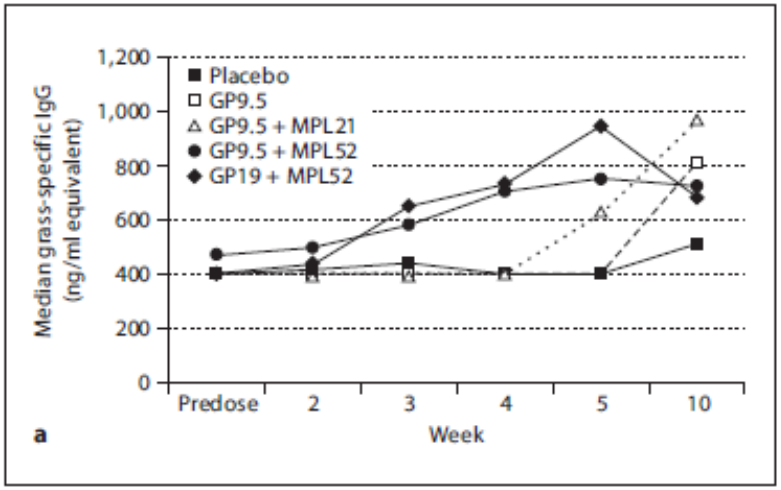
Ludger Klimek[a, b]



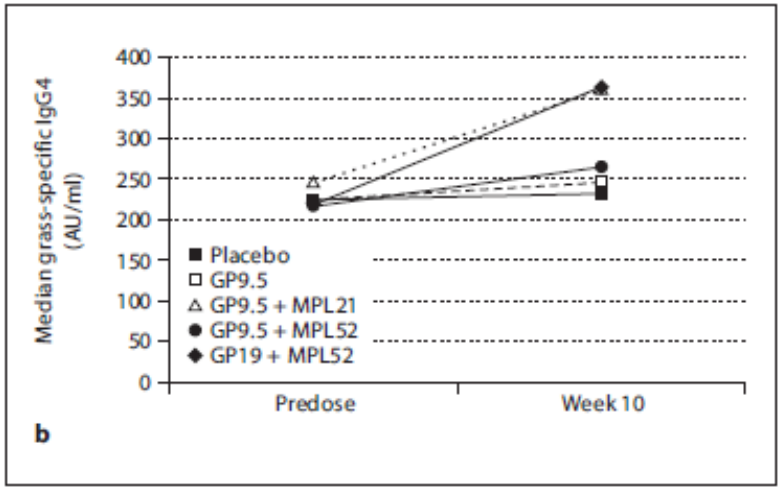


Fig. 2. a Change in median specific IgG levels. **b** Change in median specific IgG4 levels.

RECOMBINANT. PROBLEMS:

Does SIT with recombinant allergens

works better than SIT

with extractive allergens?

