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IMMUNOTHERAPY:

WHAT IS THE PREFERABLE ROUTE?

DISCLOSURE

- © Dr Larenas has received speaker's fees from Merck-Sharp-Dôhme, Astra-Zeneca, Pfizer, Novartis, MEDA; Travel grants from Sanofi, Novartis, UCB, MSD, Astrazeneca, Pfizer, Senosiain and is member of the advisory board of Pfizer, Novartis, MEDA.

WHAT IS THE PREFERABLE ROUTE?

- ⊙ Safety
- ⊙ Efficacy
 - ⊙ In trials:
Efficacy demonstrated per allergen and per allergic disease
 - ⊙ In real life:
 - Correct diagnosis
 - Adherence ~ Patient's preference
 - Long-term efficacy
 - Mono-multi allergic patients
- ⊙ Example case

SAFETY OF IMMUNOTHERAPY: CONTRAINDICATIONS

SAFETY SLIT

- ⊙ No fatalities
- ⊙ Several anaphylactic reactions (8 in total)
- ⊙ Eosinophilic esophagitis (1 report grass pollen SLIT)
 - ⊙ Hsieh, F. H. (2014). "**Oral food immunotherapy** and iatrogenic eosinophilic esophagitis: an acceptable level of risk?" Ann Allergy Asthma Immunol **113**(6): 581-582.
 - ⊙ Metanalysis: 2.7% in oral food immunotherapy.
Lucendo, A. J., et al. (2014). "Relation between eosinophilic esophagitis and **oral immunotherapy for food** allergy: a systematic review with meta-analysis." Ann Allergy Asthma Immunol **113**(6): 624-629
 - ⊙ Miehleke, S., et al. (2013). "Induction of eosinophilic esophagitis by sublingual **pollen immunotherapy**." Case Rep Gastroenterol **7**(3): 363-368.

SAFETY SCIT

- ◎ US surveillance study (Bernstein et al.):
 - ◎ 1 fatality 2008-2012
1/23.3 million injection visits
 - ◎ Very severe, WAO grade 4, SRs (near-fatal reactions)
1/1,000,000 injections
- ◎ No fatalities officially reported in rest of the world
- ◎ AAAAI members survey on SCIT under special medical conditions: contraindications or not (N = 1085)

Epstein, T. G., et al. (2014). "AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions." J Allergy Clin Immunol Pract **2**(2): 161-167

SURVEY AAAAI MEMBERSHIP 2012-13

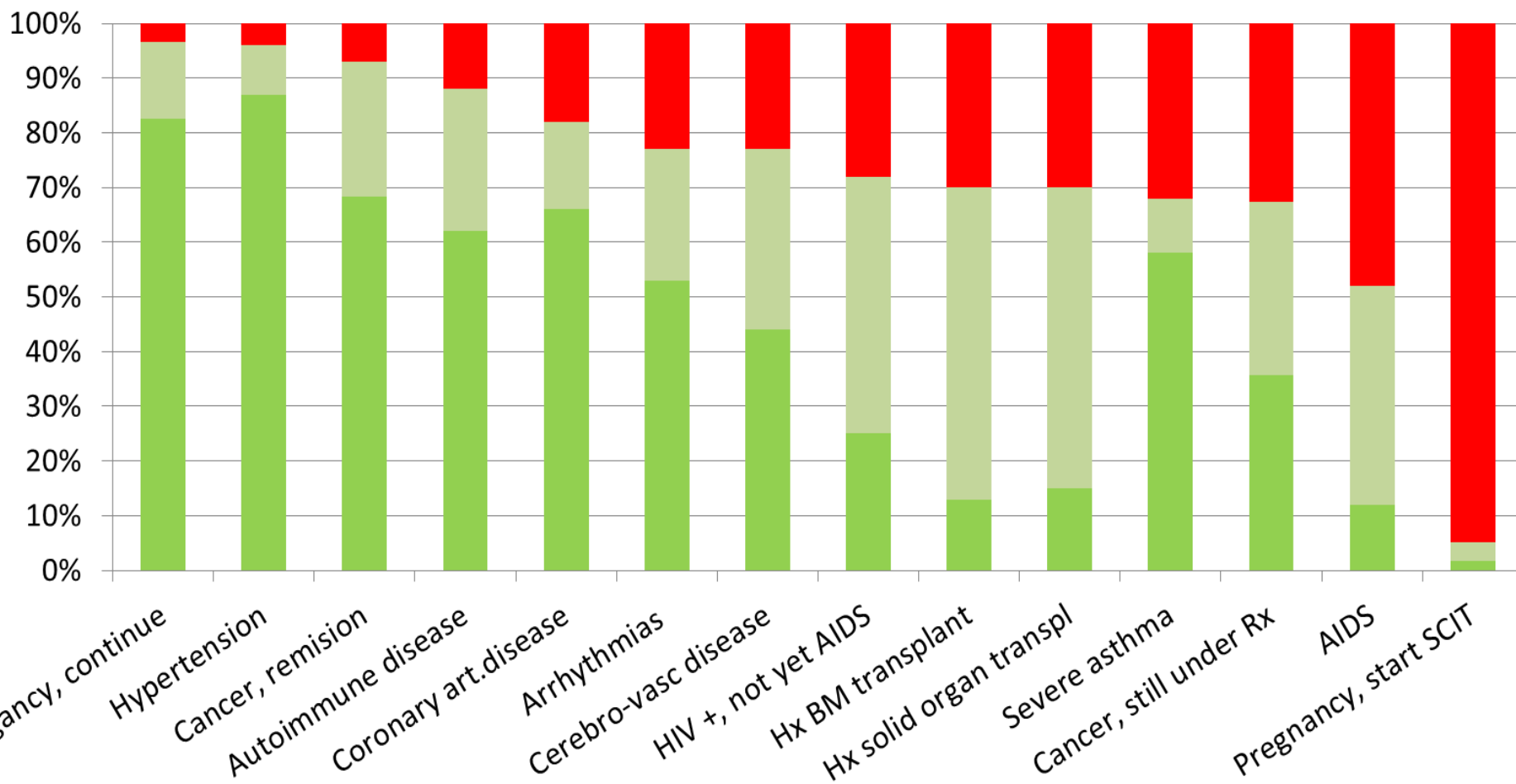
- ⊙ 21% response rate (1085 AAAAI members)
- ⊙ Expresses their experience with immunotherapy patients
- ⊙ CAVE: Recall bias

