ACCELERATED IMMUNOTHERAPY "Convenience & Safety"

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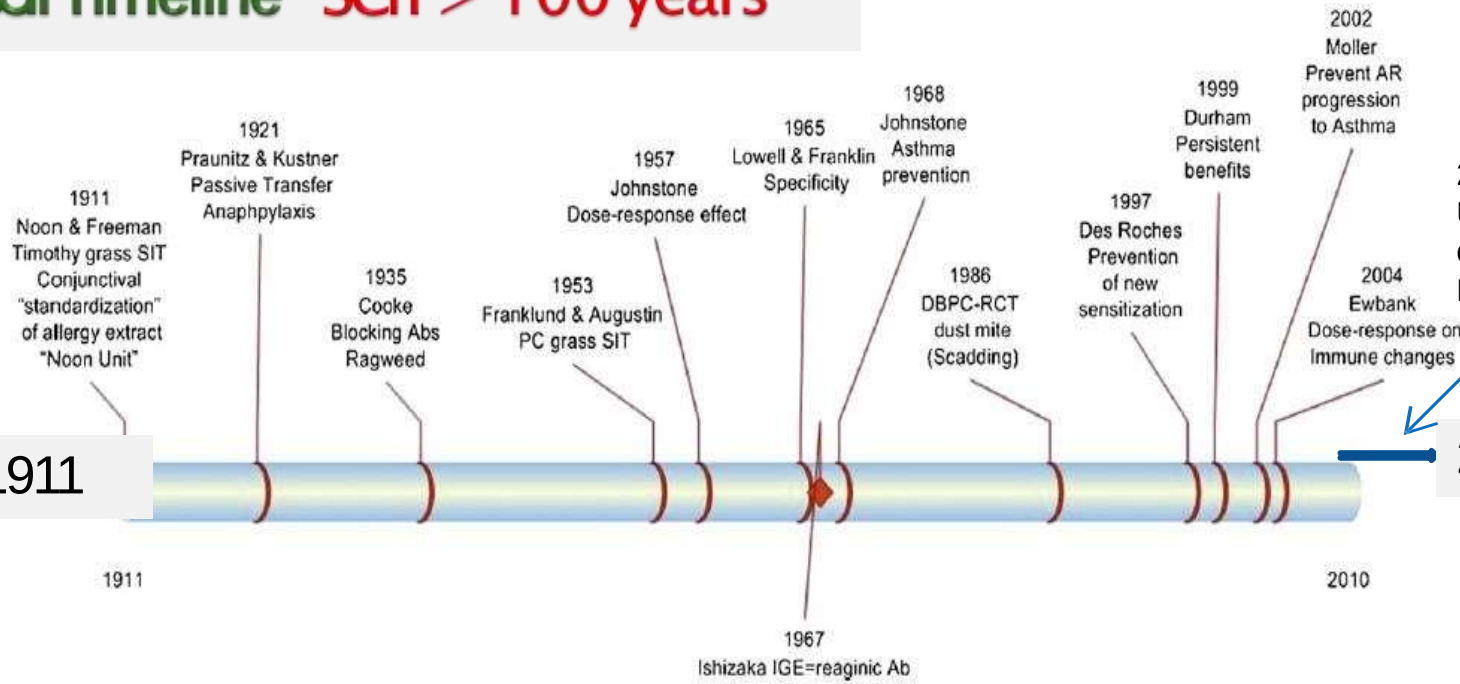
Why do Allergists Love IT?

- Subcutaneous immunotherapy (SCIT) has been used for over 100 years
- Well documented efficacy for AR and asthma secondary to pollens, HDM, and cat

- What are the **benefits** of SCIT?
  - **Relieves symptoms (⇩ progression)**
  - **Has disease-modifying effects (persistent)**
  - **May prevent new sensitization and asthma**

SCIT Timeline SCIT > 100 years



Start date 1911

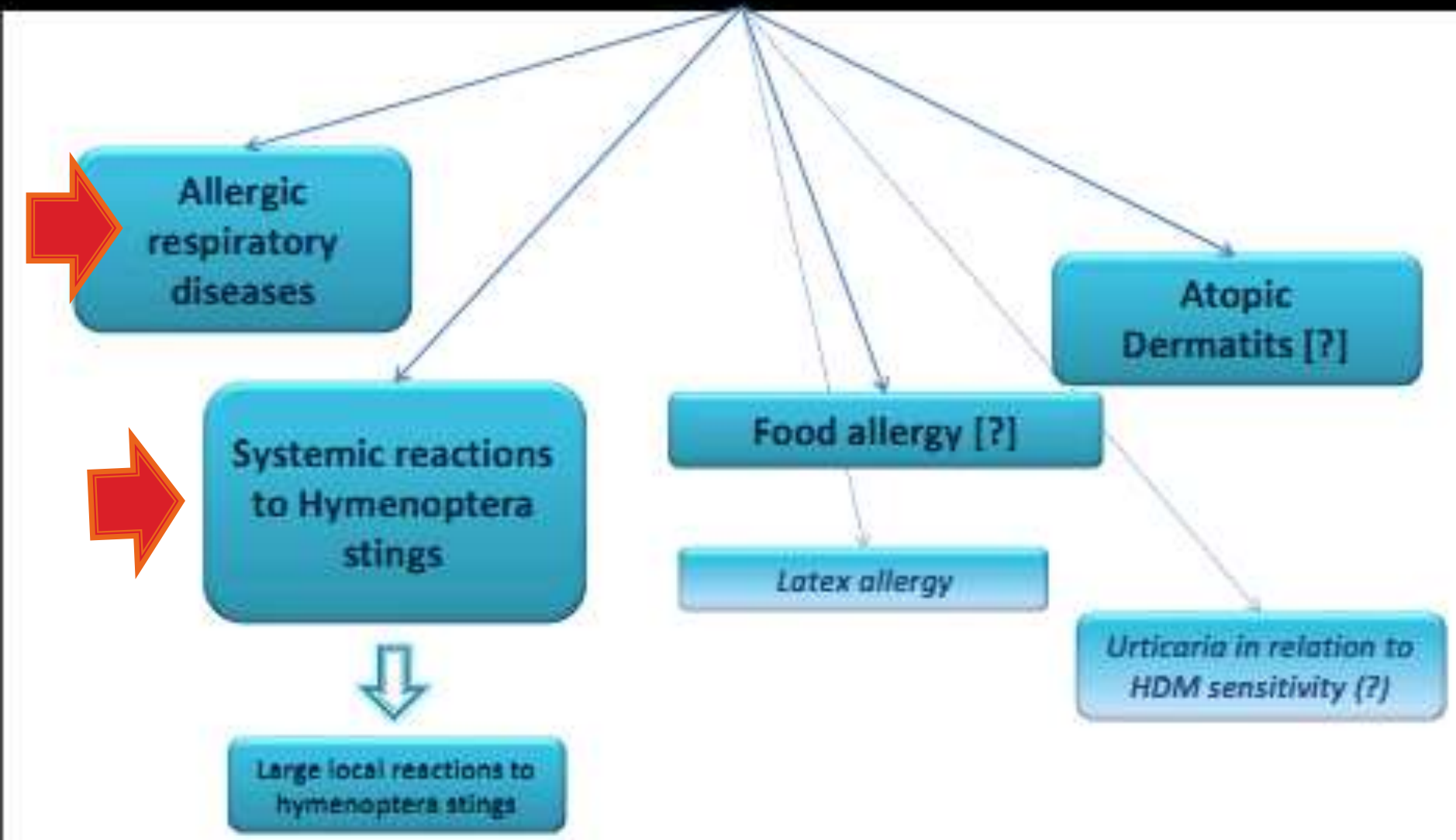
SCIT is only disease modifying treatment for allergic respiratory disease

- Can provide sustained clinical benefits after discontinuation
- Prevent new allergy sensitivities
- Prevent asthma
- **Is cost-effective** –studies have demonstrated **30 to 80%** cost-savings compared to pharmacotherapy alone

Then why look for alternative approaches??

Cox L, Wallace D. Specific allergy immunotherapy for allergic rhinitis: subcutaneous and sublingual. Immunol Allergy Clin North Am. 2011;31(3):561-99.

Indications of Immunotherapy



Safety & Efficacy: But effective dose–may vary by extract and formulation

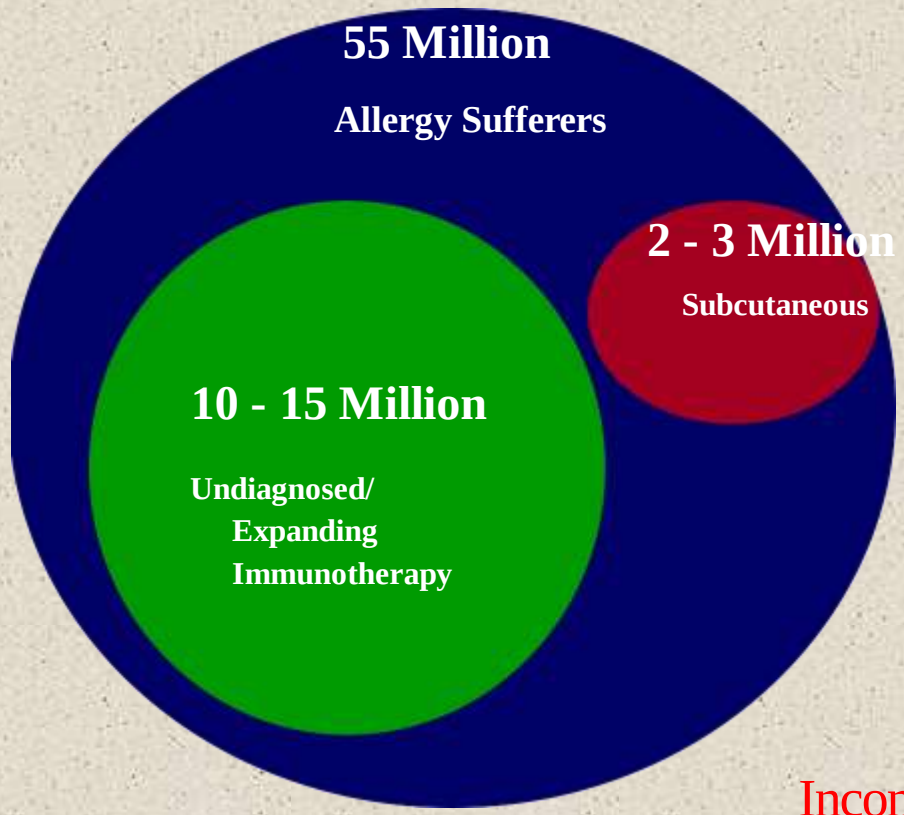
- Grass
- Dust mite
- Cat
- Ragweed
- Cockroach
- *Alternaria*
- Trees

Reality of SCIT

- Only 2% to 9% of US patients, and 4% of Canadians with AR receive SCIT, and many stop it prematurely because of frequent office visits and the 30 minute wait time after injections[1,2]
- Systemic allergic reactions occur in about 5%
- Small risk of death (1/2.5 million injections) but recent 3 year survey of 25 million showed no fatalities

1. Hankin CS. J Allergy Clin Immunol. 2013;131:1084-91.
2. Hsu NM, Reisacher WR. Int Forum Allergy Rhinol. 2012;2:280-4
3. Bernstein DI et al. *J Allergy Clin Immunol* 2004;113:1129-36

Reality of SCIT (Immunotherapy)



Cons

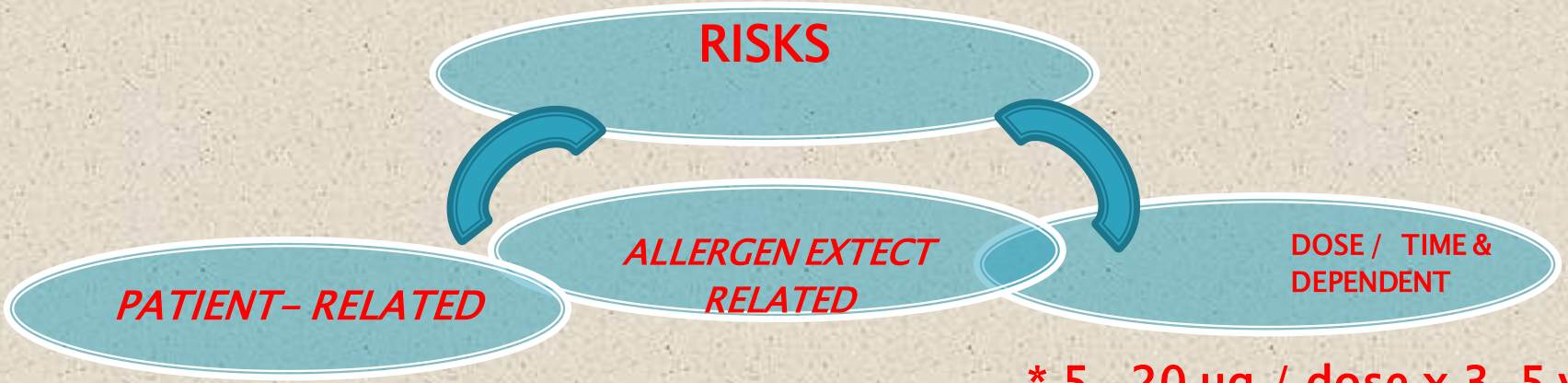
Pros/benefits

Inconvenience/patient time, cost, safety

Reduced symptom & medication scores, long term remission, prevention from disease progression

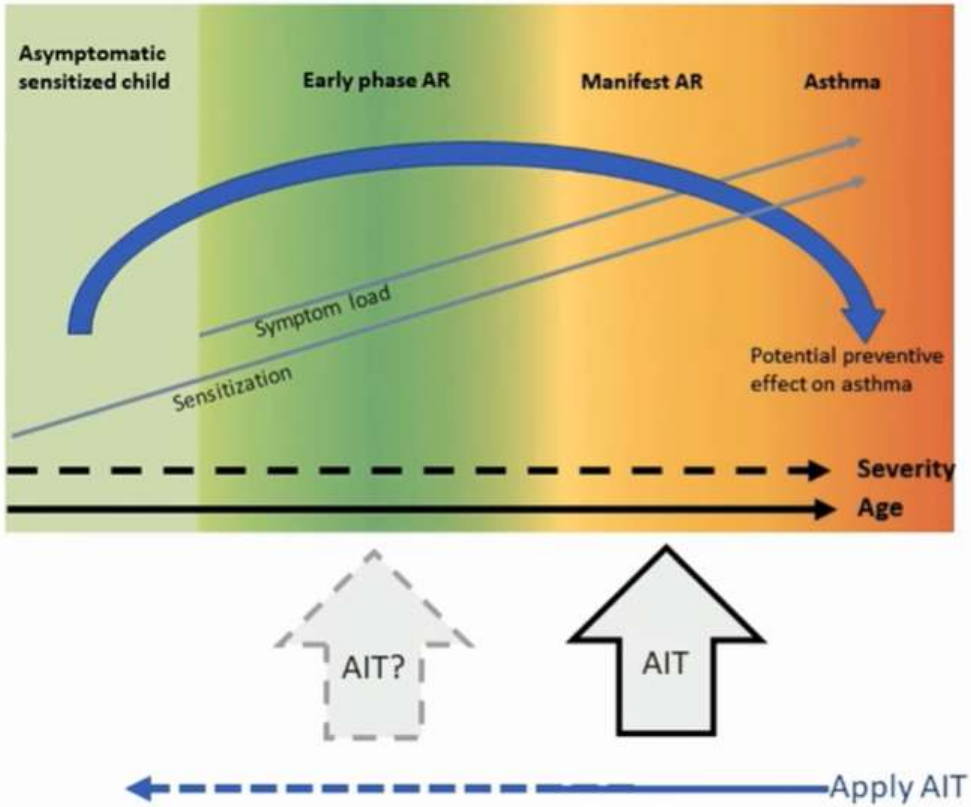
ACAAI eNews

Inconvenience due to the **time involved** in receiving allergen IT injections in a medically supervised setting is likely the reason for the low utilization of SCIT.