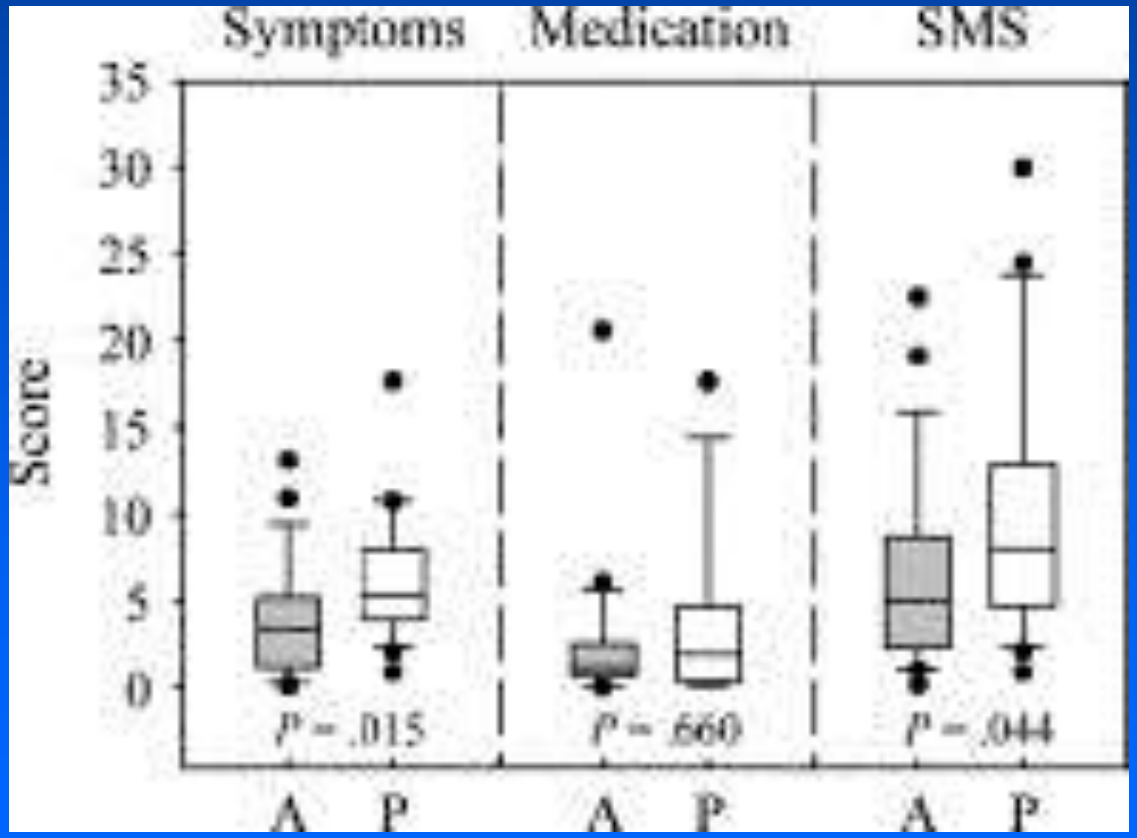
Recombinant allergens for specific immunotherapy

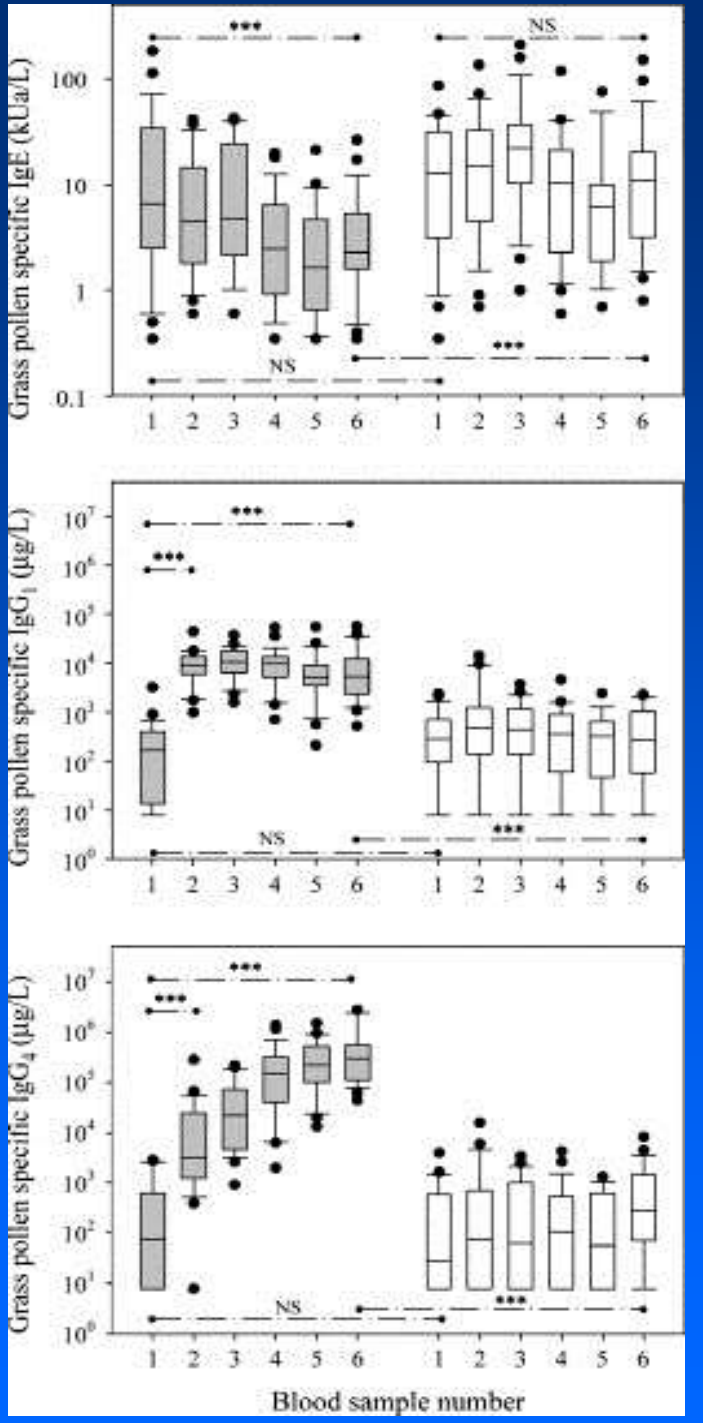
Oliver Cromwell, PhD, Dietrich Häfner, MD, and Andreas Nandy, PhD *Reinbek, Germany*

