CLUSTER IMMUNOTHERAPY "Convenience vs. Safety"

"Dr P.C.KATHURIA"

MD. (Chest) D.N.B (Resp.) DTCD,FCAI FCCP

ALLERGY –IMMUNOTHERAPIST

Senior Consultant

"NATIONAL ALLERGY CENTRE"

"BLK Super specialty Hospital, Delhi"

Why do Allergists Love IT?

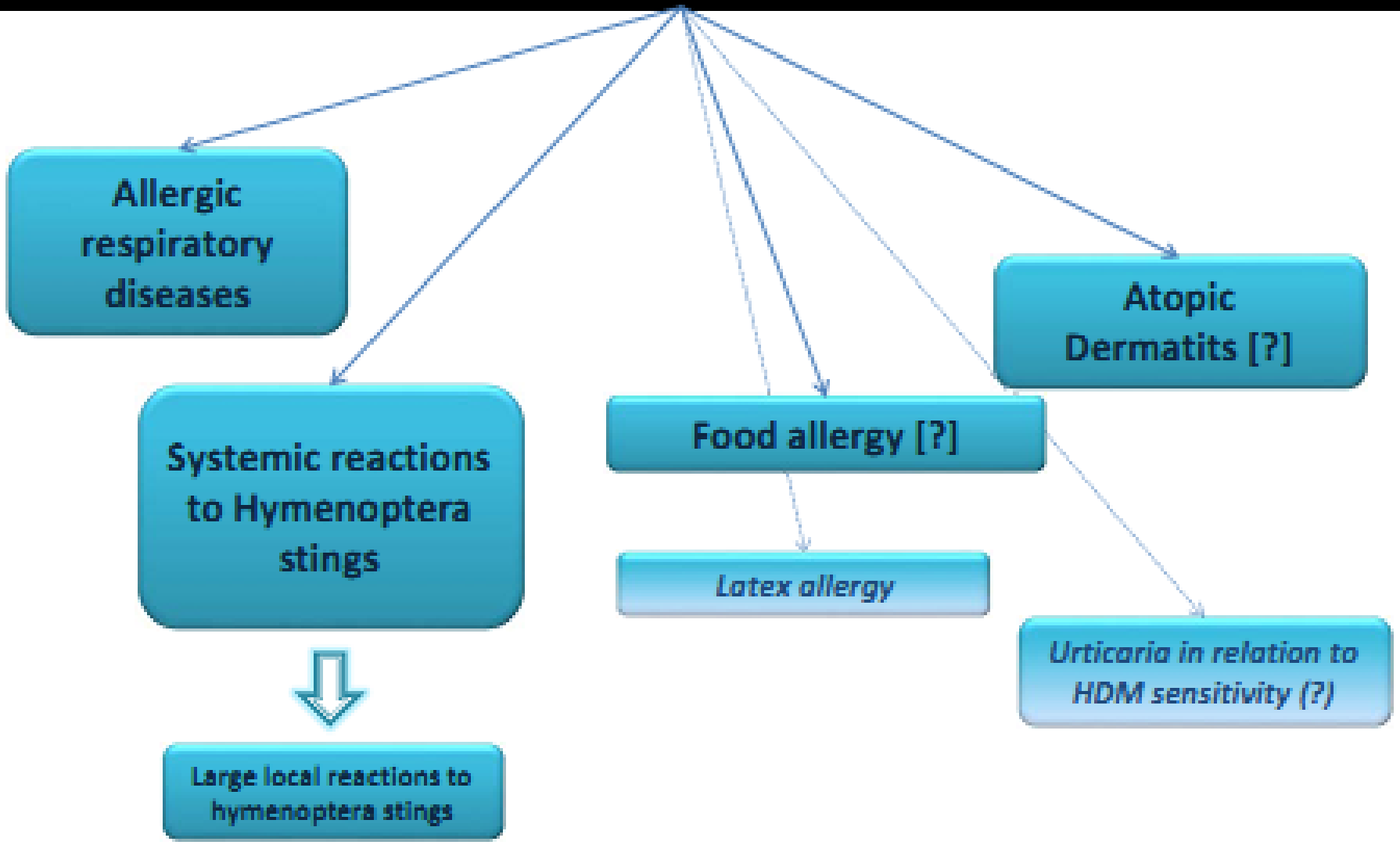
- Subcutaneous immunotherapy (SCIT) has been used for over 100 years
- Well documented efficacy for AR and asthma secondary to pollens, HDM, and cat
- What are the benefits of SCIT?
  - **Relieves symptoms (⇩ progression)**
  - **Has disease-modifying effects (persistent)**
  - **May prevent new sensitization and asthma**