In allergic patients with certain medical conditions:

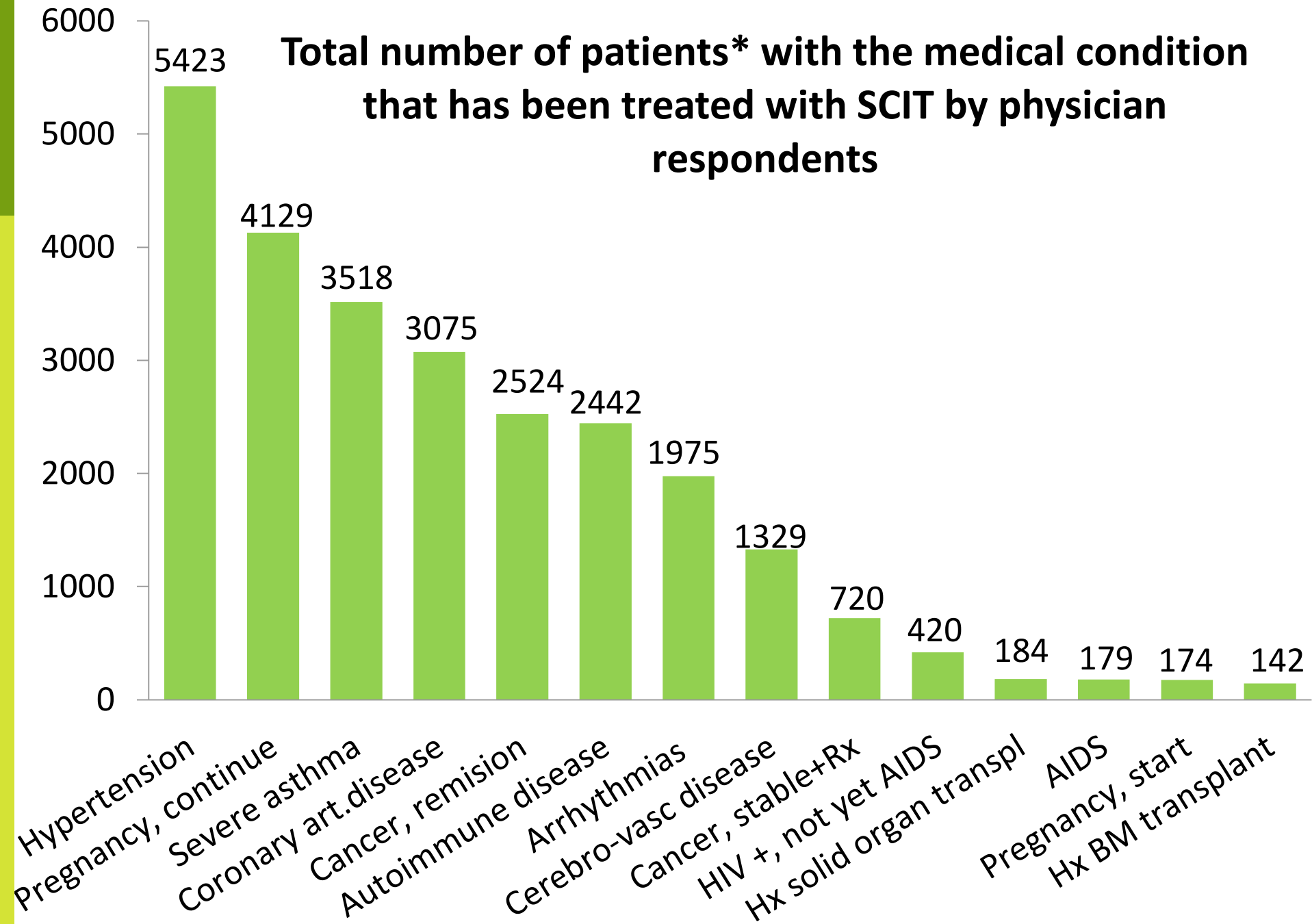
1. Do you think immunotherapy is contra-indicated?
2. What has been your experience in giving AIT to these patients?

Practicing allergists respondents that have treated, would treat or believe below conditions are a contraindication for Allergen Immunotherapy