TABLE III. Registered clinical studies with recombinant allergen preparations

Allergen source	Interventions	Study design	Reference*
Birch pollen	Bet v 1 trimer Bet v 1 fragments Placebo	SCIT DBPC	Niederberger et al[42] Purohit et al[43]
Grass pollen	Phl p 1, 2, 5a, 5b, and 6 Placebo	SCIT DBPC	Jutel et al[11]
Birch pollen	Bet v 1 folding variant Pollen extract	SCIT Open controlled	NCT00266526
Birch pollen	Bet v 1 nBet v 1 Birch pollen Placebo	SCIT DBPC	NCT00410930 Pauli et al[33]
Birch pollen	Bet v 1 folding variant Placebo	SCIT DBPC	NCT00309062
Birch pollen	Bet v 1 folding variant Placebo	SCIT DBPC	NCT00554983
Birch pollen	Bet v 1 folding variant Placebo	SCIT Immunologic and histologic evaluation	NCT00841516
Grass pollen	Phl p 1, 2, 5a, 5b, and 6 Placebo	SCIT Dose-response study	NCT00666341
Grass pollen	Phl p 1, 2, 5a, 5b, and 6 Placebo	SCIT DBPC	NCT00309036
Grass pollen	Phl p 1, 2, 5a, 5b, and 6 Placebo	SCIT DBPC	NCT00671268
Birch pollen	Bet v 1 Placebo	SLIT tablet Safety and tolerability Dose 12.5 to 100 μg	NCT00889460 Winther et al[47]
Birch pollen	Bet v 1 Placebo	SLIT tablet Safety and tolerability Dose 50 to 300 μg	NCT00396149
Birch pollen	Bet v 1 Placebo	SLIT tablet DBPC	NCT00901914
Cat	Fel d 1–MAT Placebo	Intra-lymph node	Senti et al[50]
Peanut	Modified Ara h 1, 2, and 3 encapsulated in *E coli*	Rectal	NCT00850668