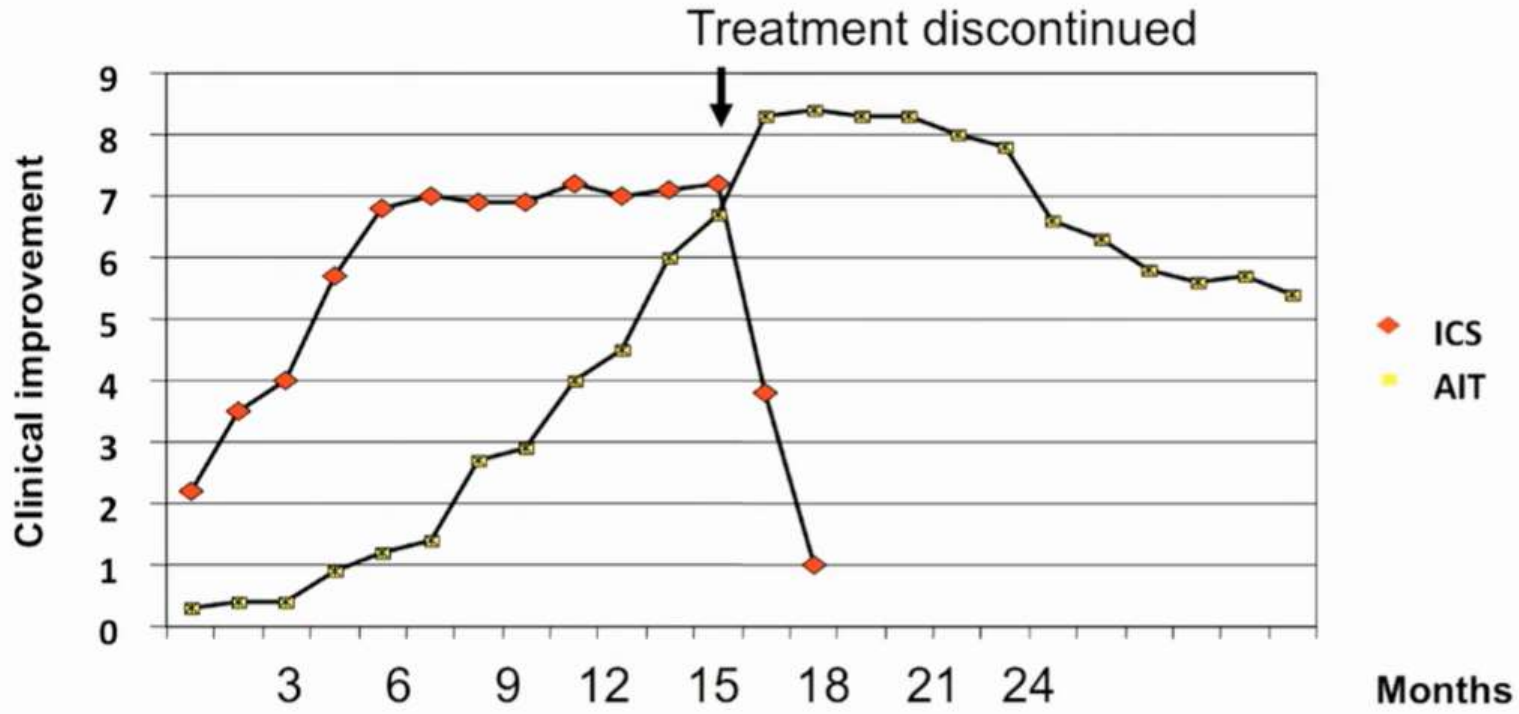
1 AIT and its preventing effect on asthma

The window of opportunity



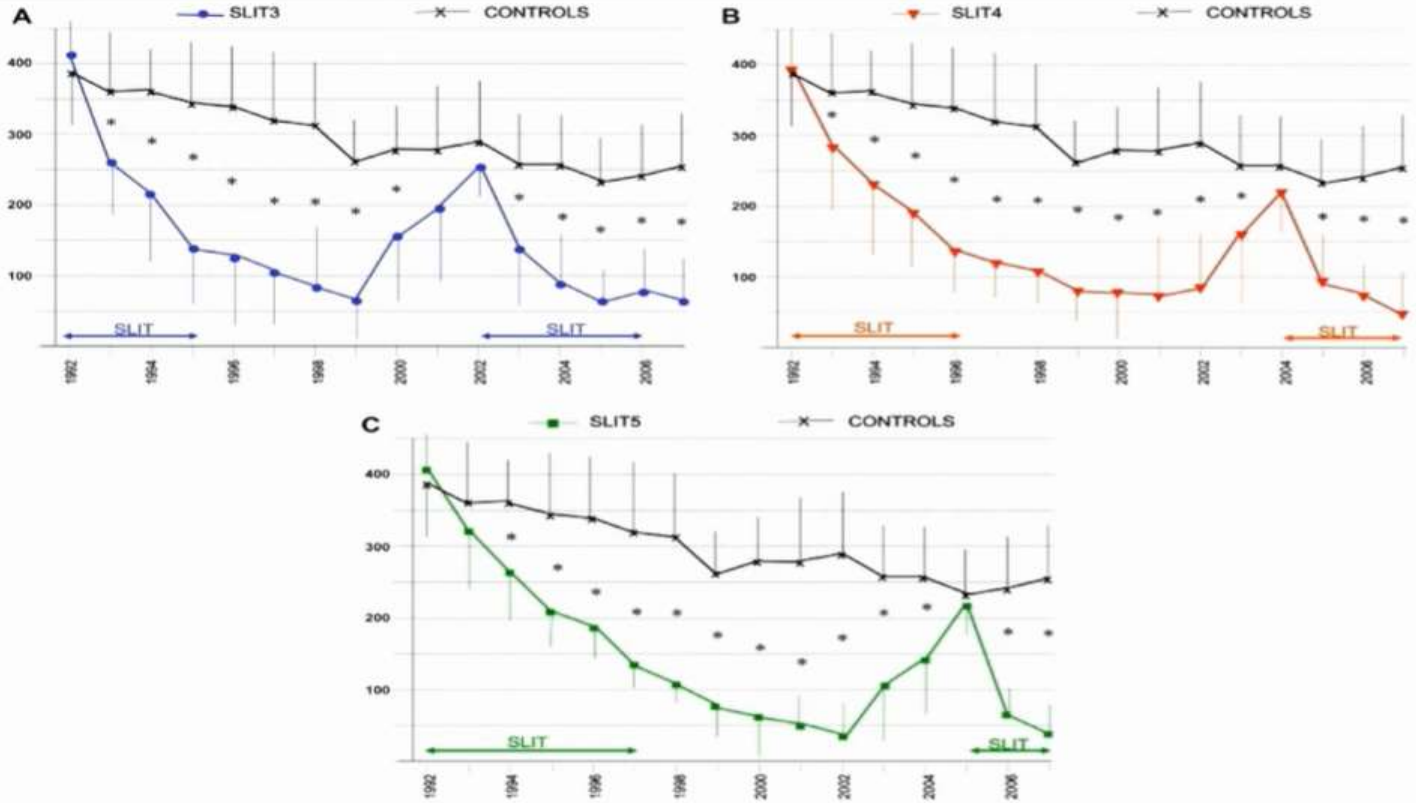
Gradman J, Halken S - J Allergy Clin Immunol Pract 2021

2 AIT and its long-lasting effect on asthma



Shaikh WA et al. – Clin Exp Allergy 1997

2 AIT and its long-lasting effect on asthma

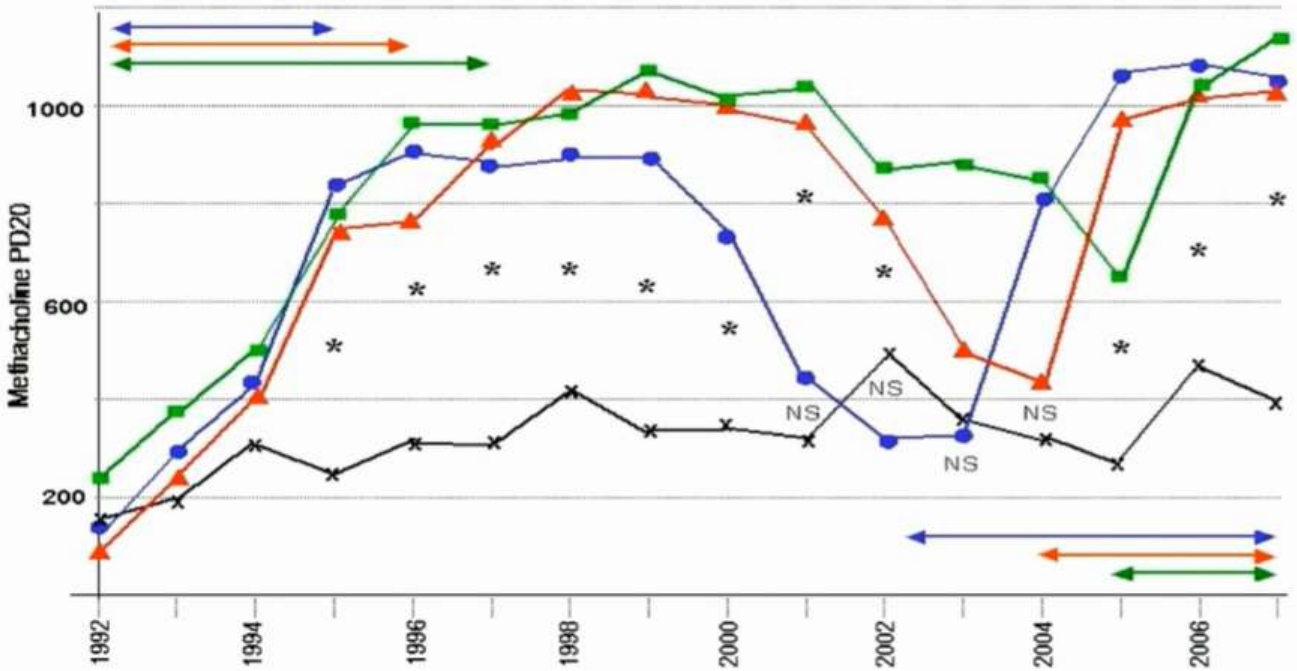


Marogna M et al. – J Allergy Clin Immunol 2010

2 AIT and its long-lasting effect on asthma

FIGURE 5

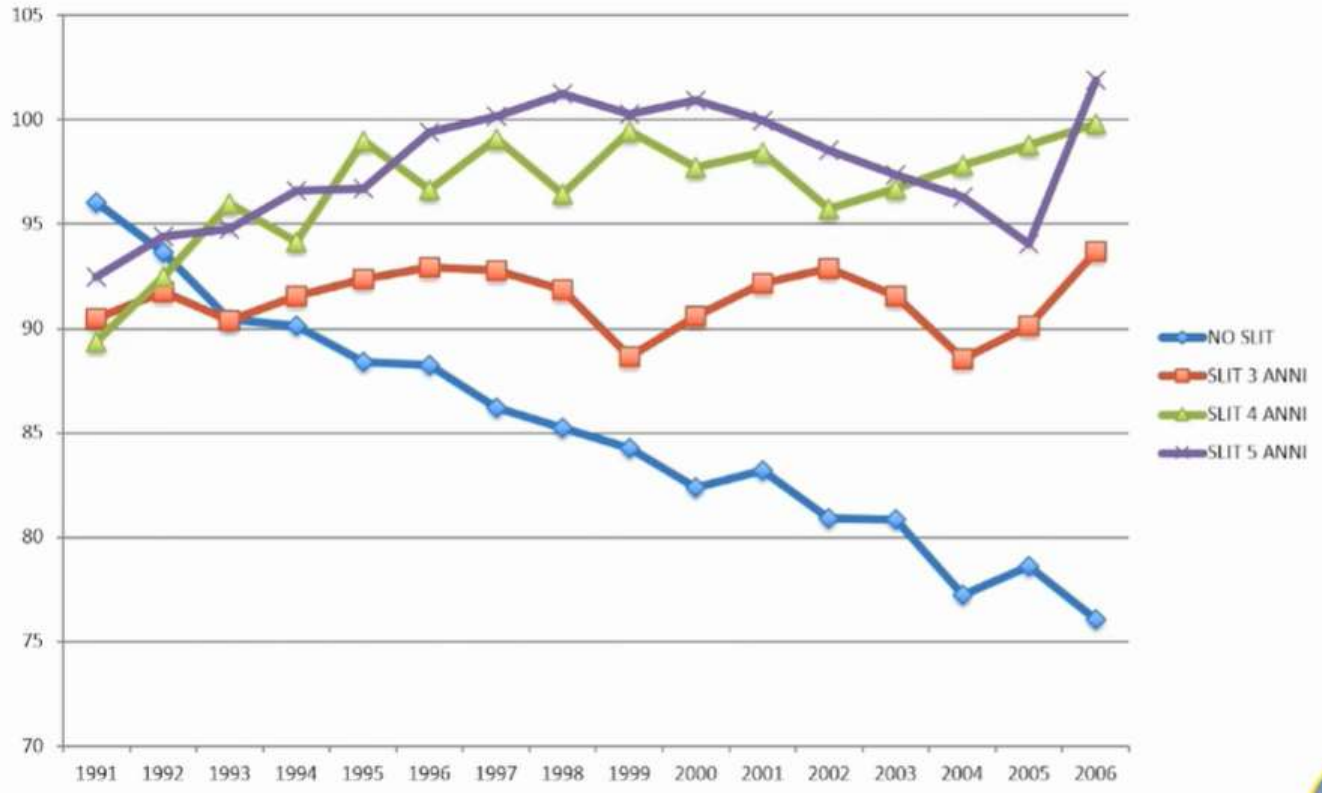
AIRWAY HYPERREACTIVITY



Marogna M et al. – J Allergy Clin Immunol 2010

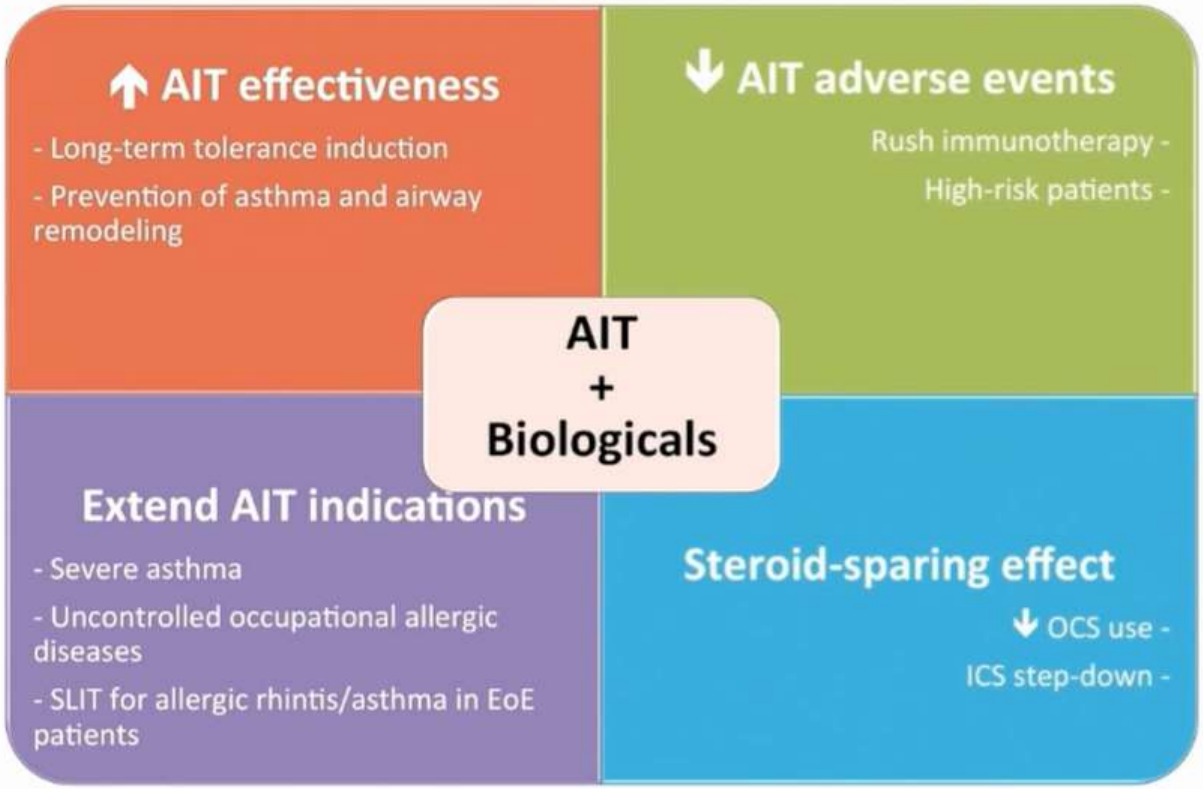
2 AIT and its long-lasting effect on asthma