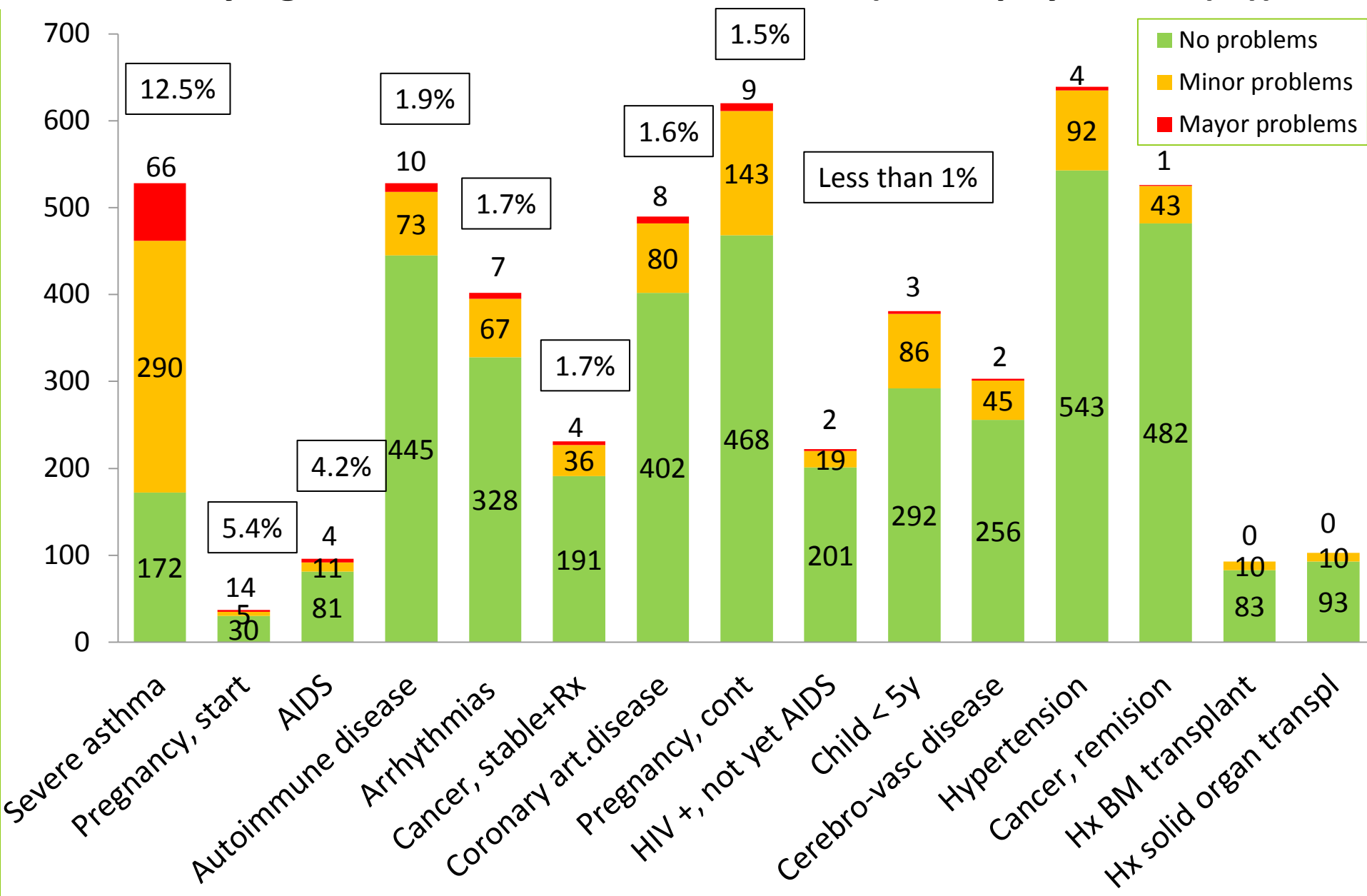
- % who thinks AIT is contraindicated in this condition
- % that would treat, but has not had any patient with the condition yet
- % that has treated patients with the medical condition



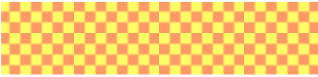




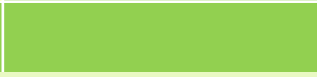
Total number of patients* with the medical condition that has been treated with SCIT by physician respondents



Experience of those respondents giving SCIT to patients with an underlying medical condition: outcomes (Nr. of physicians (%))



SAFETY

		SCIT	SLIT
Age	3+ year		
	4+ years		
	5+ years		

EFFICACY: THE TRIALS

EVIDENCE OF EFFICACY

- ➡ ◎ Dose finding studies
- ➡ ◎ Cochrane metanalysis
- ➡ ◎ Metanalysis
- ➡ ◎ Systematic reviews
- ◎ Double-blind placebo controlled trial(s)
- ◎ Open, randomized trial(s)
- ◎ Open trial(s)

Dose-effect proven: Included studies

Author	Primary Disease	Publ year	
Johnstone, multi	Asthma	1961	SCIT
Haugaard, HDM	Asthma	1993	
Olaguibel, HDM	Asthma	1997	
Franklin, ragweed	Rhinitis	1967	
Creticos, ragweed	Rhinitis	1989	
Frew, grass	Rhinitis	2006	
Ewbank, cat	Cat allergy	2003	
Nanda, cat	Cat allergy	2004	
Lent, dog	Dog allergy	2006	
Valovirta, tree	Rhinitis	2006	SLIT
Durham, grass	Rhinitis	2006	
Didier, grass	Rhinitis	2007	
Skoner, ragweed	Rhinitis	2010	

**HDM tablet: Bergmann 2013 (Stallergènes), Mosbech 2014 (ALK)
Ragweed Tablet: Creticos 2014 (ALK)**

- Calderon, M. A., Larenas-Linnemann D, et al. (2011). "EAACI TF on 'dose-response relationship in allergen-specific immunotherapy'." Allergy 66(10): 1345-1359.

Allergic rhinitis

SCIT (seasonal)

Allergen injection immunotherapy for seasonal allergic rhinitis (Review)

Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S

SMD symptoms: -0.73
SMD medication: -0.57



THE COCHRANE
COLLABORATION®

SLIT

REVIEW ARTICLE

Systematic reviews of sublingual immunotherapy (SLIT)

S. Radulovic¹, D. Wilson², M. Calderon³ & S. Durham³

¹Paediatric Allergy, King's College, London; ²Selly Oak Hospital, University of Birmingham; ³Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

SMD symptoms: -0.49
SMD medication: -0.32

To cite this article: Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; DOI: 10.1111/j.1398-9995.2011.02583.x.



THE COCHRANE
COLLABORATION®

- Systematic review of SLIT in children, quality of evidence evaluated with GRADE. Effect depends on allergen. Larenas Linnemann et al. *Annals AA&I* 2013.
- Lin et al. *JAMA* 2013: Decreases rhinitis symptoms (moderate evidence)

Allergic asthma

SCIT

[Intervention Review]

Injection allergen immunotherapy for asthma

Michael J Abramson¹, Robert M Puy², John M Weiner³

¹Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia. ²Department of Allergy, Immunology & Respiratory Medicine, The Alfred, Melbourne, Australia. ³AllergyNet Australia, Melbourne, Australia



NNT symptom: 3
NNT medication: 4

SLIT

1. Mosbech L, et al. SLIT: 111. 2010. PMID: 1116. ... nt

REVIEW ARTICLE

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GRADE:
...ined.



a medication use

DBPC big trials: HDM tablets: moderate statistically significant reduction in the ICS dose required to maintain asthma control. *Mosbech JACI 2014, Bergmann JACI 2013*

Allergic Conjunctivitis

SCIT

DBPC

SLIT

[Intervention Review]

SLIT for allergic conjunctivitis: Cochrane systematic review and meta-analysis.

Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR.
Clin Exp Allergy. 2011 Sep;41(9):1263-72

SMD symptoms: -0.41
SMD medication: -0.10 NS



Systematic review classifying evidence according to risk of bias:
Lin et al. JAMA 2013: Decreases conjunctivitis symptoms (moderate evidence)

Atopic Dermatitis

SCIT

Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials.

'SCIT has a significant positive effect on DA: NNT 3. Moderate-level evidence for the efficacy of SCIT against atopic dermatitis.'

Bae JM, Choi YY, Park CO, Chung KY, Lee KH. J Allergy Clin Immunol. 2013 Jul;132(1):110-7.

SLIT

DBPC

Venom immunotherapy

SCIT

[Intervention Review]

Venom immunotherapy for preventing allergic reactions to insect stings

Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M, Oude Elberink JN.

Cochrane Database Syst Rev. 2012 Oct 17;10:CD008838



SLIT

DBPC: large local reactions

		SCIT		SLIT	
Efficacy		Sx	Med	Sx	Med
Pathology	ARhinitis	Green	Green	Green	Green
	Asthma	Green	Green	Yellow	Checkered
	AConjunctivitis			Yellow	Orange
	Atopic dermatitis	Side effects		Yellow	
	Hymenoptera	Green		Only for large local reactions	

SCIT vs SLIT indirect comparison

- Both treatments are effective
- Trend in favor of SCIT, but NS

*Dretzke, J., et al. (2013). "Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison." J Allergy Clin Immunol **131**(5): 1361-1366.*

EFFICACY: REAL LIFE

Adherence

Long term

Mono-multi

SLIT is not SLIT

Real life: Adherence

- Dutch study: Adherence in real life (pharmacy data):
18% finishes 3 years. Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively (P < .001).
Kiel MA, et al. Allergy Clin Immunol 132(2): 353-360 e352.
- Miami: low adherence for SCIT
*Hankin et al. J Allergy Clin Immunol **127**(1): 46-48, 48 e41-43.*
- Anolik in US
*Anolik, R., et al. (2013). "Persistence with Specific Immunotherapy (SCIT & SLIT) Among AR Patients in A US Allergy Practice." J Allergy Clin Immunol **131**(2, suppl): AB186.*

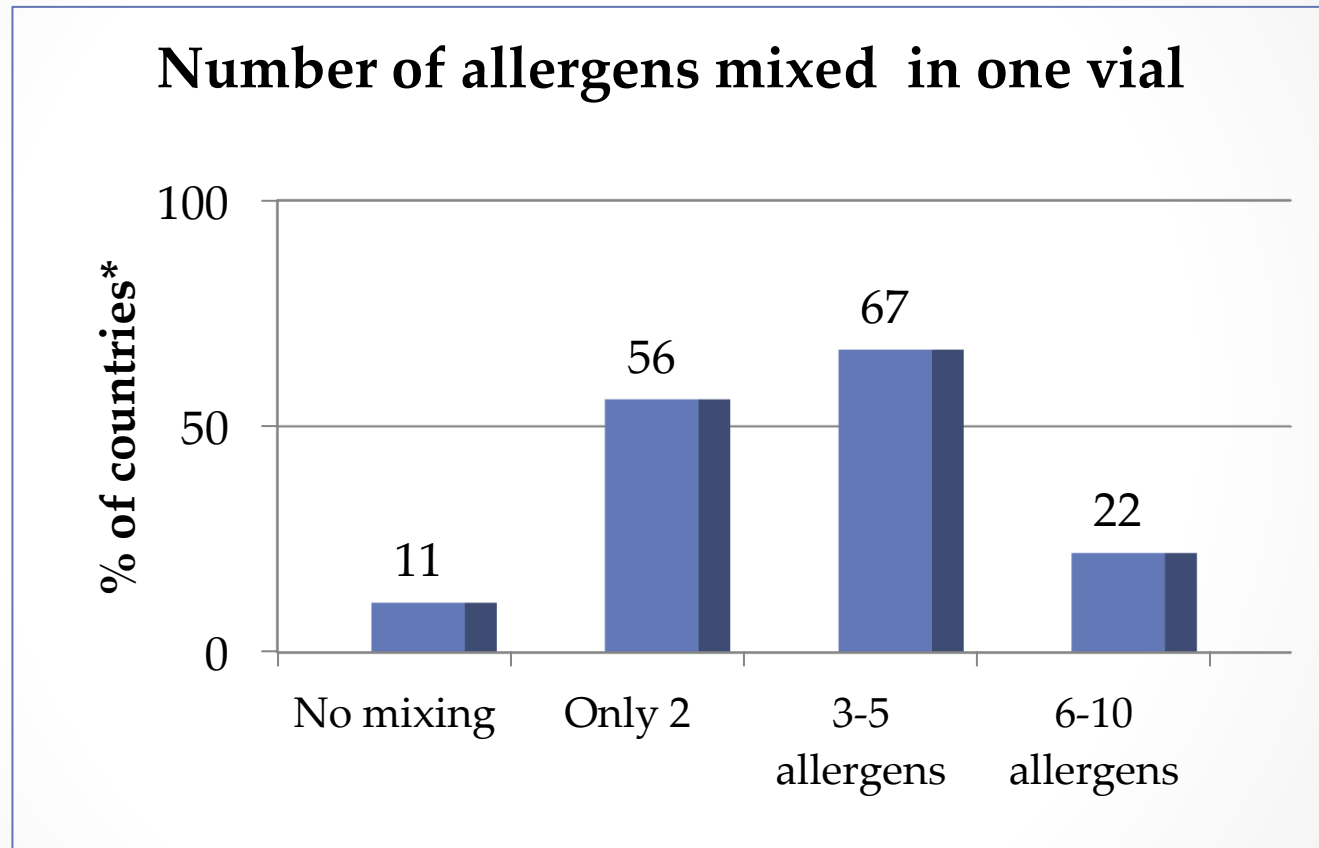
Real life: Long term efficacy

- SCIT: 7 years
 - Randomized, controlled
Jacobsen 2007
- SCIT 12 years
 - Open controlled
Eng 2008
- SLIT: 2 years
 - DBPC
Durham 2012, Didier 2013
- SLIT: 6 years (metacholine), 7-8y symptoms:
 - Retrospective: Depends on duration of SLIT: 7-8 years only after 4 years SLIT
Marogna Int Arch Allergy Immunol 2007

Real life: SLIT: Mono-Multi issues

1. Does mono-allergen SLIT work in multi-sensitized patients?
2. Is mono-allergen SLIT safe in multi-sensitized patients? (pollen)
3. Does duo-allergen SLIT work in duo-allergic patients?
4. Does multi-allergen SLIT work in allergic patients?