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

Indications of Immunotherapy



ACAAI eNews

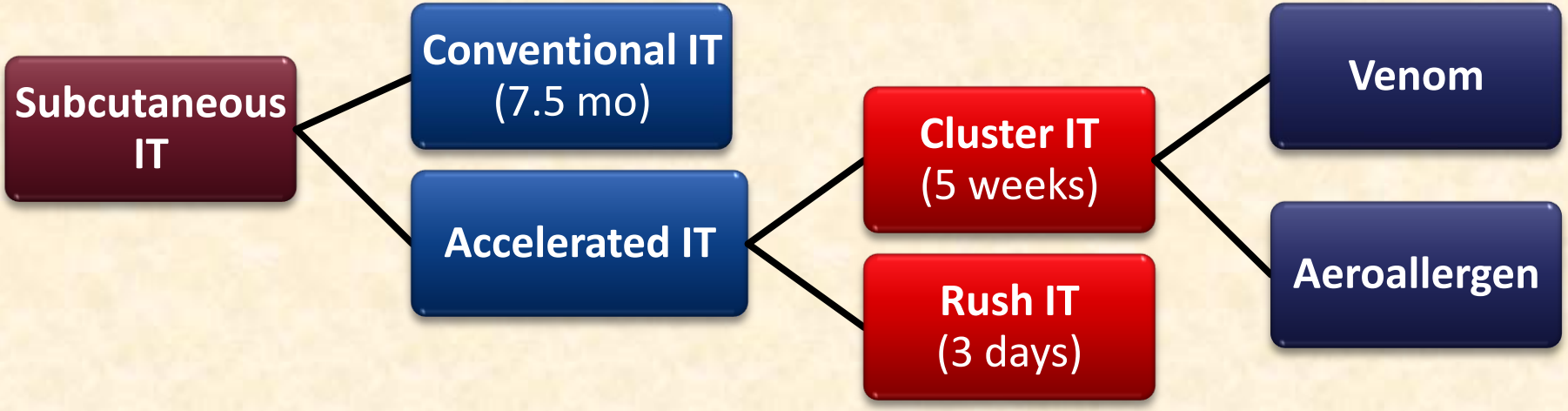
Inconvenience due to the **time involved** in receiving allergen IT injections in a medically supervised setting is likely the reason for the low utilization of SCIT.

* AGE
* ASTHMA
* STR

* SPECIFICITY
*STANDARDIZATION
* SATBILITIY
* SAFTY

* 5 -20 µg / dose x 3-5 yrs

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



ACCELERATED AIT SCHEDULES DATE BACK TO EARLY1900'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."