LUNG FUNCTION DECLINE



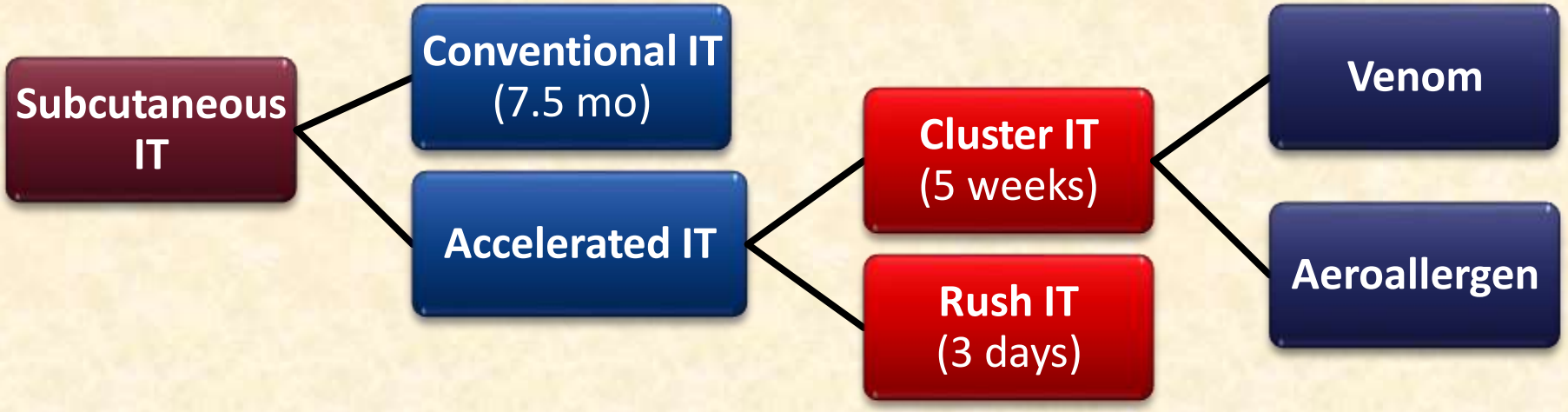
Heffler E et al – *in preparation*

6 AIT and biologicals



Malipiero G et al. - Curr Opin Allergy Clin Immunol 2021

Main difference: time required to reach maintenance dose.(MTD)



Accelerated Immunotherapy Schedules , Premedication and Medications to be Used with Caution

Accelerated AIT Schedules Date Back to early 1900's

FIG 2. John Freeman. (Courtesy of St Mary's Hospital)

"In 1909, Noon and I began inoculating hay-fever patients with a grass pollen extract…. inoculations were given weekly merely because our out-patients at St. Mary's Hospital were in the habit of coming every week.

Dr. Freeman noted the **inconvenience of the weekly build-up** and began experimenting with more rapid schedules . He concluded the advantages of the "rush" method were: the saving of time, convenience and patient compliance

"Rush desensitization" with associated SR

7 year-old girl with **horse-asthma** *desensitized over 4 days but developed urticaria, fluttering heat and felt "funny" and dose was decreased. Able to ride her pony without discomfort*

Cluster candidates

- **ACAAI instant reference:**
  - "while there are no firm indications for accelerated schedules, the following patients and/or situations may benefit from such schedules"
    - **Poor adherence** or systemic rxns with conventional IT
    - Work/life schedule precludes **weekly injections** for a prolonged time
    - **Asthmatics** that can only be controlled long enough to reach a maintenance dose with an accelerated schedule

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- **David Khan, MD – Patient selection for rush and cluster IT (presented at AAAAI 2010)**
  - "Summary: **Any patient who is considered a candidate for IT is a candidate for cluster or RIT."**

J ALLERGY CLIN IMMUNOL
SEPTEMBER 2007

Definition

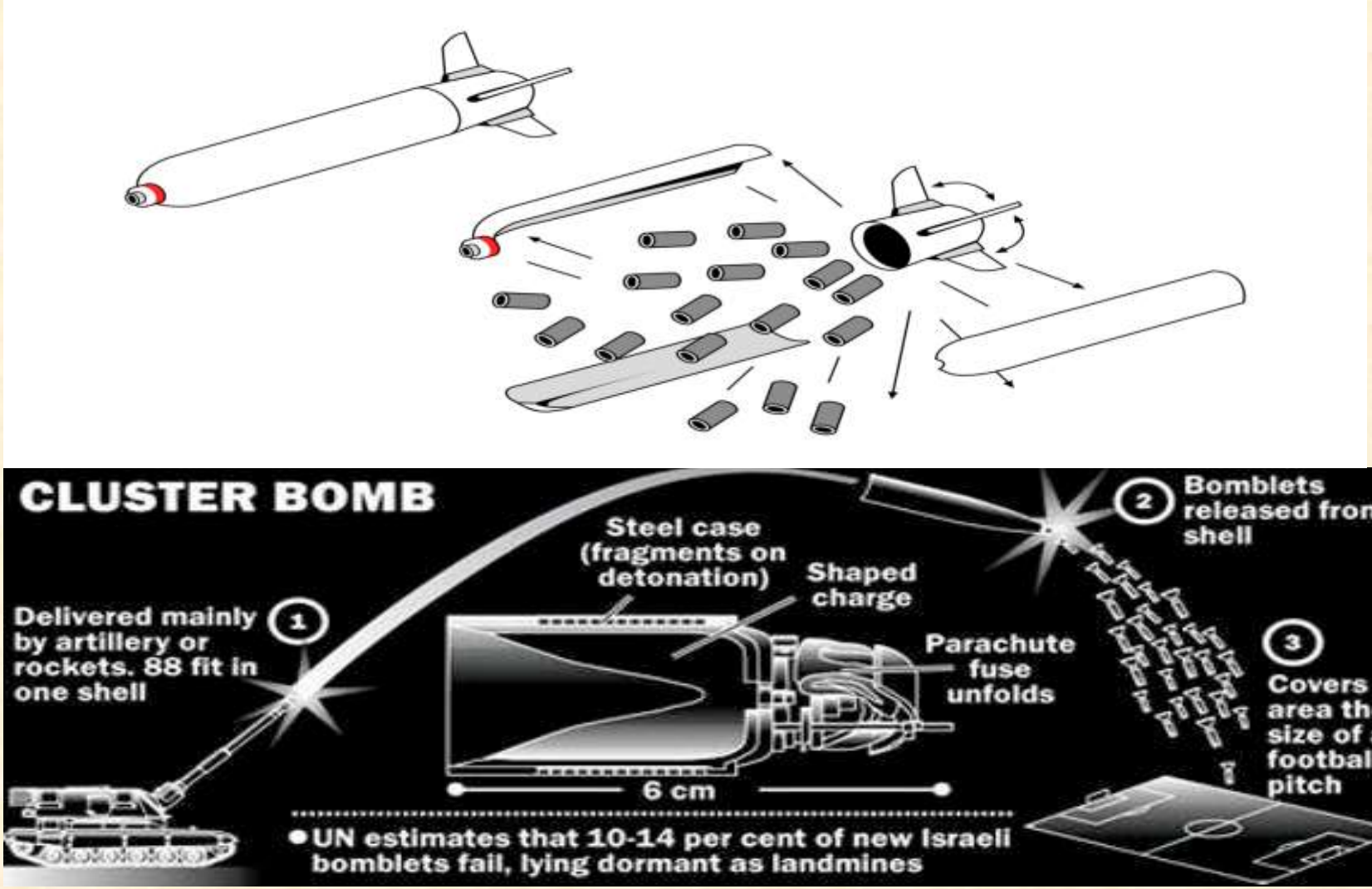
Allergen immunotherapy: A practice parameter second update

- **Cluster immunotherapy**
  - Accelerated build-up schedule
  - Entails administering several injections at increasing doses **(generally 2-3 Allergens shots per visit)** sequentially in a single day of treatment on nonconsecutive days **(generally within 4 to 8 weeks)**
  - The maintenance dose is generally achieved more **rapidly** than with a conventional (single injection per visit) build-up schedule

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Why not accelerate IT?

- AIPP: "…slightly increased frequency of systemic reactions"
- >1 injection per visit, >1 opportunities to have a reaction at that visit



Why accelerate IT?

Adherence
Better compliance

(1) A saving of time. Not only does the patient become desensitised in a shorter space but there is a saving of tiresome details, such as remembering to go for and getting the dose, and perhaps afterwards waiting for possible reactions. All this amounts to an unconscionable dislocation of affairs if repeated day by day.

- **Clinical benefit of IT obtained sooner (reach maintenance vial promptly before allergy season)**
- **Increased adherence to schedule? The most common reasons for noncompliance with IT included inconvenience, precluding medical conditions, and adverse systemic reactions (More, Annals 08)**
- Patients that turn down conventional IT might choose cluster if given the option. **Only 5% of patients with allergic asthma and/or AR receive IT.**

Why accelerate IT?

Accelerated Immunotherapy Schedules

Onset of Efficacy

Time course of improvement. Summary Statement 22: Clinical and physiological improvement can be demonstrated very shortly after the patient reaches a maintenance dose. A

Compared to Cluster…		
Conventional	**7.5 month**	**30 inj/30 visits**
Cluster	**5 weeks**	**18inj/ 8 visits**

Definition

Allergen immunotherapy: A practice param
second update

Visit Number	Volume (mL)	Dilution (v/v)	Vial Color	Dose (mg)	Cum Dose (mg)
1	0.10	1:1000	green	0.1	0.1
	0.40	1:1000	green	0.4	0.5
	0.10	1:100	blue	1.0	1.5
2	0.20	1:100	blue	2.0	3.5
	0.40	1:100	blue	4.0	7.5
	0.07	1:10	yellow	7.0	14.5
3	0.10	1:10	yellow	10.0	24.5
	0.15	1:10	yellow	15.0	39.5
	0.25	1:10	yellow	25.0	64.5
4	0.35	1:10	yellow	35.0	99.5
	0.50	1:10	yellow	50.0	149.5
5	0.07	1:1	red	70.0	219.5
	0.10	1:1	red	100.0	319.5
6	0.15	1:1	red	150.0	469.5
	0.20	1:1	red	200.0	669.5
7	0.30	1:1	red	300.0	969.5
	0.40	1:1	red	400.0	1,369.5
8	0.50	1:1	red	500.0	1,869.5

APPENDIX 3. Example of a build-up schedule for weekly immunotherapy

Dilution (vol/vol)	Volume (mL)
1:1000	0.05
	0.10
	0.20
	0.40
1:100	0.05
	0.10
	0.20
	0.30
	0.40
	0.50
1:10	0.05
	0.07
	0.10
	0.15
	0.25
	0.35
	0.40
	0.45
	0.50
Maintenance concentrate	0.05
	0.07
	0.10
	0.15
	0.20
	0.25
	0.30
	0.35
	0.40
	0.45
	0.50

Total injections to maintenance: 30

CONVENTIONAL IMMUNOTHERAPY (7.5 month)30 inj/visits.

January

S	M	T	W	T	F	S
					1	2
3		5	6	7	8	9
10		12	13	14	15	16
17		19	20	21	22	23
24		26	27	28	29	30
31						

February

S	M	T	W	T	F	S
		2	3	4	5	6
7		9	10	11	12	13
14		16	17	18	19	20
21		23	24	25	26	27
28						

March

S	M	T	W	T	F	S
		2	3	4	5	6
7		9	10	11	12	13
14		16	17	18	19	20
21		23	24	25	26	27
28		30	31			

April

S	M	T	W	T	F	S
				1	2	3
4		6	7	8	9	10
11		13	14	15	16	17
18		20	21	22	23	24
25		27	28	29	30	

May

S	M	T	W	T	F	S
						1
2		4	5	6	7	8
9		11	12	13	14	15
16		18	19	20	21	22
23		25	26	27	28	29
30						

June

S	M	T	W	T	F	S
		1	2	3	4	5
6		8	9	10	11	12
13		15	16	17	18	19
20		22	23	24	25	26
27		29	30			

July

S	M	T	W	T	F	S
				1	2	3
4		6	7	8	9	10
11		13	14	15	16	17
18		20	21	22	23	24
25		27	28	29	30	31

Dilution from maintenance concentrate	Vol/vol label	No.	Color
Maintenance concentrate	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

CLUSTER IMMUNOTHERAPY (5 weeks) 18inj / 8visits.

January

S	M	T	W	T	F	S
					1	2
3		5	6		8	9
10		12	13		15	16
17		19	20		22	23
24		26	27	28	29	30
31						

February

S	M	T	W	T	F	S
		2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28						

March

S	M	T	W	T	F	S
		2	3	4	5	6
7		9	10	11	12	13
14		16	17	18	19	20
21		23	24	25	26	27
28		30	31			

April

S	M	T	W	T	F	S
				1	2	3
4		6	7	8	9	10
11		13	14	15	16	17
18		20	21	22	23	24
25		27	28	29	30	

May

S	M	T	W	T	F	S
						1
2		4	5	6	7	8
9		11	12	13	14	15
16		18	19	20	21	22
23		25	26	27	28	29
30						

June

S	M	T	W	T	F	S
		1	2	3	4	5
6		8	9	10	11	12
13		15	16	17	18	19
20		22	23	24	25	26
27		29	30			

July

S	M	T	W	T	F	S
				1	2	3
4		6	7	8	9	10
11		13	14	15	16	17
18		20	21	22	23	24
25		27	28	29	30	31

Dilution from maintenance concentrate	Vol/vol label	No.	Color
Maintenance concentrate	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

Subcutaneous Cluster Schedule

- Cluster entails administering several injections at increasing doses (generally 2-3 per visit) sequentially in a single day of treatment on nonconsecutive days.
- Cluster schedule associated with the same or a slightly increased frequency of SRs compared with conventional schedules.
- Few studies compare safety and most used single allergen: *can safety be extrapolated to multiallergen?*

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

Visit	Dose (mL)	Concentration as dilution of maintenance vial
1	0.10	1:1000 vol/vol
	0.40	1:1000 vol/vol
	0.10	1:100 vol/vol
2	0.20	1:100 vol/vol
	0.40	1:100 vol/vol
	0.07	1:10 vol/vol
3	0.10	1:10 vol/vol
	0.15	1:10 vol/vol
	0.25	1:10 vol/vol
4	0.35	1:10 vol/vol
	0.50	1:10 vol/vol
5	0.07	1:1 vol/vol
	0.10	1:1 vol/vol
6	0.15	1:1 vol/vol
	0.20	1:1 vol/vol
7	0.30	1:1 vol/vol
	0.40	1:1 vol/vol
8	0.50	1:1 vol/vol

Example of a 8 visit 18 injection schedule in the 2nd and 3rd ITPP updates*

Cox L et al, Allergen immunotherapy: a practice parameter third update.. J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55.