Number of allergens mixed in one vial: Latin American countries

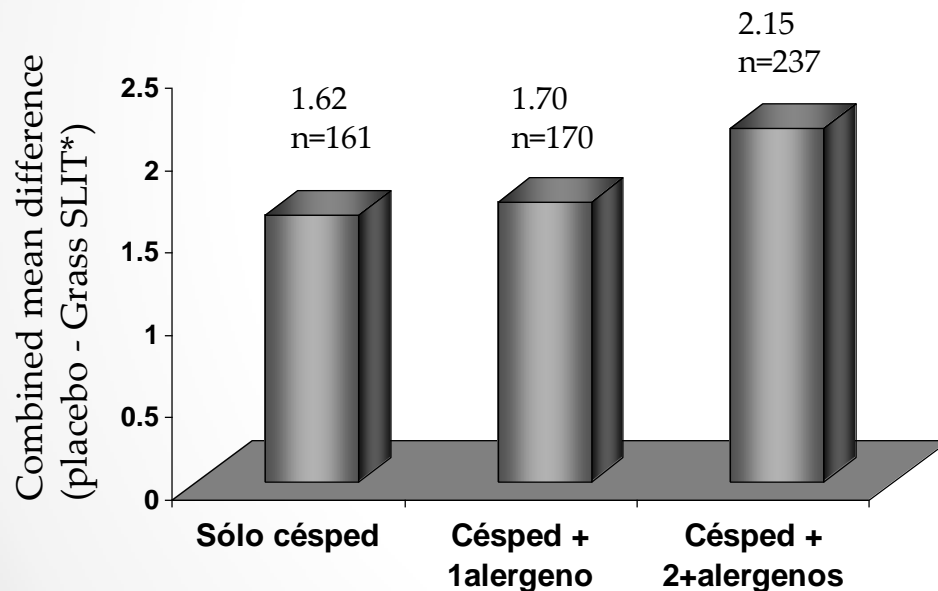


* In some countries several answers were given by respondents, we scored them all

Baena-Cagnani, C. E., Larenas-Linnemann D, et al. (2013). "Allergy training and immunotherapy in Latin America: results of a regional overview." *Ann Allergy Asthma Immunol* **111**(5): 415-419 e411.

Efficacy Grazax® in Mono vs. sensitized: Difference in sympt-medication scores (mean)

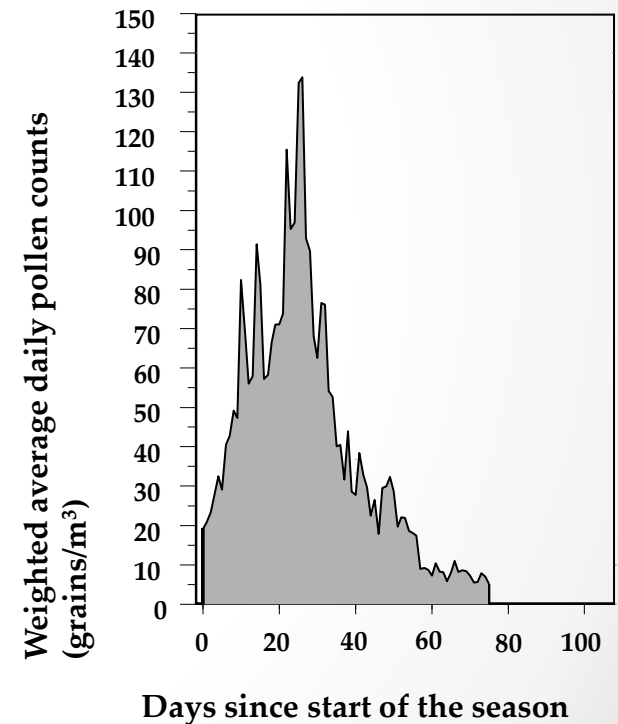
Mean combined difference
grass SLIT vs. placebo