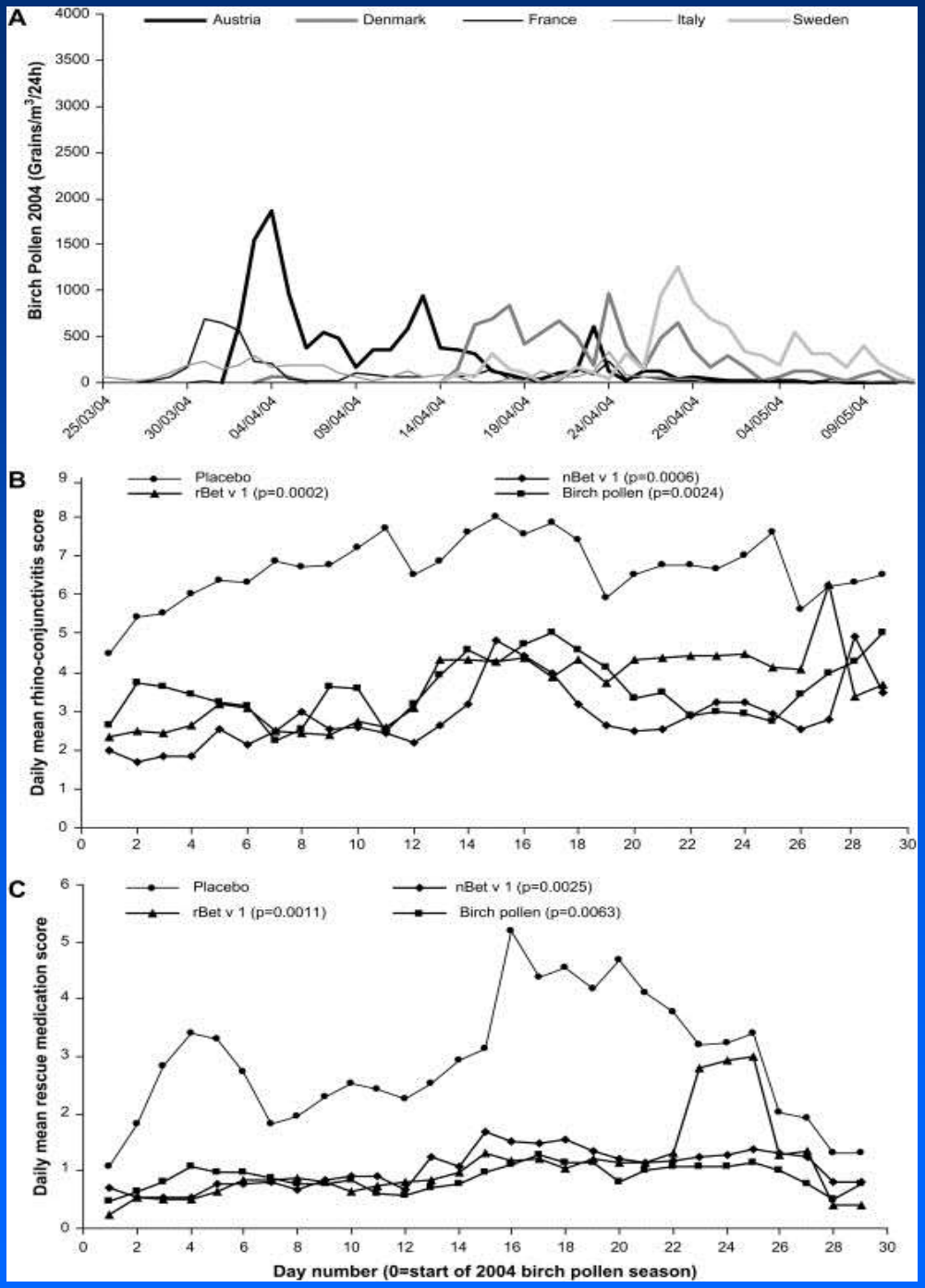
Allergen-specific immunotherapy with recombinant grass pollen allergens. *Jutel et al. JACI 2005*