Cluster vs. Conventional IT

- Very few studies compare cluster with conventional IT head-to-head

- **Few studies use the same:**
  - Cluster (or conventional) injection schedule
  - Allergens
  - Patient population
  - Target maintenance dose
  - Definition of systemic reaction
  - **Some studies premedicate!**
  - **Measures of clinical efficacy**
  - Length of study

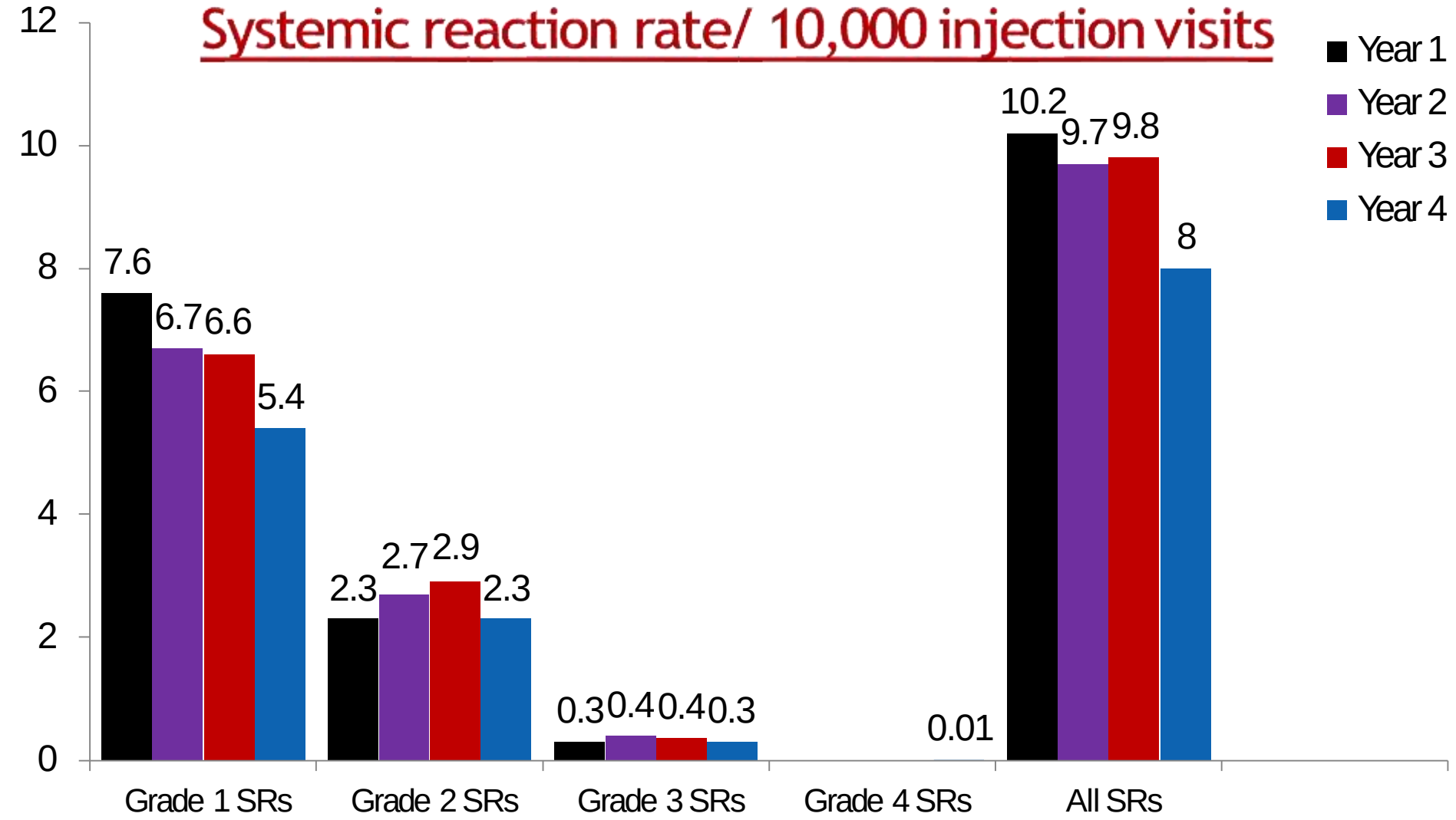
WAO Subcutaneous Immunotherapy Systemic Reaction Grading Systems

- **5 Grades**: based on organ system involved and severity.
  Organ systems are defined as:
  - Cutaneous, conjunctival, upper respiratory,
  - Lower respiratory, gastrointestinal, cardiovascular and other.
- **Grade 1**: single organ system such as cutaneous, conjunctival, upper respiratory, **but not** asthma, gastrointestinal or cardiovascular
- **Grade 2 & 3.** Symptoms from >1 organ system or asthma, gastrointestinal, cardiovascular
- **Grade 4**: Respiratory failure, hypotension ±loss of consciousness
- **The Grade is determined by the physician's clinical judgment after the event is over.**

Endorsed by AAAAI, ACAAI, the Latin American Society of Allergy and Immunology, the Asia Pacific Association of Allergy, Asthma and Clinical Immunology,

AAAAI/ACAAI Survey Years 1-4

Systemic reaction rate/ 10,000 injection visits



Bernstein *AAACI* 2010, Epstein *AAACI* 2011, 2013

Conventional –IT – 2–7%

- **SCIT SR rate** varies greatly depending on several factors: allergen dose, extract type , induction schedule, premeditation, extract type, etc.
- **SR rate:** review of SCIT studies that reported SR rate from 1995 -2010:*
  - Per injection frequency was ~0.2%
  - Per patient rate of 2% to 7% in US studies with conventional schedules
- Purported advantage of accelerated schedules
  - Reduced number of visits to target dose BUT
  - Possible with increased risk of SR
    - Rush increased risk with aerollergen but not venom (except fire ant)
    - Cluster risk may be the same or increased

Cox L, et al J Allergy Clin Immunol. 2010;125(3):569-74

Higher Systemic reaction rate with aeroallergen cluster immunotherapy in a clinical practice

- **Risk factors** for a systemic reaction included: female sex, asthma, age 21 to 40 years, and inclusion of certain allergens in the immunotherapy vaccine.
- **Conclusions** Cluster buildup may lead to a higher rate of systemic reactions. Identifying risk factors for systemic reactions will help improve the safety of cluster immunotherapy.

Table 7. Concentration of Immunotherapy Extract Leading to Systemic Reactions

Concentration of extract (vol:vol)	No. of patients (%)
1:1,000	0 (0)
1:100	6 (12.5)
1:10	25 (52.1)
1:1	17 (35.4)

Table 8. Time from Eliciting Injection until Onset of Reaction

Time until onset of reaction (minutes)	No. patients (%)
<15	6 (13.3)
15–30	14 (31.1)
31–60	12 (26.7)
>60	13 (28.8)

Copenhaver et al. Ann Allergy Asthma Immunol. 2011;107(5):441–7..

Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

10.9%

Methods: A retrospective, observational review in a large, multicenter group regarding cluster IT safety

Maintenance dose based on AIPP guidelines, most premedicated

Results: Data from 441 cluster patients. 48 patients (10.9%) experienced SRs

Based on the WAO SCIT SR Grading System,

- 18 grade 1 reactions (38.3%),
- 23 grade 2 reactions (48.9%),
- 5 grade 3 reactions (10.6%),

87.2%

Compared with clinics conventional IT during 2-yr period with 12,963 receiving SIT:

SR rate 0.043% of IT visits and 2.2% of patients

Copenhaver et al. Ann Allergy Asthma Immunol. 2011;107(5):441-7.

Systemic tolerability of SCIT with IR- standardized allergen extracts administered using clustered regimens

- Methods: Retrospective, observational, multicenter study in 1,147 patients who were treated with one of 9 cluster regimen
- Results: 39 patients **(3.4%)** experienced 42 SRs (0.6% of doses). observed a higher risk of SRs in patients who received an initial dose higher than 0.3 index of reactivity (IR); only
- Only 2 reactions occurred after initial dose both with 0.4 IR. Remainder never with a dose lower than 0.35 IR.
- **Conclusions:** Clustered regimens with IR-standardized extracts are an alternative to classic immunotherapy initial dose no greater than **0.35** IR to minimize the incidence of SRs.

Table 5. Details of the Most Common Dosing Schedules

Regimen 6[a]				Regimen 9[b]			
Day	Vial No.[d]	Dose, mL	Dose, IR	Day	Vial No.[d]	Dose, mL	Dose, IR
0	2	0.3	0.3	0	3	0.1	1
		0.3	0.3			0.2	2
7	3	0.1	1	7	3	0.4	4
		0.2	2			0.4	4
14	3	0.4	4				
		0.4	4				

Table 1. Major Allergen Contents[a] of Final Extracts Corresponding to 100 IR/mL

Extract	Major allergen	Content, μg/mL
Dermatophagoides pteronyssinus	Der p 1	20
	Der p 2	4
Dermatophagoides farinae	Der f 1	50
Grasses	Group 5	7
Olive	Ole e 1	10

Serrano et al, Ann Allergy Asthma Immunol. 2009;102(3):247-52.

Studies Comparing Cluster and Conventional Immunotherapy Schedule

- DBPC study of 239 pts with dust mite AR ± asthma comparing 6-week with a 12-week conventional schedule found:[1]
  - No differences between the 2 schedules in terms of AEs
  - Improved clinical and objective parameters in the cluster 6 weeks before conventional group
- Randomized study of 96 patients with dust mite AR comparing 6 week cluster with 14 week conventional found:
  - **Cluster reduced time to maintenance dose by 57%.**
  - No differences in SRs compared with conventional schedule.[2]

1. Taber et al., J Allergy Clin Immunol 2005; 116:109-18
2. Zhang et al., Int Arch Allergy Immunol 2009;148:161-9.

Premedication with accelerated immunotherapy schedules.

Summary Statement 57:

Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy build-up protocols. A

Cox et al, J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55

Instant Reference for Health Professionals

Published by the American College of Allergy, Asthma & Immunology

Procedure for Rush and Cluster Immunotherapy

Premedication

Rush ImmunoTherapy (RIT)

Patients receiving 1 or 2-day RIT should receive premedication starting 2 days prior to the procedure to reduce the likelihood of a systemic reaction.

H-1 antagonist

- Cetirizine
- Fexafenadine
- Diphenhydramine

H-2 antagonist

- Ranitidine

Corticosteroid

- Prednisone

Leukotriene receptor antagonist

- Monteleukast

Procedure for Rush and Cluster Immunotherapy Instant Reference for Health Professionals Published ACAAI

Advantages & Disadvantages of Accelerated Immunotherapy Schedules

8.4–28.6% without premedication

TABLE I. Comparison of different immunotherapy build-up schedules for aeroallergens

Schedule	Rush immunotherapy	Cluster immunotherapy	Conventional immunotherapy
No. of visits during build-up phase	1-3	8*	30*
No. of injections	8†	18*	30*
Time to reach maintenance dose	1-3 d	5 wk*	15 wk at a frequency of 2 times per week or 7.5 mo if injections administered once a week
Premedication‡	Recommended in the AIPP but no specific protocol provided. H1 antihistamine and corticosteroids were used in all protocols§ in addition to other medications (eg, H2 antihistamines, leukotriene antagonists, theophylline, and ketotifen).	Antihistamine recommended by AIPP with notation that 2 hours before has been shown to decrease SR and local reactions.	Not routinely recommended but rarely studied: one study found reduced frequency of severe SR and increased the proportion of patients who achieved the target dose with fexofenadine premedication.
Range of SRs‡			
Without premedication	5% to 100% of patients	3% to 79% of patients (100% in 1 study classified as cluster, but protocol had 5 injections per visit; allergen: *Cladosporium* species)	8.4% to 28.6% of patients; mean, 12.9%; SD, 10.8%§
With premedication	14.7% to 38% of patients	0 to 33% of patients	NA

3–79% without premedication

0–33% with premedication.

Cox L. Advantages & disadvantages of accelerated immunotherapy schedules. J Allergy Clin Immunol 2008; 122:432-4. 2

Measures to Improve Safety Premedication

Antihistamines

- Studies with RIT & cluster suggest decreased incidence of local and SRs. Than Conventional IT:
  - One DBPC study found premedication with fexofenadine reduced # of severe SRs, & ↓ time to MTD.

Leukotriene receptor antagonist

- Anecdotal reports of reductions in SR rates . One DBPC study demonstrated ↓ LLR during venom RIT with moneleukast[2]

1.Ohashi et al, Ann Allergy Asthma Immunol 2006; 96
2. Wohrl et al., Int Arch Allergy Immunol 2007;144:137-42

Premedication with montelukast reduces local reactions of allergen immunotherapy

- **Methods:** 15 pts with hymenoptera anaphylaxis received 19 injections administered over 5 consecutive days. Counted # of injections until an LR of >3 cm occurred. Randomized to 3 treatment groups: premedication with placebo, 10 mg montelukast or 5 mg of desloratadine.
- **Results**: Compared with placebo, LRs (>3 cm) was significantly delayed by montelukast ($p < 0.01$) but not by desloratadine ($p = 0.19$).
  - Difference between montelukast and desloratadine was close to significant ($p = 0.054$)..
- Conclusion: Montelukast can be useful in the prevention of LRs after specific immunotherapy.

Wohrl et al, Int Arch Allergy Immunol 2007; 144:137-142

Premedication

J ALLERGY CLIN IMMUNOL
SEPTEMBER 2007

Allergen immunotherapy: A practice parameter second update

The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Antihistamine premedication in specific cluster immunotherapy: A double-blind, placebo-controlled study

Lone Nielsen, MD, Claus R. Johnsen, MD, Holger Mosbech, MD, Lars K. Poulsen, PhD, and Hans-Jørgen Malling, MD *Copenhagen, Denmark*

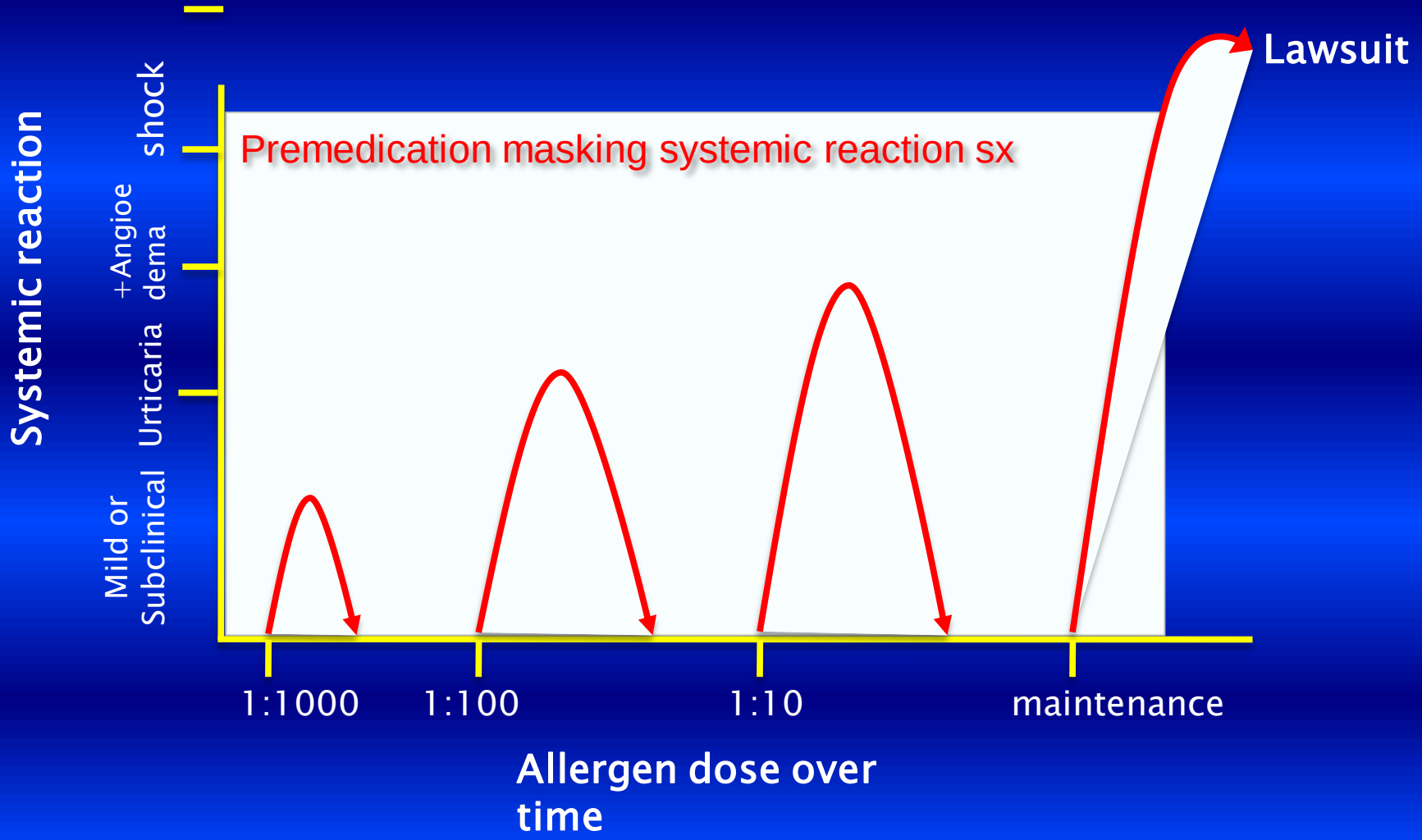
Premedication

H-1 antagonist
- Cetirizine
- Fexafenadine
- Diphenhydramine

H-2 antagonist
- Ranitidine

Corticosteroid
- Prednisone

Leukotriene receptor antagonist
- Monteleukast



Premedication

Antihistamine premedication in specific cluster IT: A DBPC study (Nielsen, JACI 1996)