*75,000 SQ-T/2,800 BAU *Phleum pratense*, ALK-Abelló

* Percentage reduction rounded to 1 d.p

2005 pollen season

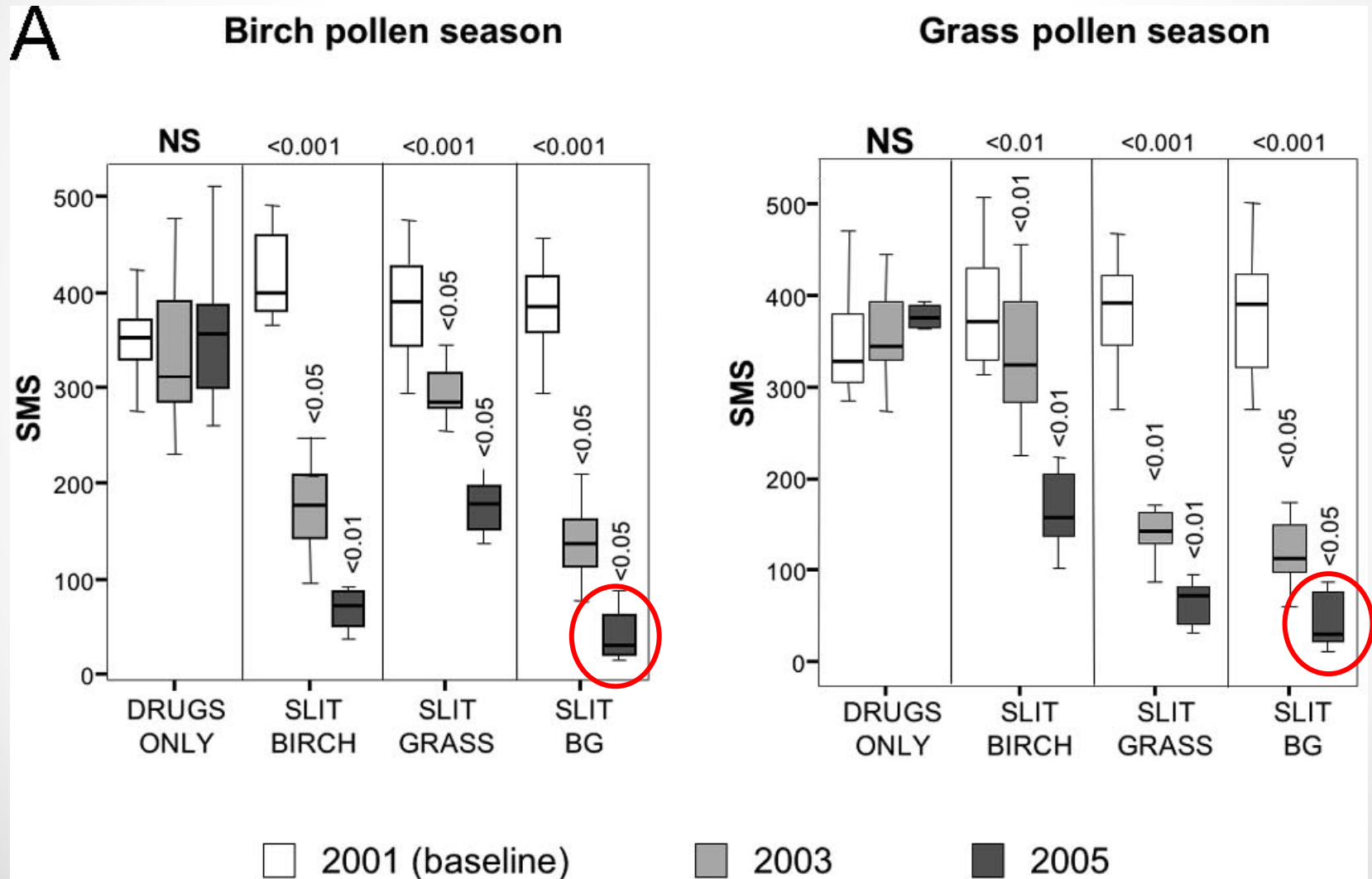


Subjects with SLIT presenting treatment related adverse events: no differences between the mono- vs polysensitized

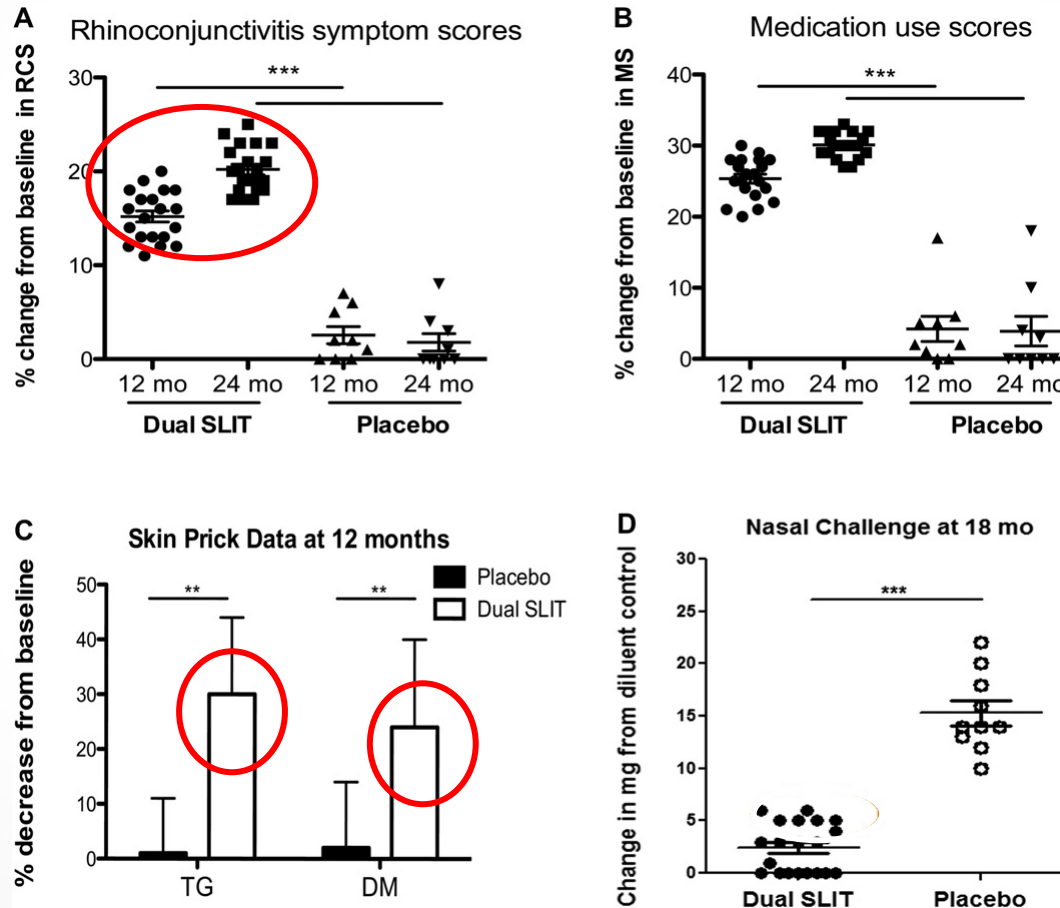
	Pollen sensitization type			
	One grass	Grass + 1 allergen	Grass + 2 or more allergens	
Treatment	Grass SLIT	Grass SLIT	Grass SLIT	P-value**
TEAE: Sí No	74 17	79 11	112 23	0.7159
Relación c/ Tx: Sí No	63 28	71 19	103 32	0.2720
Prurito oral: Sí No	41 50	43 47	61 74	0.3191
Nasofaringitis No	14 77	16 74	17 118	0.9985
Edema boca: Sí No	13 78	17 73	28 107	0.5030
Influenza: Sí No	7 84	3 87	13 122	0.4260
Prurito oído: Sí No	16 75	12 78	10 125	0.2303
Irritación garganta: Sí No	9 82	9 81	12 123	0.3413
Cefalea: Sí No	4 87	1 89	4 131	0.4304