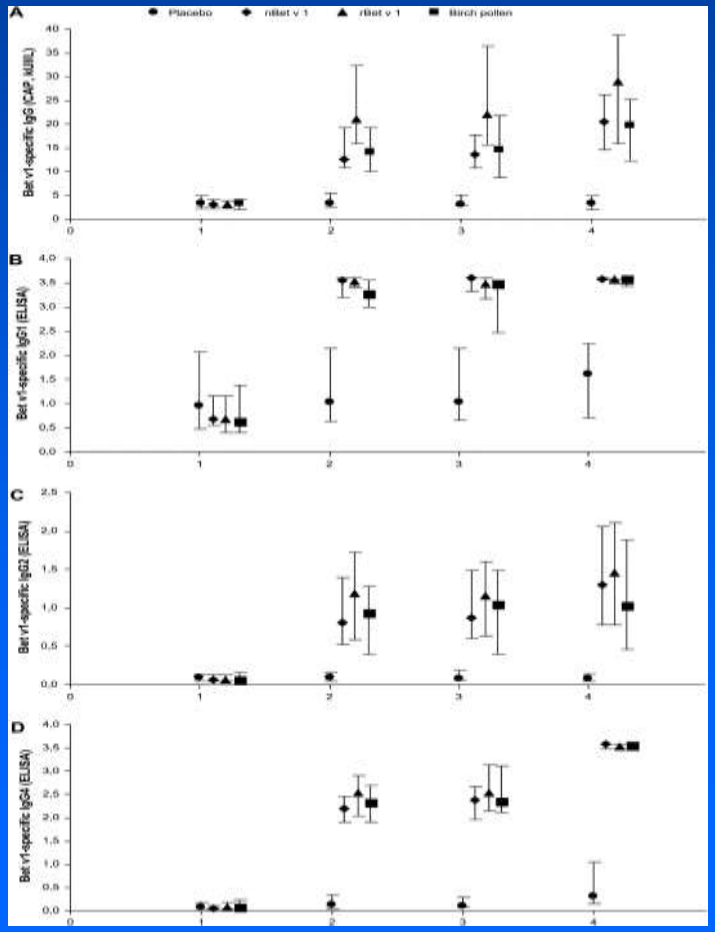




Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis

Pauli et al, JACI 2008





Recombinant allergens for specific immunotherapy

Oliver Cromwell, PhD, Dietrich Häfner, MD, and Andreas Nandy, PhD *Reinbek, Germany*

Recombinant DNA technology provides the means for producing allergens that are equivalent to their natural counterparts and also genetically engineered variants with reduced IgE-binding activity. The proteins are produced as chemically defined molecules with consistent structural and immunologic properties. Several hundred allergens have been cloned and expressed as recombinant proteins, and these provide the means for making a very detailed diagnosis of a patient's sensitization profile. Clinical development programs are now in progress to assess the suitability of recombinant allergens for both subcutaneous and sublingual immunotherapy. Recombinant hypoallergenic variants, which are developed with the aim of increasing the doses that can be administered while at the same time reducing the risks for therapy-associated side effects, are also in clinical trials for subcutaneous immunotherapy. Grass and birch pollen preparations have been shown to be clinically effective, and studies with various other allergens are in progress. Personalized or patient-tailored immunotherapy is still a very distant prospect, but the first recombinant products based on single allergens or defined mixtures could reach the market within the next 5 years.
(J Allergy Clin Immunol 2011;127:865-72.)

Abbreviations used
DBPC: Double-blind, placebo-controlled
SMS: Symptom-medication score

materials. In the latter case the relative concentrations of various allergens are dictated by the source material, except in those instances in which some postextraction purification is undertaken. In practice, it is usually only realistic to define the activity of an allergen extract in terms of its total IgE-binding activity and the concentration of 1 major allergen. Recombinant products, on the other hand, can be defined with respect to the concentration and activity of each component and the optimal dose for the required application. In addition, recombinant preparations contain only allergens and none of the nonallergenic proteins and polysaccharides present in extracts of natural source materials. Some of the difficulties posed by working with natural source materials, such as the need to demonstrate the lack of contamination of pollen preparations with foreign pollens or pesticides, can be avoided.[5] Recombinant forms of animal allergens might very well find greater acceptance than extracts of natural tissue, thus increasing the practice of immunotherapy for cat allergy, for ex-

Consequences

- These products (**diagnostics** as well as **therapeutics** - SIT) have to comply with the regulatory requirements of the "pharmaceutical world".
  - Production
  - Clinical Trials
  - Marketing Authorisation (MA)
- For recombinant molecules (additional)
  - Centralised MA Procedure (EMEA)

WHERE IS AIT GOING

IN THE REST OF THE WORLD?

CME review article

This educational activity is supported by an educational grant from GlaxoSmithKline

Comparison of allergen immunotherapy practice patterns in the United States and Europe

Linda Cox, MD,* and Lars Jacobsen, MSc†

Table 1. Comparison of the Differences Between US and European Allergen Extracts and Specific Immunotherapy Practice Patterns

Variable	United States	Europe
Regulatory agency	FDA	EMEA
Standardization		
Method	$ID_{50}EAL$	Nordic
Test technique	Intradermal	Percutaneous
End point	Extract dilution that produces sum of erythema of 50 mm	Extract dilution that produces a wheal equal to the histamine control
Potency determination	Comparison with CBER reference control	Compared with in-house reference
Future focus	Overall allergenicity	Major allergen content
Potency units	BAU, wt/vol, PNU, milligrams of major allergen for ragweed and cat	Varies; each company essentially has its own potency units, some provide milligrams of major allergen
Extract formulation		
Location	Prepared in physicians offices	Prepared at extract manufacturer site
No. of allergens	Multiple	Generally 1
Allergen extract types	Aqueous and glycerinated unmodified extracts, alum-precipitated depot extracts	Approximately 100% depot extract, 20% allergoid, <5% adjuvants
SLIT	Approximately 5.9% of allergists, no FDA-approved formulation	Approximately 45% of prescribed SIT, solution and tablets available, some are registered
Reimbursement	Covered as a medical service by government and private insurers, prices can be negotiated but private insurers often use government schedule	Varies, extract companies negotiate coverage with each country