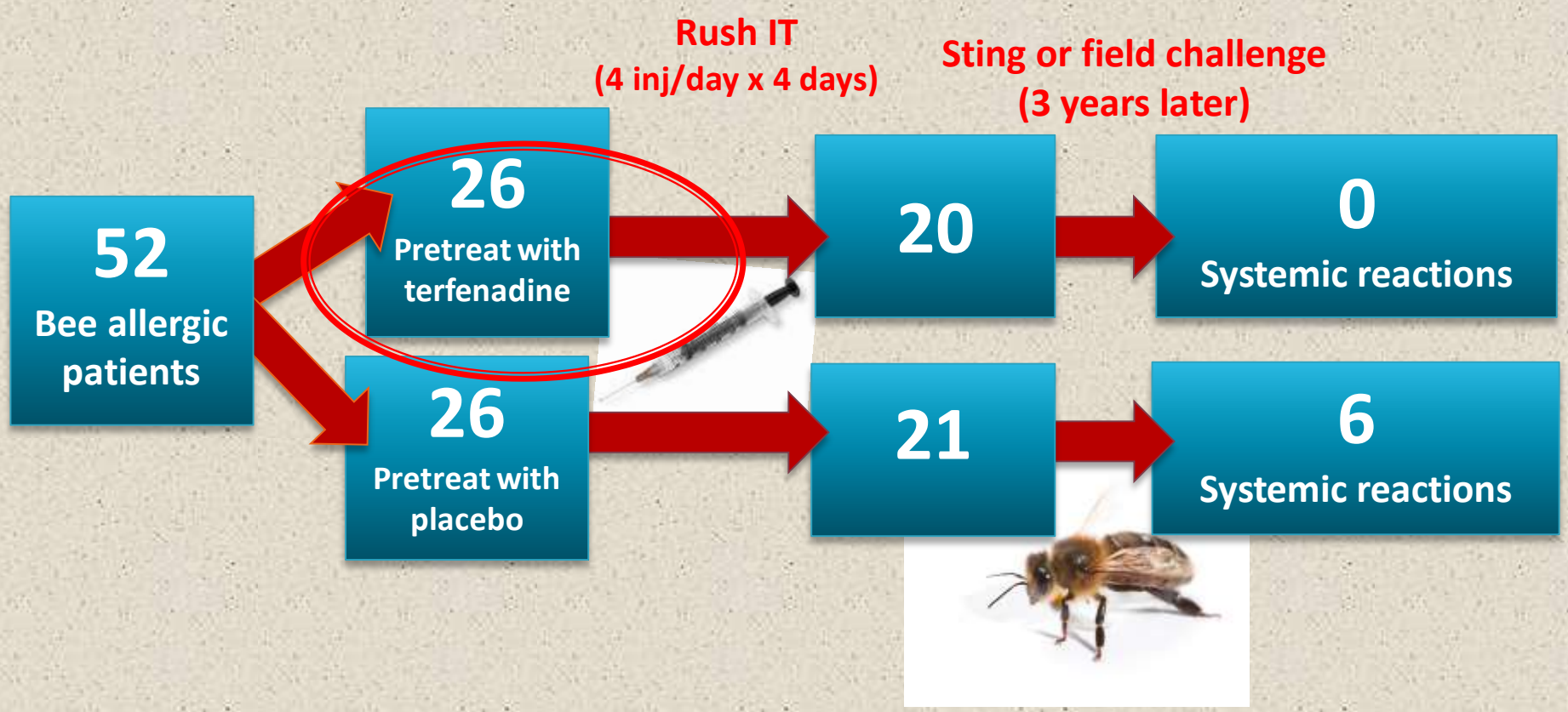
Subjects: Adult, AR to birch tree or timothy grass, premed taken 2h before inj	IT Schedule	Adverse rxn rate
Placebo (24)	7 wks (3/2/2/2/2/2/1 inj per wk) with birch **OR** timothy	•No serious systemic rxns/anaphylaxis in either group •Early systemic rxn rate: loratadine**1.6%** per inj, placebo **3.1%** per inj •Loratadine did not delay onset of systemic rxns, and significantly decreased severity of systemic rxns vs. placebo
Loratadine 10 mg (21)		

Allergen	Maint dose	Probable eff. dose
Phlp 5	25 µg	15 - 20 µg
Bet v 1	23 µg	3.28 - 12 µg

Systemic reactions not broken down by allergen used for immunotherapy

Premedication

- Does premedication alter the efficacy of IT?



Premedication with antihistamines may enhance efficacy of specific-allergen IT (Muller, JACI 2001)

Omalizumab Premedication and Allergen Immunotherapy

- **Summary Statement 58:** Omalizumab pretreatment has been shown to improve the safety and tolerability of cluster and rush immunotherapy schedules in patients with moderate-persistent asthma and allergic rhinitis, respectively. Additionally, omalizumab used in combination with immunotherapy has been shown to be effective in improving symptom scores compared to immunotherapy alone. A

Cox L, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55.

Effect of pretreatment with omalizumab on the tolerability of SIT in allergic asthma

DBPC study 248 patients with at least moderate persistent allergic asthma inadequately controlled with inhaled corticosteroids randomized to receive with omalizumab or placebo, followed by SIT to at least 1 of 3 perennial allergens (cat, dog, & HDM)

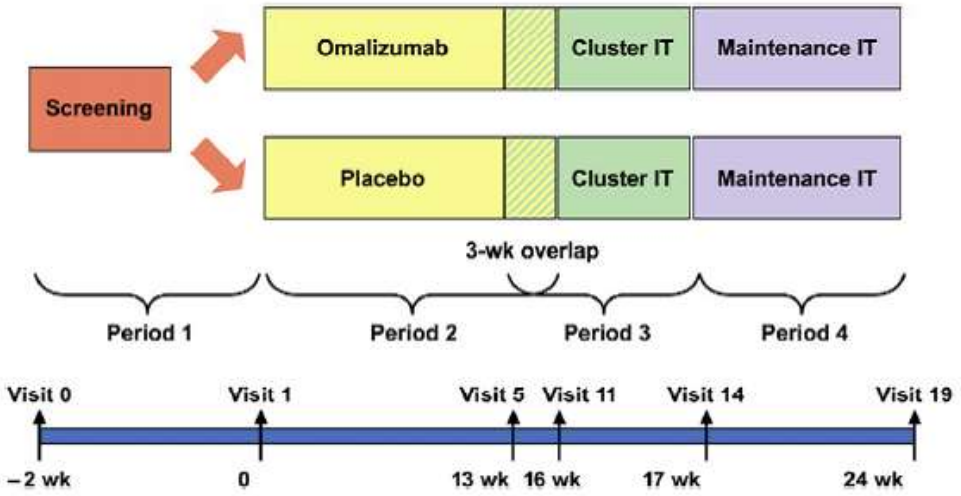


FIG 1. Study design.

Massanari et al, J Allergy Clin Immunol. 2010;125(2):383-9

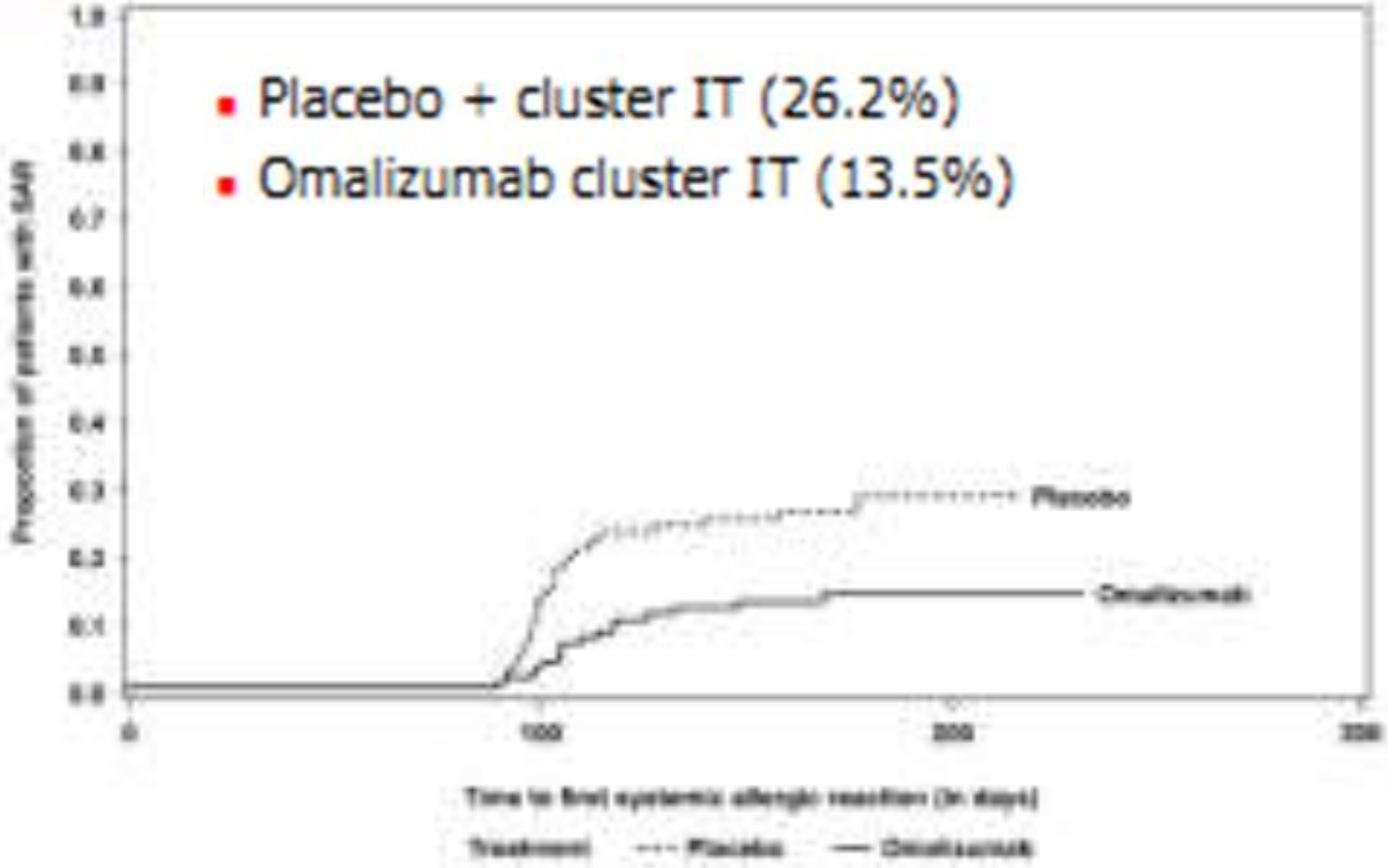
Omalizumab and Cluster IT

- Multicenter double blind study to evaluate omalizumab pretreatment (n=126) vs. placebo (n=122) in patients with moderate persistent asthma treated with cluster IT to at least 1 perennial allergen (cat, dog, dust mite)
- Cluster IT: 4 weeks (18 injections)
- Systemic reactions less with omalizumab
  - Placebo + cluster IT (26.2%)
  - Omalizumab cluster IT (13.5%)

Massanari M et al. J Allergy Clin Immunol 2010;125:383-9.

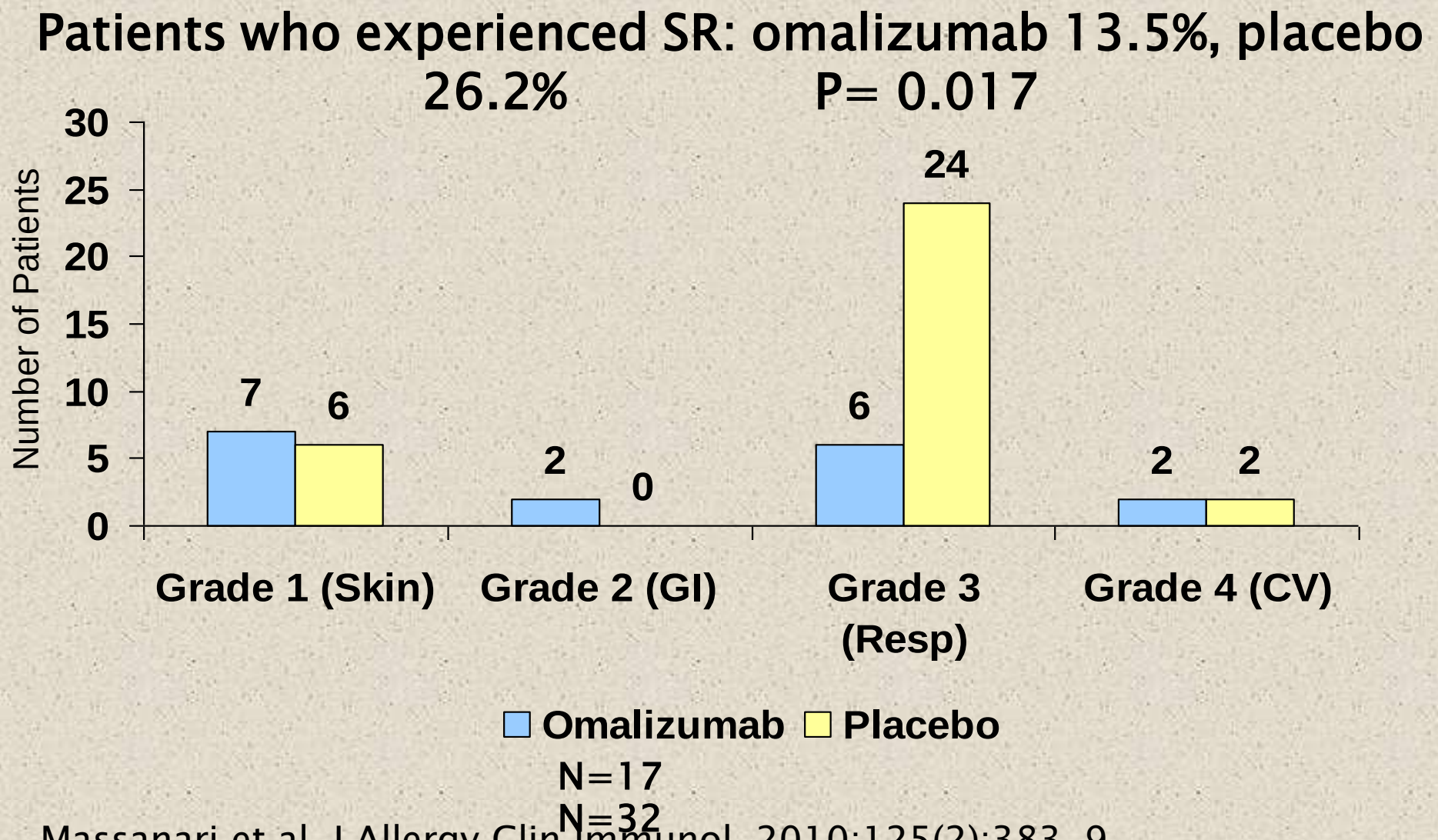
Systemic Reactions to Cluster IT : Placebo vs omalizumab pretreatment

- Placebo + cluster IT (26.2%)
- Omalizumab cluster IT (13.5%)



Massanari M et al. J Allergy Clin Immunol 2010;125:383-9.

Severity of First Systemic Allergic Reaction



Massanari et al, J Allergy Clin Immunol. 2010;125(2):383-9

Safety of Accelerated Schedules of Cluster Allergen Immunotherapy with House dust mites in Sixty Five Patients with Perennial rhinitis & BR. Asthma

Dr. PC. Kathuria, & Dr. Neelam et al

Allegy & Asthma Clinic, BLK Super-speciality Hospital, National Allergy Centre, New Delhi, INDIA

Rationale - The success of allergen Immunotherapy is dose and time dependent as well the quality of allergen extract used & Compliance by the patients. The conventional subcutaneous Immunotherapy (SCIT) is a slow treatment that often leads to poor compliance or discontinuation of treatment. Accelerated Immunotherapy build up schedules may provide a safe alternative to conventional build up schedules to achieve Immuno-tolerance without a significant increase in risks.