Dual SLIT in dual-allergics

SLIT Birch only / grass only / Birch + grass



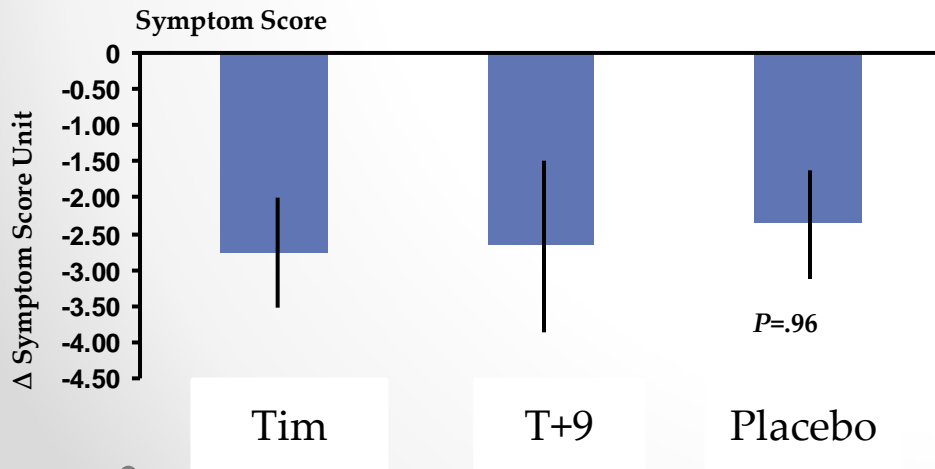
Dual grass-HDM SLIT drops reduces symptoms, medication and improves SPT and nasal challenge



Swamy, R. S., et al. (2012). "Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy." *J Allergy Clin Immunol* **130**(1): 215-224 e217

Multi-mix SLIT: The Amar-Nelson Study

	Symptoms	Medication	Nasal provocation	Titrated SPT	Specific IgE	Specific IgG ₄
Tim	NS	NS				
Tim+9	NS	NS				
Placebo	NS	NS				



SLIT : Mono-Multi issues

Yes

Does mono-allergen SLIT work in multi-sensitized patients?

Yes

Is mono-allergen SLIT safe in multi-sensitized patients?

(pollen)

Yes

Does duo-allergen SLIT work in duo-allergic patients?

Less

Does multi-allergen SLIT work in allergic patients?

SLIT IS NOT SLIT

Quantity

Concentration

'Device'

Relative monthly SLIT doses

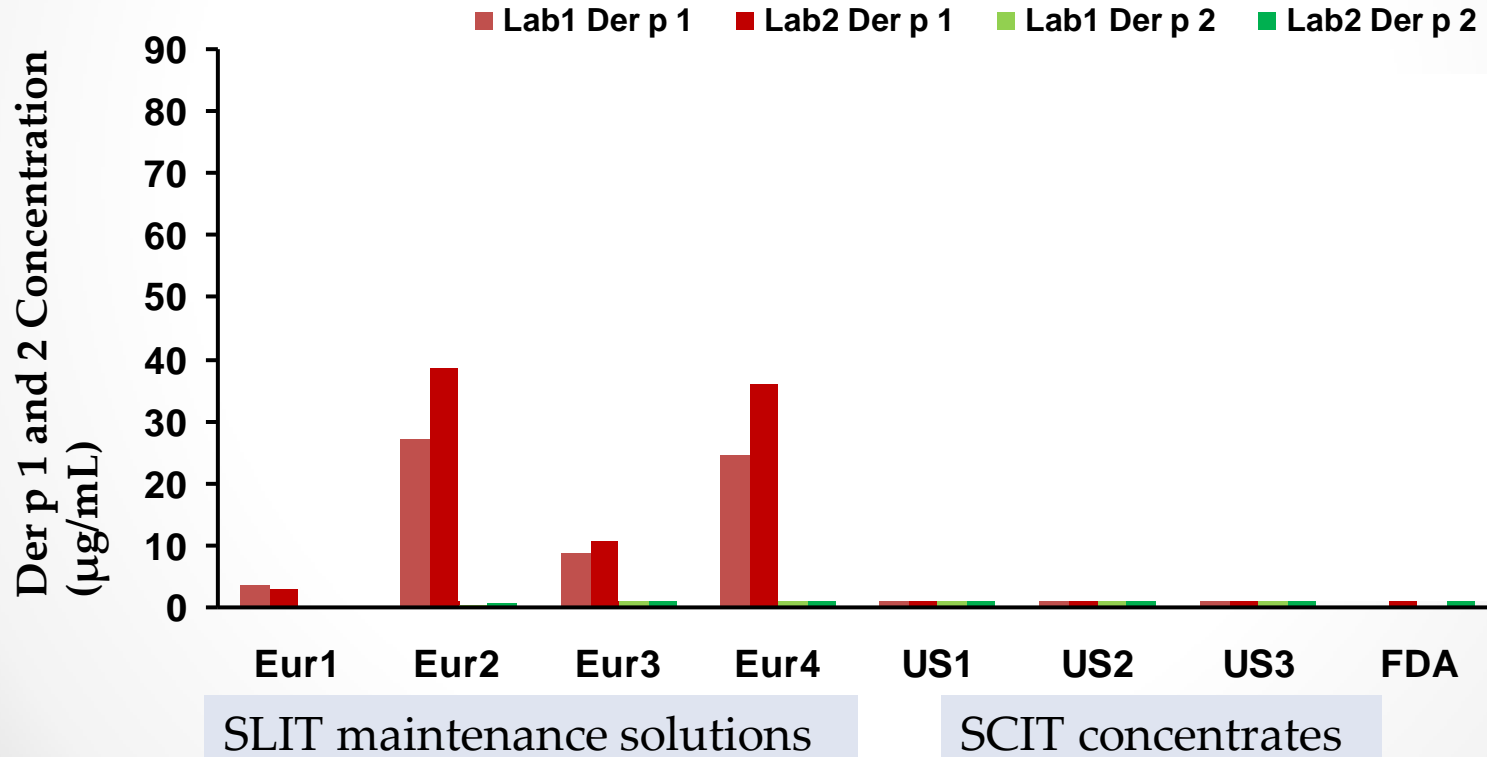
Monthly doses of SLIT maintenance therapy given with the products of four prominent European manufacturers, relative to the US recommended SCIT monthly maintenance dose*