Abbreviations: BAU, bioequivalent allergy units; CBER, Center for Biologics Evaluation and Research; EMEA, European Medicinal Agency; FDA, Food and Drug Administration; PNU, protein nitrogen units; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

PractALL – Washington Sep 2014

How to use and prescribe SLIT?

BOARD

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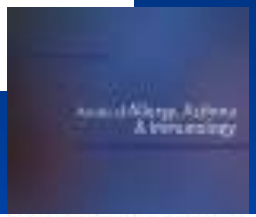
Efficacy VS SCIT
Safety
Regimens
Missing doses

Selection of patient
Pediatric aspects
Pharmacoeconomics
Legal issues

Duration
Pre-medication
Adherence

Allergy training and immunotherapy in Latin America: results of a regional overview

Carlos E. Baena-Cagnani, MD*; Désirée Larenas Linnemann, MD†; Maximiliano Gómez, MD‡; Sandra González Díaz§; Dirceu Solé‖; Mario Sánchez Borges, MD¶; Jean Bousquet, MD#; Juan Carlos Sisul, MD**; Giorgio Walter Canonica, MD††; José Gereda, MD‡‡; and Giovanni Passalacqua, MD††; on behalf of the SLAAI Immunotherapy Working Group



Questionnaire Part 1: Training of Allergists

1. In my country, allergology is:
   - ☐ A specialty
   - ☐ A subspecialty
   - ☐ There is no official training of allergists in my country
2. If allergology is considered a specialty in your country, the title of (pediatric) allergist is given by:
   - ☐ The university
   - ☐ The scientific society
   - ☐ Other, which? _____
3. Is there board certification of allergists in your country? Mark the most complete answer.
   - ☐ No
   - ☐ Yes, by the scientific community: it is a formality of documentation
   - ☐ Yes, by the scientific community: only those who pass an examination are certified
   - ☐ Yes, by the scientific community, with board examination and mandatory recertification every __ years
   - ☐ Yes, by another body; specify: _____

9. What kind of immunotherapy is administered in your country? (Check all that apply.)
   - ☐ Subcutaneous
   - ☐ Sublingual
   - ☐ Another, specify: _____
10. Can allergen immunotherapy be administered by a physician not specialized in allergology in your country?
    - ☐ Yes, sublingual immunotherapy and subcutaneous immunotherapy
    - ☐ Yes, but only sublingual immunotherapy
    - ☐ No, immunotherapy can be administered only by a physician specialist in allergology
11. Is there specific legislation concerning allergen immunotherapy in your country? (Check all that apply.)
    - ☐ Concerning the person who can administer allergen immunotherapy
    - ☐ With regard to standardization/potency of allergenic extracts

11 LA COUNTRIES: Argentina, Brasil, Chile, Colombia, Ecuador, Mexico, Paraguay, Peru, Dominican Rep., Uruguay, Venezuela.

New approaches for Immunotherapy

NEW INDICATIONS
- Food allergy
- Latex
- Atopic dermatitis
- Nickel?

ADMINISTRATION
- Liposomes
- Intralymphatic (ILIT)
- Epicutaneous (EPIT)
- Biolistic injection
- Mucoadhesive substances

ADJUVANTS
- Alum-alginates
- Bacterial wall derived
- DNA-adjuvants

RECOMBINANT/ ENGINEERED
- Recombinant purified
- Hypoallergenic isoforms
- Peptides
- Chimeric proteins (constructs)

GENIC VACCINATION
- c-DNA
- Plasmids
- Replicons

Sublingual immunotherapy for hazelnut food allergy: A randomized, double-blind, placebo-controlled study with a standardized hazelnut extract
Enrique E et al. JACI 2005

Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract
Fernandez-Riva, Allergy 2009

Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization.
Kim et al JACI, 2011

Oral immunotherapy for cow's milk allergy

Giovanni Passalacqua[a], *Massimo Landi*[b], *and Giovanni B. Pajno*[c]

Table 1. Clinical trials of oral desensitization for Cow milk allergy

Author (reference)	Design	Number of patients	Age range	Duration of induction	Main results
Patriarca *et al.* [27]	Open controlled nonrandomized	6 OIT 10 avoidance	3–14	12 months	Tolerance obtained in all patients.
Patriarca *et al.* [28]	Open controlled, nonrandomized	29 OIT 16 no treatment	13 adult 16 child	4 months	5 dropout; 5 discontinued for severe side effects. 19 patients achieved tolerance. Significant increase in IgG4.
Meglio *et al.* [29]	Prospective not controlled	21	6–10	6 months	15/21 full tolerance; 3/21 partial tolerance; 3 discontinued for side effects. No change in specific IgE.
Staden *et al.* [30]	Randomized open controlled	14 OIT 10 avoidance	1–13	67 days	Results not reported separately for cow's milk and egg. Overall 48% tolerant, 16% partly tolerant; 16% failure.
Martorell *et al.* [31]	Prospective not controlled	4	2–5	5 days	Full tolerance in all patients (200 ml), maintained at 3 years. Decrease in IgE and cutaneous reaction.
Morrisset *et al.* [33]	Randomized, open, controlled	30 OIT 27 avoidance	1.5–6.5	6 months	SBPCFC positive after 6 months in 11% of OIT patients and 50% of avoidance patients.
Staden *et al.* [32]	Prospective not controlled	9	3–10	3–7 days	6/9 full tolerance (120 ml); 3/9 partial tolerance limited by side effects.
Longo *et al.* [34]	Randomized, open, controlled	30 OIT 30 avoidance	5–17	10 days (hospital) + 3 months (home)	11/30 full tolerance (150 ml); 16/30 partial tolerance (5–150 ml); 3 discontinued for persistent side effects. Significant difference between groups at the DBPCFC.
Skripak *et al.* [35]	Randomized, DBPC	13 OIT 7 placebo	6–21	23 weeks	Significant increase in the threshold dose of cow's milk protein (40 vs. 8,140 mg) after OIT. No change in placebo group. Increase in IgG4.
Zapatero *et al.* [36]	Prospective	18	4–8	10–32 weeks	16/18 full tolerance (200 ml); 1 /18 partial tolerance; 1 dropout. Decrease cutaneous reaction.
Pajno *et al.* [37▪▪]	Randomized, SB controlled	15 OIT 15 soy milk	4–10	18 weeks	2/15 dropout; 2/13 failed for side effects; 1/15 partial tolerance; 10/15 full tolerance. Significant increase in IgG4.
Kaneko *et al.* [38]	Prospective not controlled	10	4–14	200 days	8/10 full tolerance (250 ml), 2 stopped due to side effects.
Martorell *et al.* [39▪]	Randomized, open controlled	30 OIT 30 avoidance	2–3	1 year	Full tolerance in 90% OIT patients vs. 23% in controls. Significant decrease IgE.

DBPCFC, double blind placebo controlled food challenge; DBPC, double blind placebo controlled; OIT, oral immunotherapy; SDBPCFC, single double blind placebo controlled food challenge.

EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy

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Clinical and Translational Allergy

We call upon Europe's policy-makers to coordinate actions and improve individual and public health in allergy by:

- Promoting awareness of the effectiveness of allergen specific immunotherapy
- Updating national healthcare policies to support allergen specific immunotherapy
- Prioritising funding for allergen specific immunotherapy research
- Monitoring the macroeconomic and health economic parameters of allergy
- Reinforcing allergy teaching in medical disciplines and specialties

The unsustainability of allergy's current symptomatic treatments

What allergen specific immunotherapy can achieve

The promise for a cure and the role of allergen specific immunotherapy

Major milestones for allergen specific immunotherapy

Major bottlenecks for further diffusion of allergen specific immunotherapy

Promoting allergen specific immunotherapy awareness

Update national healthcare policies to support allergen specific immunotherapy

Prioritize funding for allergen specific immunotherapy research

Thank you !!!

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