Aim - we have designed protocol of cluster Immunotherapy to achieve maximum tolerance dose (MTD) in duration of six weeks in immunological significant sensitive forty nine (49) patients to House dust mites in perennial rhinitis & Br asthma

Methods - Open observational study among 65 patients comparison of three groups

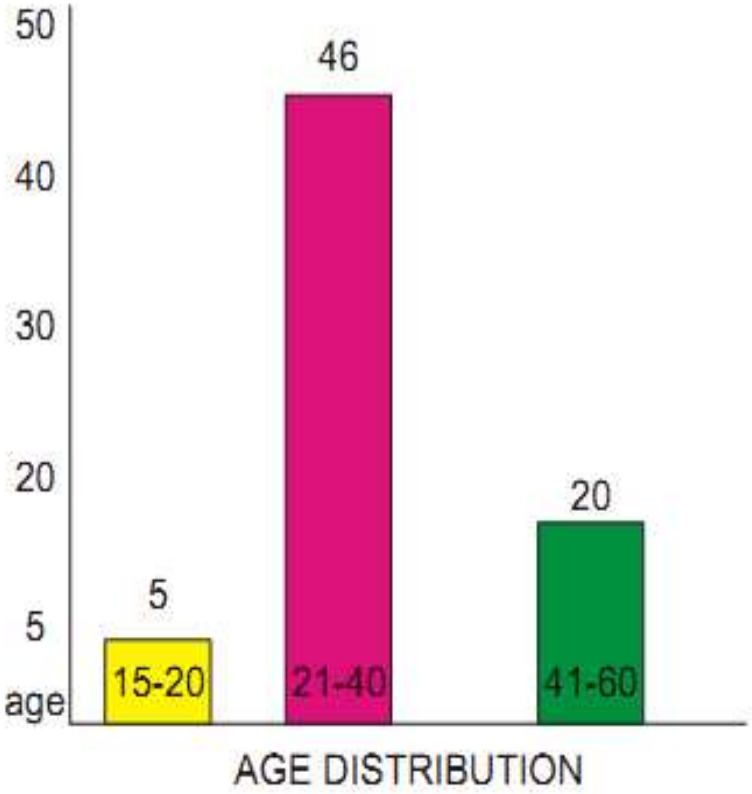
A) combined Omalizumab (Anti-IgE) + Cluster Immunotherapy - (9)

B) Cluster Immunotherapy - (40)

C) Conventional Immunotherapy -(16)

SELECTION OF PATIENTS

1) Typical H/O perennial rhinitis & (Mild to Moderate) Br asthma > 5 yrs
2) Positive S.P.T > 5-7mm with 10,000 AU of standardized HD Mites (D.farinae, & D pternoyssinus)
3) Positive Level of serum specific IgE to D.farinae, & D pternoyssinus > 3.5 KU ml, CAP system, Pharmacia and Total IgE > 300 to 700iu / ml
4) FEV1 / FVC > 70% & PEFM < 10% Variability with Regular medication (LABA + ICS, ALRI & Ketotifen)
5) Other Allergens (Pollens, fungii etc) Positive but not Immunologically significant (HEP)

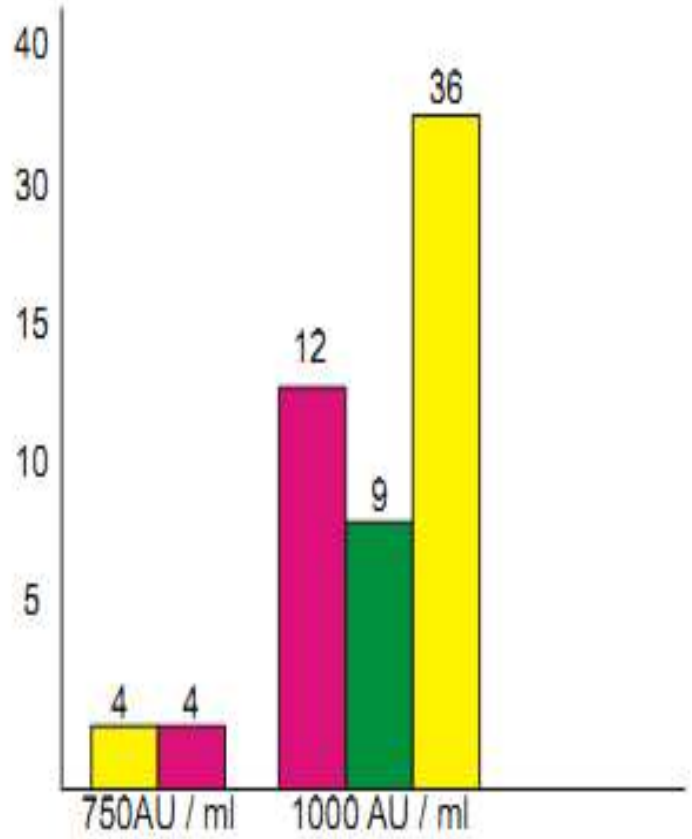


AGE DISTRIBUTION

	Combined Omalizumab (Anti-IgE)+ Cluster immunotherapy (9)	Cluster immunotherapy (40)	Conventional immunotherapy (16)	
Female	6	30	12	
Male	3	10	4	

SEX DISTRIBUTION

RESULTS -



Combined (Omalizumab (anti-IgE) + Cluster Immunotherapy - (9)

Cluster Immunotherapy - (40)

Conventional Immunotherapy (16)

MTD (MAXIUM TOLERANCE DOSES)

ALLERGEN EXTRACTS (1000 Au/ml) (Standardized HD Mites - 50% of D.farinae, & D pternoyssinus)

Source - Greer Allergy Immunotherapy lenoir USA

MTD (MAXIUM TOLERANCE DOSES)

ALLERGEN EXTRACTS (1000 Au/ml) (Standardized HD Mites - 50% of D.farinae, & D pternoyssinus)

Source - Greer Allergy Immunotherapy lenoir USA

A					B					C				
Combined Omalizumab (Anti-IgE) + Cluster Immunotherapy (9)					Cluster Immunotherapy **(40)**					Conventional Immunotherapy **(16)**				
Visits	Days	Concs	Doses	Volumes	Visits	Days	Concs	Doses	Volumes	Visits	Days	Concs	Doses	Volumes
1	0	50%	500AU	0.1	1	0	30%	300AU	0.5	1	0	5%	50AU	0.05
				0.2					0.10	2	3	10%	100AU	0.10
				0.2					0.15	3	6	20%	200AU	0.20
2	15	75%	750AU	0.2	2	10	50%	500AU	0.15	4	12	30%	300AU	0.30
				0.2					0.15	5	22	40%	400AU	0.40
				0.35					0.20	6	35	50%	500AU	0.50
3	36	100%	1000AU	0.30	3	25	75%	750AU	0.20	7	50	60%	600AU	0.60
				0.35					0.25	8	68	70%	700AU	0.70
				0.35					0.30	9	89	80%	800AU	0.80
					4	46	100%	1000AU	0.30	10	113	90%	900AU	0.90
									0.35	11	140	100%	1000AU	1CC
									0.35					

	Combined Omalizumab (Anti-IgE) + Cluster immunotherapy **(9)**	Cluster immunotherapy **(40)**	Conventional immunotherapy **(16)**
Total Visits	3	4	11
Duration	36 Days (1month)	46 Days (1½month)	140 Days (>4½month)
Repeat Skin Prick Tests ↓ (7mm) after maintainance dose	**3mm / 7mm**	**3mm / 7mm**	**4mm / 7mm**
Symptoms Scoring (VAS) ↓	>70%	>50%	>50%
Systemic Reactions	Non - specific Reaction	**(20%)** 8/40(IgE specific Reaction)	**(18.7%)** 3/16 (IgE specific Reaction)

Build up Dosing phase - House Dust Mites Immunotherapy local reaction (Oedma, pruritus and pain)

Type of Side Effects	% of Allergen Vaccine Reaction Which Induced Local Side Effects			Time of Incidence	Management
	Combined Omalizumab (Anti-IgE) + Cluster immunotherapy (9)	Cluster immunotherapy (40)	Conventional immunotherapy (16)		
local oedema (5-10cm)	3/9 (33%)	15/40 (37.5%)	4/16 (25%)	Late 6-24hrs.	Spontaneously resolves
local oedema (>10cm)	0/9 (0%)	10/40 (25%)	3/16 (18.75%)	Late 6-48hrs.	Antihistamine (Fexofenadine) + Methylpredisolone
PRURITUS at the site of allergen vaccine Injection	7/9 (77%)	30/40 (75%)	10/16 (62.5%)	Late 6-48hrs.	Cold Compresses
PAIN at the site of allergen vaccine Injection	4/9 (44%)	10/40 (25%)	2/16 (12.5%)	Late 6-48hrs.	Cold Compresses Antihistamine (Fexofenadine)

No Early reaction

- Late Reaction after 6hrs. < 10cm = 22/65 (33.8%), > 10cm = 12/65 (18.4%)
- Large Local reaction > 10cm predicts the systemic reaction and was given Fexofenadine 180mg & Methyl - prednisolone 8mg

Subcutaneous House Dust Mites Immunotherapy Systemic reaction Grading System.

(Cough, sneezing, Running nose, wheezing urticaria, Anaphylaxis, abdominal cramps, vomiting or diarrhea & less than 40% PEF or FEV1 drop)

Combined Omalizumab (Anti-IgE) + Cluster immunotherapy (9)	Cluster immunotherapy (40)	Conventional immunotherapy (16)
3/9 (33.3%) (Headache, Pharyngitis acute appendicitis Non - specific Reaction	IgE mediated reaction 8/40 **(20%)** grade II, (3) grade III, (5)	IgE mediated reaction 3/16 (18.7%) grade II, (2) grade III, (1)

CONCLUSIONS

1. Combined (anti - IgE) omalizumab and cluster Immunotherapy is without an IgE mediated adverse systemic reaction & maintenance maximum tolerance dose (MTD) of 1000 / ml achieved in 3 visits in 36 days (> 1month) in our 9 patients

2. Cluster Immunotherapy in 40 patients is efficacious, well tolerated than conventional immunotherapy of 4 months of single Allergen Injection as maintenance maximum tolerance dose (MTD) of 1000 - Au achieved in more than 75% in 4 visits of 46 days duration but 20% of patients in cluster Immunotherapy develop grade II/III adverse systemic reaction (J Allergy Clin Immunol 125:569-574, e567 2010)

3. Waiting period after allergen vaccine was one hour if there is H/O of large local reaction of >10cm, size of weal >7mm (HEP), positive specific IgE to D.farinae, and D pteronyssinus > 3.5 ku/ ml, Total IgE > 300 to 700 / ml, in poly - sensitized patients, On high doses of ICS (>1000ug) & variability in PEFM > 10% with FEV1 / FVC > 70% , In such cases Fexofenadine 180mg & Methyl - prednisolone 8mg was given three hours before cluster immunotherapy to minimize adverse systemic reaction

4. In our patients, if there is > 50% reduction of weal size after repeat S.P.T (7mm to 3mm) and > 50% reduction of symptoms scoring, gives us an indirect measurement of MTD (maximum tolerance dose.)

5 We Could not find any influence of gender and numbers of allergy shots (injections) as development of adverse systemic reaction

Studies Comparing Cluster and Conventional Immunotherapy Schedule

- DBPC study of 239 pts with dust mite AR ± asthma comparing 6- week cluster with a 12-week conventional schedule found:[1]
  - No differences between the 2 schedules in terms of AEs
  - Improved clinical and objective parameters in the cluster 6 weeks before conventional group

Randomized study of 96 patients with dust mite AR comparing 6 week cluster with 14 week conventional found:[2]

- **Cluster reduced time to maintenance dose by 57%**
- Earlier symptom/medication reduction.
- No differences in SRs compared with conventional schedule.

1. Taber et al., J Allergy Clin Immunol 2005; 116:109-18
2. Zhang et al., Int Arch Allergy Immunol 2009;148:161-9.

Comparison studies

Single Cluster Allergen IT

DB comparative study of cluster and conventional IT schedules with *D. pteronyssinus* (Tabar, JACI 05)

Subjects:pediatric& adult, asthma and/or AR	IT Schedule	Adverse rxn rate	Clinical efficacy
Cluster (120)	6 wk (4/3/2/2/2/1 inj per wk)	• No difference between schedules • All systemic rxn mild (grade ≤2); **0.22%** of inj	Cluster ≥ conv. at 6, 12, 52 wks (asthma sx score, rhinitis score, PEFR variability)
Conventional (119)	12 wk (1 inj per wk)		

Systemic reactions not broken down by phase of IT Premedication

Comparison studies

Single Cluster Allergen IT

Comparative Study of Cluster and Conventional IT Schedules with *D. pteronyssinus* in the Treatment of Persistent AR (Zhang, Int Arch All Imm 09)

Subjects: Adult, AR	IT Schedule	Adverse rxn rate	Clinical efficacy
Cluster (48)	6 wk (3/2/2/2/2/1 inj per wk)	• No difference between schedules • All systemic rxn mild (grade ≤2); **1%** of cluster inj, **1%** of convinj	Cluster ≥ conv. at 6, 14, 52 wks (sx score, rhinitis score, med use score, RQLQ)
Conventional (48)	14 wk (1 inj per wk)		

Systemic reactions during build-up phase: 0.8% of cluster inj vs. 0.74% of convinj

Comparison studies
Single Cluster Allergen IT

Safety and Immunogenicity of Cluster IT in Children with Asthma and Mite Allergy (Schubert, Int Arch All Imm 2009)		
Subjects : Peds, mild-mod asthma with $FEV_1 \geq 70$	**IT Schedule**	**Adverse rxn rate**
Cluster (22)	6 wk (3/3/3/2/1/1 inj per wk)	• No difference between schedules •All systemic rxn mild (cough and dyspnea, grade ≤2); **3.5%** of cluster inj vs. **4.6%** of convinj (build-up)
Conventional (12)	14 wk (1 inj per wk) 31/2	

- Did not assess clinical efficacy
- Maintenance dose of Derp 1 was 5000 TU(?)
- Small study excluding severe asthma

Community Based Experience with Cluster IT (Harvey, JACI abstract 2/2006)

•Peds/adult with asthma/AR, (?allergen), 9 wk cluster (n=48) vs. 22 wk conventional (24)

• Systemic rxn mild (tx with antihistamines); ***0.3% of cluster inj vs. 0.2% conventional*** **inj**

Prospective studies
Single Cluster Allergen IT

Study	Subjects	IT Schedule	Adverse rxns
Ewbank, JACI 03	28 cat allergic adults with AR ± intermittent asthma, pre-medicated with loratadine 10 mg PO	5 wks (6/5/4/3/1 inj per wk) to a maint dose of 0, 0.6, 3, or 15 µgFeld 1	• **No** systemic rxns • 1 subject with repeated LLR
Nanda, JACI 04	*As above + zafirlukast 20 mg PO*	*4 wks (8 visits) to a maint dose of 0, 0.6, 3, or 15 µgFeld 1*	• 1 subject with pruritus, treated with diphenhydramine

- Probable effective dose for cat immunotherapy: 11-17 µgFeld 1

Cluster Immunotherapy: Immunological changes at 5 weeks predictive of 52 weeks

- 3 studies (28 pts each) that investigated dose response of **cat or dog extract** compared placebo, 0.5, 3 and 15 mcg of Fel d 1[1,2] or Can f 1[3]
- Found **15 mcg** had the greatest/most consistent efficacy in terms of objective parameters
- Immunological changes at 5 weeks reflective of 52 weeks
- Loaratadine +zarfirluscast 2 hrs before: 1 SR in 3 studies-urticaria 1st dose in vial 1 (loratadine +zafirlucast) [2]

1. Ewbank JACI 2003; 111: 155-161
2. Nanda et al, JACI; 2005 114: 1339-1344
3. Lent et al, JACI 2006 118: 1249-125

Prospective studies

Safety of Two Cluster Schedules for SCIT in AR or Asthma Patients Sensitized to Inhalant Allergens (Pfaar, Int Arch All Imm 2009)

Subjects: Adult, AR and/or asthma	IT Schedule	Adverse rxn rate
HDM IT (47) **•Derp 1&Derf 1**	3 wks (3/2/2 inj per wk)	•All systemic reactions mild; pollen **0.1%** of inj, dust mite **0.3%** of inj • LLR; pollen **3.6%** of inj, DM **1.9%** of inj
Pollen IT (110) **• 5 grass mix** **• olive + 3 grass mix** **• 3 tree mix**	4 wks (3/3/2/2 inj per wk)	

- Clinical efficacy not reported
- Maintenance doses a little questionable

Allergen	Maint dose	Probable eff. dose
Derp 1	8 µg	3.25 - 12 µg
Phlp 5	5.6 µg	15 - 20 µg
Bet v 1	40 µg	3.28 - 12 µg