Definition

J ALLERGY CLIN IMMUNOL
SEPTEMBER 2007

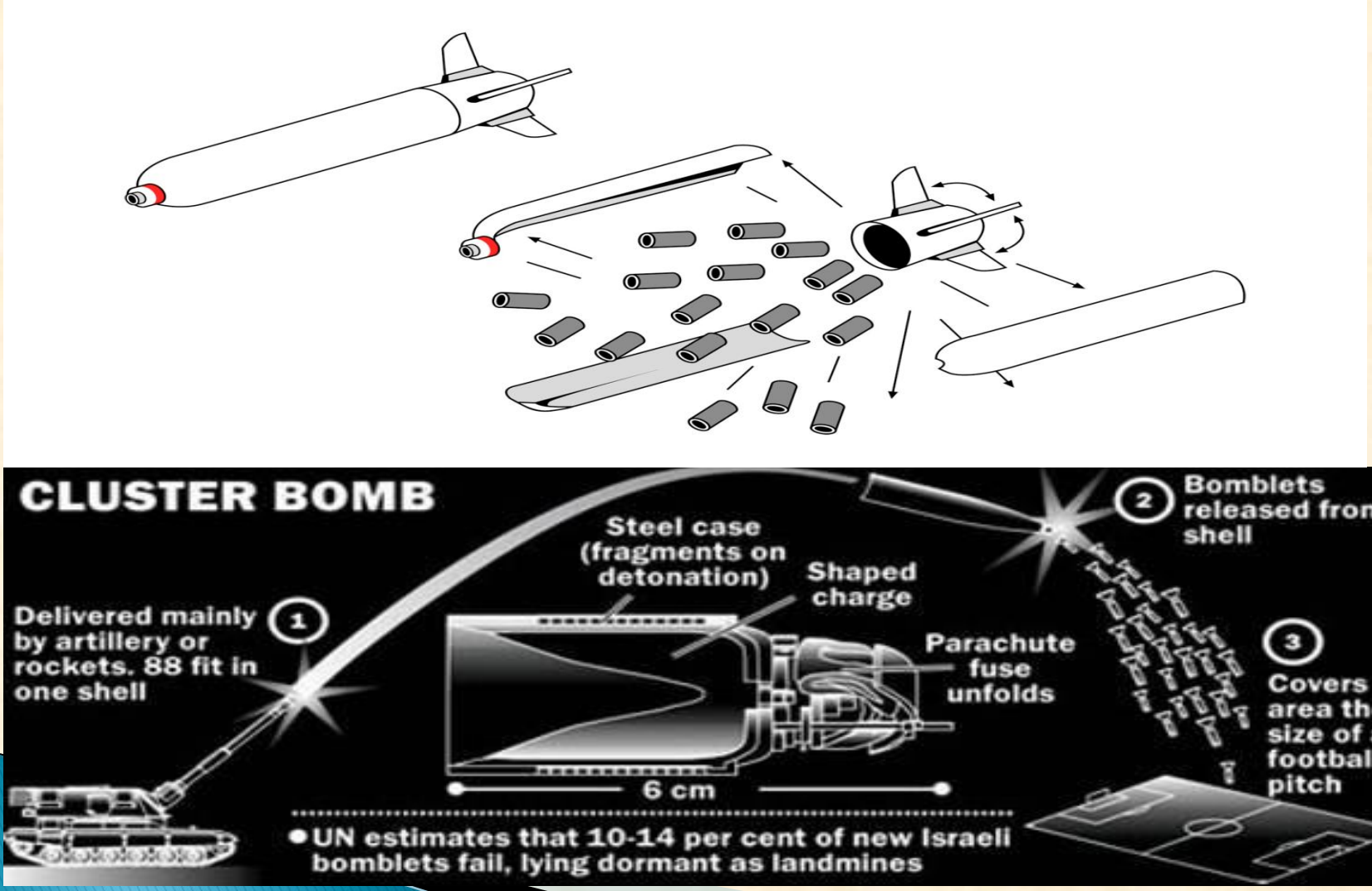
Allergen immunotherapy: A practice parameter second update

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

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?

(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

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

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

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 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

Advantages & Disadvantages of Accelerated Immunotherapy Schedules

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	15% 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

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

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

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

Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

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%),

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.