Manufacturers	<i>D pteronyssinus</i>	
Eur1	1	
Eur2	1	
Eur3	3	
Eur4	16	

* Monthly probably effective doses recommended in US for SCIT are given a relative value of 1. For house dust mite 1 = 1000AU, timothy grass pollen 1 = 2000BAU, cat 1 = 3.8 Fel d 1 Units and Short Ragweed pollen 1 = 9 Amb a 1 Units.(2)

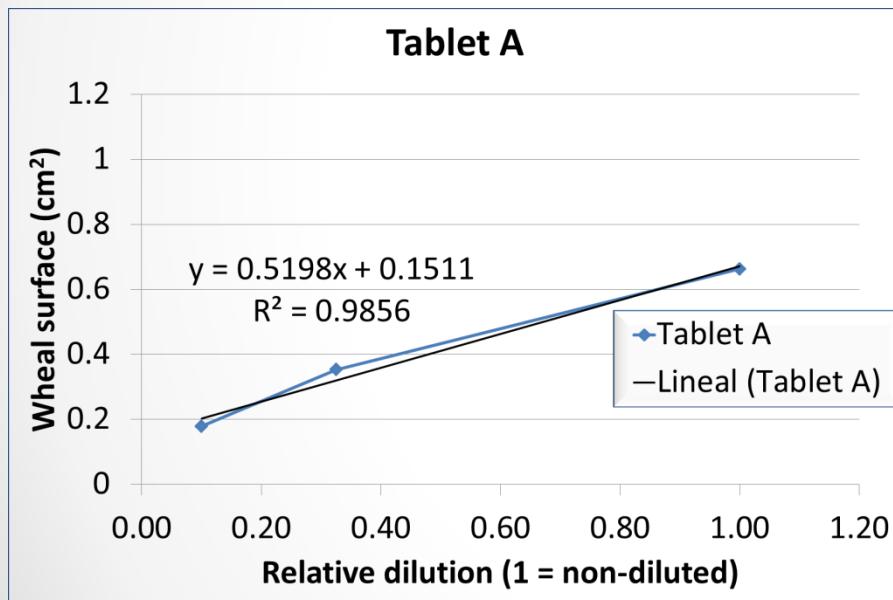
Diferente composición extractos de ácaros: EEUU y Europea

Content of major allergens Der p 1 and Der p 2

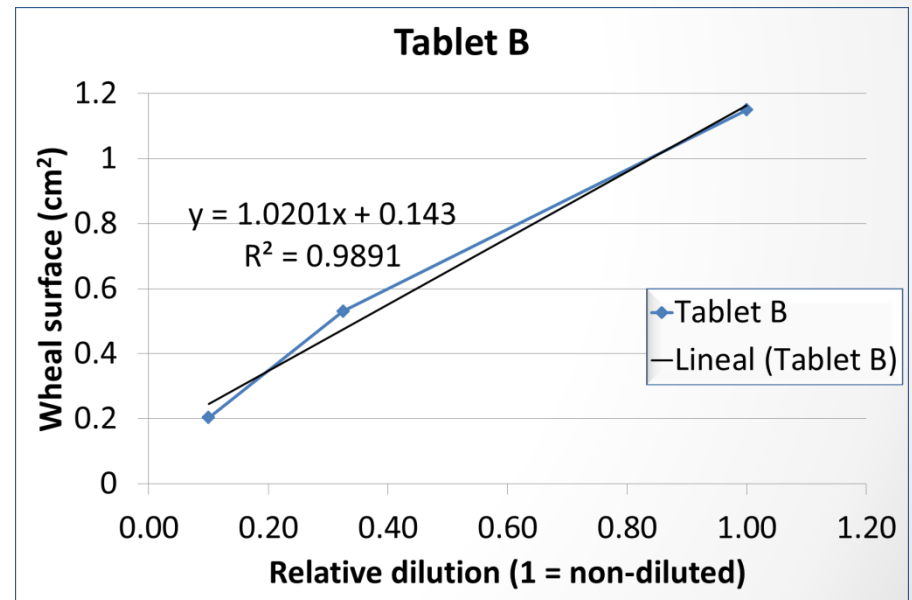


Relative potency (BAU) of grass Tablets

- Grazax® 2.800 BAU
- 10.000 BAU *Phleum pratense* 1.56cm² wheal surface.
- Tablets wheal surfaces correspond with 4.200 – 7.300 BAU



4.200BAU



7.300 BAU

WHAT IS THE PREFERABLE ROUTE? DEPENDS ON:

- ⊙ Correct diagnosis: which allergens?
- ⊙ Availability of quality products
 - ⊙ SCIT standardized, where possible
 - ⊙ SLIT: high local concentration
 - ⊙ Multi-allergic: SCIT might be preferable
- ⊙ Allergic disease:
SCIT/SLIT have different efficacy and safety profiles
- ⊙ (Age of the patient)
- ⊙ Logistics and Preference of the patient: ADHERENCE

COOPERATION

US

Latin-America



Far-East

Europe

EXAMPLE CASE



- ⊙ France: 57yo female with allergic rhinitis symptoms all year long, exacerbating in spring, when she cleans the dusty environment and in her daughter's home where there is a cat. She does not want to take so much medication any more.
- ⊙ SPT positive for *D farinae*, cat, *Alternaria* and *Dactylis glomerata* and *Phleum pratense*.
- ⊙ Would you give Immunotherapy?
- ⊙ SCIT or SLIT?
- ⊙ If SLIT: drops or tablets, mono or multi?