Prospective studies

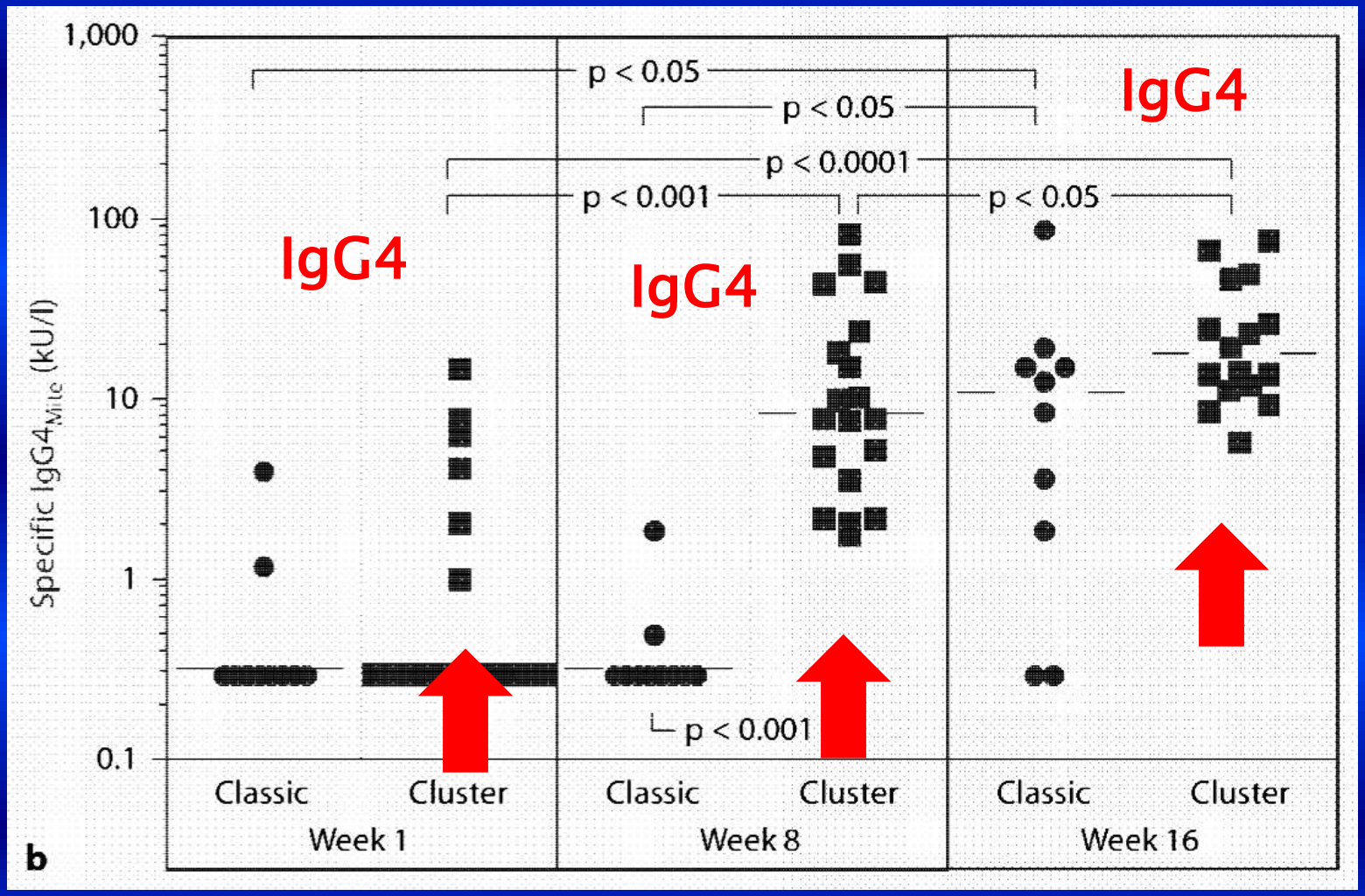
Three Clusters Schedule

Prospective safety study of IT administered in a cluster schedule
(Serrano, J Invest AllergolClinImm 2004)

Subjects: Adult, AR and/or mild-moderate asthma	IT Schedule	Adverse rxn rate
***D. Pteronyssinus*IT(38)**	6 wk (3/3/2/2/2/2 inj per wk)	•Systemicrxn rate **2%** of inj; epi usage rate **0.38%**, worst reaction was anaphylaxis (2) • No systemic rxn in DM group, **15%** of pts pollen group and **57%** of pts in Alternaria group
Perennial Ryegrass IT (8) **Olive tree IT (3)** **Ryegrass + olive IT (35)**		
***A.Alternata*IT (7)**		

- Did not assess clinical efficacy
- Maintenance dose unclear to me, unstandardized extracts

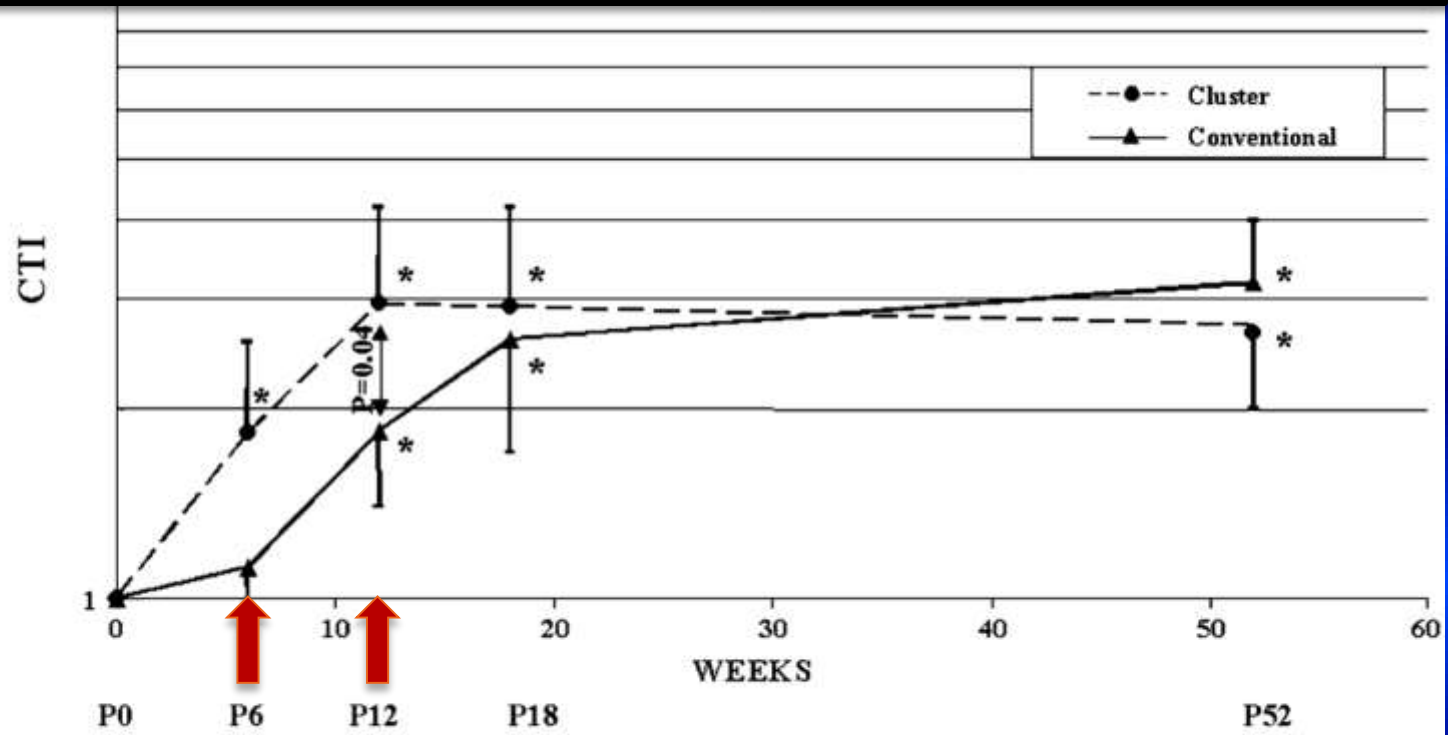
Immunogenicity



Safety and Immunogenicity of Cluster IT in Children with Asthma and Mite Allergy (Schubert, Int Arch All Imm 2009)

Skin test reactivity

Cutaneous Tolerance Index (CTI) = number of times in which it is necessary to multiply the concentrations of an extract, in order to obtain the same wheal areas as those obtained by the same concentrations of another extract



Cumulative Dose IT BU			
Cluster	25.3	25.3	41.3
Conventional	0.85	22.65	38.65

* Difference from P0; $p<0.05$

DB comparative study of cluster and conventional IT schedules with *D. pteronyssinus*(Tabar, JACI 05)

A novel approach in Immunotherapy

combination of SLIT plus SCIT

- Study 51 dust-mite asthmatic children randomized to SCIT, SLIT, **SCIT plus SLIT,** or pharmacotherapy for 18 months (ALK Alutard SQ & glycerinated extract)
- Build-up and maintenance phases was
  - 1.5 and 52.8 mcg of Der p 1 in SLIT group,
  - 16.2 and 44.1 mcg of Der p 1 in the SCIT group
  - 16.2 and 43.2 mcg of Der p 1 in **the SCIT plus SLIT**

TABLE E1. Immunotherapy schedule of the groups for 1 year

		SLIT group	SCIT group	SCIT + SLIT group
Build-up phase	Dose scheduled	Vial 0: 1-5 drops	Vial 1: 0.2, 0.4, 0.8 mL	Vial 1: 0.2, 0.4, 0.8 mL
		Vial 1: 1-5 drops	Vial 2: 0.2, 0.4, 0.8 mL	Vial 2: 0.2, 0.4, 0.8 mL
		Vial 2:1-5 drops	Vial 3: 0.2, 0.4, 0.6, 0.8 mL	Vial 3: 0.2, 0.4, 0.6, 0.8 mL
		Vial 3: 1-5 drops	Vial 4: 0.1, 0.2, 0.4, 0.6, 0.8, 1 mL	Vial 4: 0.1, 0.2, 0.4, 0.6, 0.8, 1 mL
		Vial 4: 1-5 drops		
	Duration	30 d	16 wk	16 wk
	Cumulative dose (Der p 1)	1.5 μg	16.2 μg	16.2 μg
	Cumulative dose (Der f 1)	1.5 μg	22.9 μg	22.9 μg
		750.7 STU	331.540 SQ-U	331.540 SQ-U
Maintenance phase	Dose scheduled	5 drops of vial 4 three times a week	1 mL of vial 4 per month	5 drops of vial 4 three times a week
	Cumulative dose (Der p 1)	52.8 μg	44.1 μg	43.2 μg
	Cumulative dose (Der f 1)	52.8 μg	62.1 μg	43.2 μg
		26.400 STU	900.000 SQ-U	21.600 STU

SQ U, Standard quality unit; *STU*, skin test unit.

Keles et al, Journal of Allergy and Clinical Immunology. 2011;128(4):808-15 e7

A novel approach in Immunotherapy

combination of SLIT plus SCIT

- Asthma attacks and ICS decreased compared with baseline values at the months 4, 12, and 18 in the SCIT and **SCIT plus SLIT groups** but only at month 12 in SLIT group
- Rhinitis **VAS** was **significant only in the SCIT plus SLIT group.**
- Increases in the levels of regulatory and TH1 cytokines were observed both in the SCIT and SLIT groups, with some differences in dynamics.
- Antigen-specific **IgG4** levels increased in the SCIT and **SCIT plus SLIT groups** but not in the SLIT group

Keles et al, Journal of Allergy and Clinical Immunology. 2011;128(4):808-15 e7

Cluster IT Disparities
U.S. vs. Europe

- Differences in extracts
- 1-2 allergen IT vs. multiple allergens
- Dosing differences

Europe

- Extracts standardized by in-house reference and were depot extracts adsorbed on aluminum hydroxide or calcium phosphate
- Clinical experience from US suggests a higher rate of systemic reactions than conventional IT & European cluster studies
- 92.3% premedicated
  - Antihistamine, montelukast, or both

Faster Up-dosing Can be Achieved With Hypoallergenic Preparations

Subcutaneous immunotherapy (SCIT) traditionally includes an updosing phase injecting increasing doses of allergen over a period of several weeks or months, followed by a maintenance phase

Hypoallergenic depot preparations have an establish updosing schedules – where the maintenance dose can be reached in 4-8 weeks

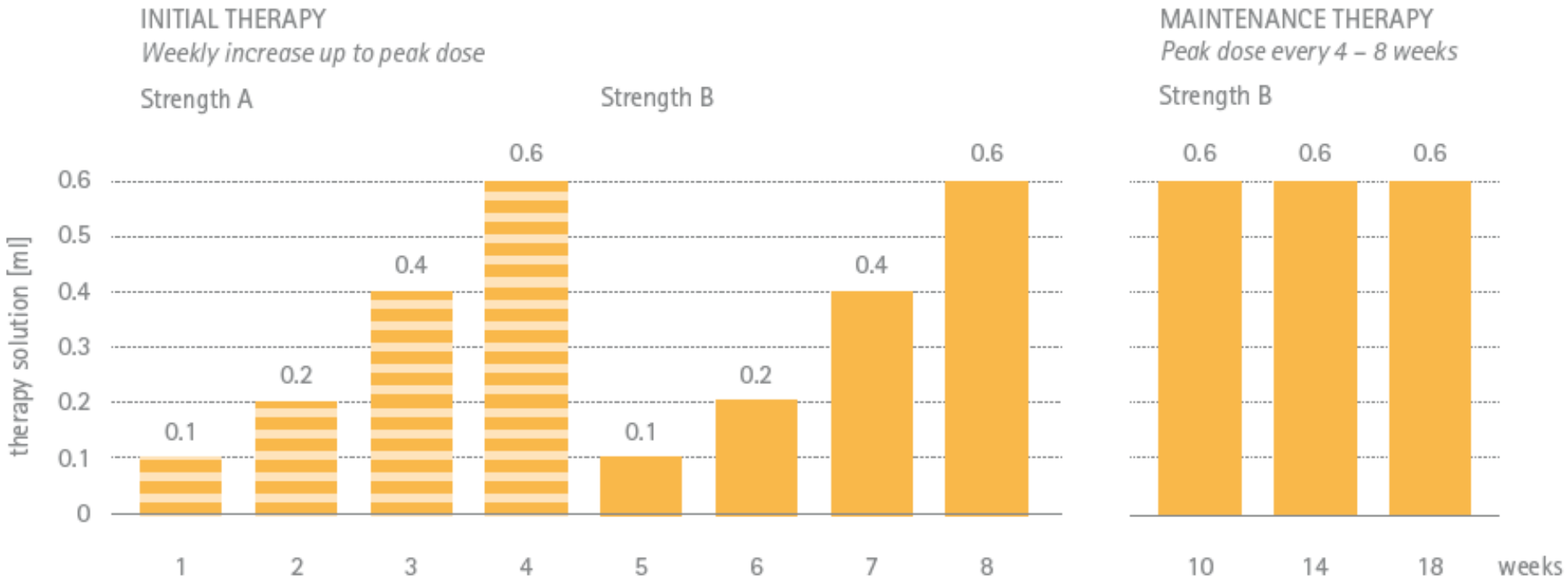
Shorter and more convenient updosing schedules

Dokic D, et al. Allergo J 2005;14:337-43.
Eng PA, et al. Allergy 2006;61:198-201.
Nieto García A, et al. Eur Ann Allergy Clin Immunol. 2013 May;45(3):78-83.

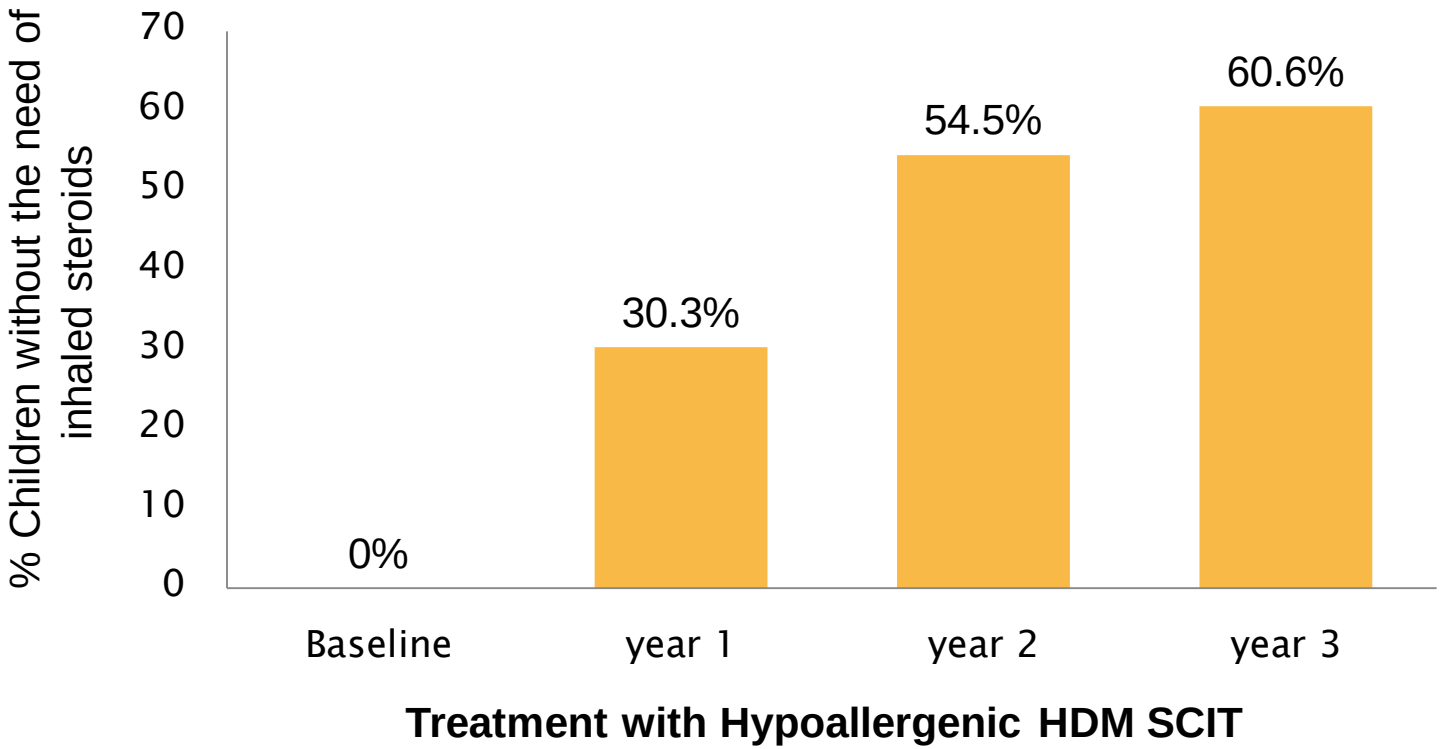
Advantages of Allergoids (Europe)

Feature of Allergoids	Effect	Clinical Implications
Reduced allergenicity	Improved safety profile	Reduced risk of systemic adverse events
Retained immunogenicity	Efficacy retained	Efficacy proven in clinical trials
Convenient dosing	Significantly shortened up-dosing phase	Better patient and physician acceptance Better compliance

Dosing Schedule Allergoids (Europe)



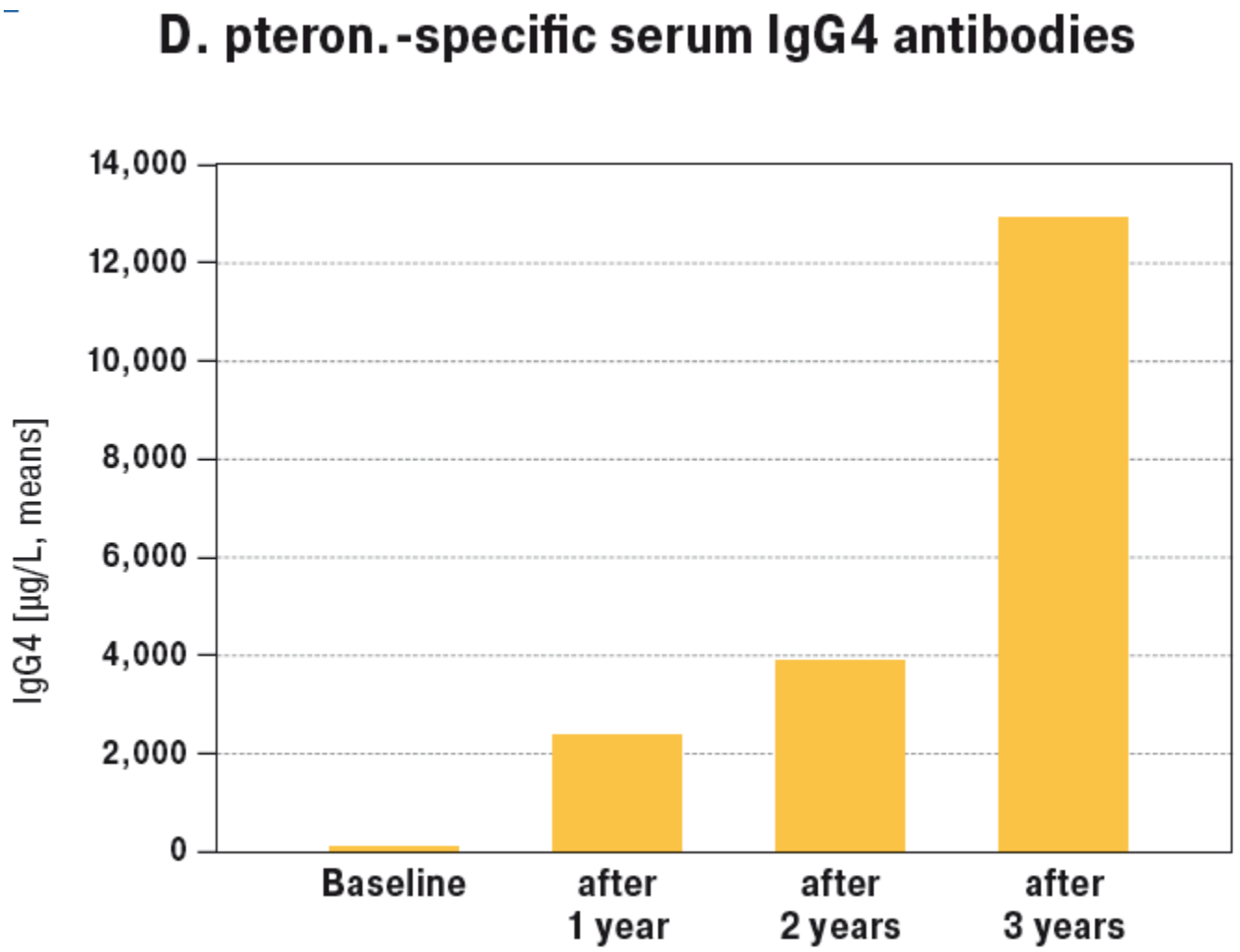
Reduction in usage of Inhaled Corticosteroids in Asthmatic Children after Treatment with Hypoallergenic SCIT



60.6% of house-dust mite allergic asthmatic children don‘t need any ICS after 3 years of hypoallergenic HDM SCIT

Rudert M et al., EAACI-Congress 2012

Increases in IgG4 with therapy



Rudert M et al., EAACI-Congress 2012

Evidence from Real-life Clinical Assessment: Reduced Allergenicity

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment

- A total of 4363 different courses of AIT (AIT treatments) were initiated and monitored in 4316 patients (SCIT: 3398 treatments, 77.9%)
- For SCIT, 49.8% of treatments were based on **hypoallergenic** preparations

Table 4 Evaluation of risk factors (using a multivariate regression analysis model) for SRs and anaphylaxis during SCIT

Risk factor	Odds ratio with 95%CI	*P* value
For SRs during SCIT		
Type of extract (natural *vs* allergoid)	2.739 (1.612–4.878)	**0.001**

Calderon MA, et al. Allergy 2017; 72: 462–472.

Hypoallergenic Depot Standardized Preparations to Reduce AE & Recurrent Injections

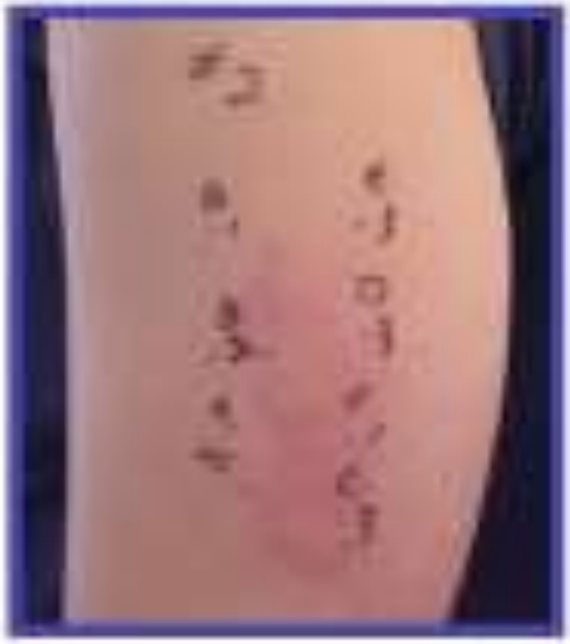
Improved safety	Hypoallergenic preparations pursued the therapeutic objective of producing allergen extracts with reduced potential of side-effects
Lesser injections	Through introduction of depot preparations it became possible to reduce the number of injections and the risk of adverse events
Faster updosing	Hypoallergenic preparations allow maintenance doses to be reached much earlier (~1-2 months) as compared to conventional AIT
Improved compliance	Hypoallergenic preparations are associated with improved compliance rates as compared to conventional AIT

Thum-Oltmer S, et al. Mod. Asp. Immunobiol. 2005;15:15-18
Egert-Schmidt, et al. Patient Preference and Adherence 2014:8 1475–1481

Final thoughts

- Cluster immunotherapy is as safe and cheaper/faster than conventional IT.
- Use of a premedication to be administered between 15 and 60 minutes before the first administration of each cluster, especially in asthmatic patients.
- Use of depot preparations (Aluminum hydroxide adjuvant)
- Not more than 4 administrations per cluster.
- Administration of one to two clusters per week.
- Let's do premedicated cluster IT here!
  Get your shots and goooooooo!

Rush Immunotherapy



Subcutaneous Rush Schedule

- RIT incremental doses of allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved
- RIT schedules for inhalant allergens can be associated with a greater risk of SR, particularly in high-risk patients and premedication appears to reduce the risk associated with aeroallergen RIT
- However, venom RIT does not appear to a similar high incidence of systemic reactions and premedication does not appear to be necessary.
- Conflicting data with fire ant in terms of premedication

Cox L, Li J, Lockey R, Nelson H. Allergen immunotherapy: A practice parameter second update. JACI 2007;120:S25-S85.

Premedication with accelerated immunotherapy schedules.

Summary Statement 57:

Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy build-up protocols. A

Cox et al, J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55

Instant Reference for Health Professionals

Published by the American College of Allergy, Asthma & Immunology

Procedure for Rush and Cluster Immunotherapy

Premedication

Rush ImmunoTherapy (RIT)

Patients receiving 1 or 2-day RIT should receive premedication starting 2 days prior to the procedure to reduce the likelihood of a systemic reaction.

H-1 antagonist

- Cetirizine
- Fexafenadine
- Diphenhydramine

H-2 antagonist

- Ranitidine

Corticosteroid

- Prednisone

Leukotriene receptor antagonist

- Monteleukast

Procedure for Rush and Cluster Immunotherapy Instant Reference for Health Professionals Published ACAAI

Modified One Day Protocol: Reduced SR Rate When Target Dose Decreased to 0.1 ml of 1:10v/v

Comparison of RIT protocols with different final target doses*

Dose ≥ 0.2 ml of 1:10 v/v: SR 18.1% (n=72):

Dose 0.1 ml of 1:10 v/v : SR 7.2% (n=111):, all mild (no epinephrine)

Recommended UT Southwestern RIT: 2-hour Protocol		
Time (minutes)	Concentration (volume:volume)	Volume (cc)
0	1:10,000	0.3
30	1:1,000	0.3
60	1:100	0.1
90	1:100	0.3
120	1:10	0.1

All patients observed 90 minutes after final dose

*Alvares M et al. AAAAI 2012 Orlando

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Recommended AIT build-up protocol following 2 hour RIT

Week	Concentration	Volume (cc)
0 (Day of RIT)	1:10 v:v	0.1
1	1:10 v:v	0.1
2	1:10 v:v	0.2
3	1:1 v:v (concentrate)	0.05
4	1:1 v:v	0.1
5	1:1 v:v	0.2
6	1:1 v:v	0.3
7	1:1 v:v	0.4
8	1:1 v:v	0.5
10	1:1 v:v	0.5
13	1:1 v:v	0.5

Pre-med of prednisone 40 mg for 1st post RIT dose

Generally recommend all pts take AH during build-up

Maintenance dose at 8 weeks with weekly post-RIT build-up (4 weeks with twice weekly build-up)

Alvares M et al. AAAAI 2012 Orlando

Slide provided and modified with permission David Khan. MD

Subcutaneous Venom Rush Schedule (VIT)

- Ultrarush stinging insect protocols achieve the maintenance dose in 2.5 to 4 hours
- VIT not associated with a higher incidence of SR as inhalant RIT
- May be well tolerated in 'high-risk' patients (e.g. SR with conventional venom IT) [1,2]
- Conflicting data on safety of fire ant (FA) RIT without premedication
  - 1-day FA RIT: 37 pts without premedication reported 24.3% experienced SR most being urticaria and pruritus.[3]
  - "Further studies are needed to clarify the risk of fire ant rush immunotherapy, and premedication might be considered." (*from the 2011 Allergen Immunotherapy Practice Parameter 3rd Update)*

1. Golberg et al, Ann Allergy Asthma Immunol 2003;91:405-10. 2.Sturm J Allergy Clin Immunol. 2002;110:928 –933. 3 Dietrich et al, Ann Allergy Asthma Immunol. 2009;103(6):535-6

Fastest SCIT Rush Schedule for Inhalant Allergens

- The most accelerated schedule for inhalant allergens: 7 injections administered over day 4 hours in a one day protocol. Premedication 1 day before and morning of RIT
  - Prednisone 40 mg, cetirizine 10 mg, ranitidine 300 mg and montelukast 10 mg/zafirlukast 40mg
  - 38 % SR Rate

Table 1. Rush Immunotherapy Protocol

Injection No.	Time, min	Concentration, volume:volume	Volume, mL
1	0	1:10,000	0.3
2	30	1:1,000	0.3
3	60	1:100	0.1
4	90	1:100	0.3
5	120	1:10	0.1
6	180	1:10	0.2
7	240	Undiluted concentrate	0.05

88% of reactions

Harvey et al Ann Allergy Asthma Immunol. 2004;92(4):414-9.

Risk Factors for Rush Systemic Reactions

FEV_1 & STR

Protocol: 125 mite-allergic asthma pts (age 4 -57) underwent a 3-day RIT.

Target dose: 3000 BU (4 μg of Der p 1) in subjects > 10 yrs and 1500 BU in < 10 yrs

	Hour	BU
DAY 1	9	30
	9:30	150
	10	300
	11	600
	14	1200
DAY 2	9	1800
	11	2400
DAY 3	9	3000

Adverse reactions: Severe SR in 34.4%.

35 pts had asthma SR, 8 pts had anaphylaxis and 5 pts had > 1 SRs

The two significant differences between pts with severe SR and those with mild or no SR were:

- Skin prick end point titration
- FEV_1 ($p<0.001$) before RIT

  73% of pts with FEV1 < 80% had asthma rx during RIT vs. 12.6 % of pts with FEV1 > 80%.

Bousquet et al, J Allergy Clin Immunol 1989; 83 (4) 797-801

Summary: Alternative Schedules & Premedication

- **Aeroallergen RIT** -greater risk , **cluster**- data conflicting
- **Venom RIT** appears as safe as conventional with no predmedication- but verdict out on fire ant
- **Risk Factors For Systemic Reaction With Accelerated AIT**
  - Degree of skin test reactivity
    - Portnoy et at found that the most important predictor of a systemic reaction was the initial wheal size.
    - Bousquet et al found a correlation with STR & SR
  - FEV_1 < 80% predicted
  - Dose: increased SR with > vial 2 (1:10 v/v) 0.1 ml
- Premedication reduced SR rate in RIT & Cluster aeroallergen studies
- Premedication does not increase severity or frequency of SR by masking early warnings.

Who Is The Winner? This Should Determined By Patient Preference And Physician Judgment

Efficacy	favours cluster immunotherapy
Safety	favours cluster immunotherapy
Compliance	favours cluster immunotherapy
Cost-effectiveness	favours cluster immunotherapy

Thanks

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