Premedication

J ALLERGY CLIN IMMUNOL
SEPTEMBER 2007

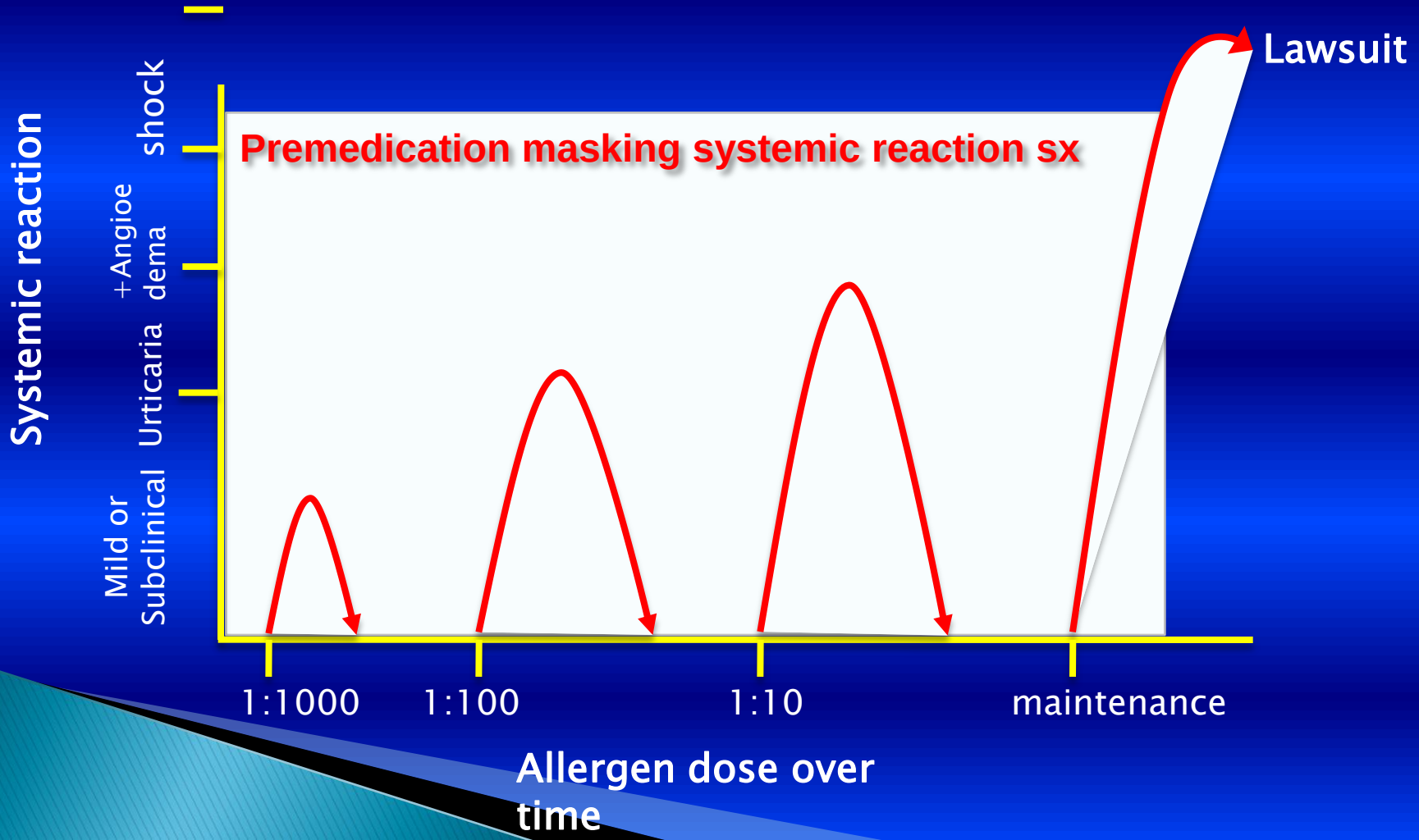
Allergen immunotherapy: A practice parameter second update

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



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

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

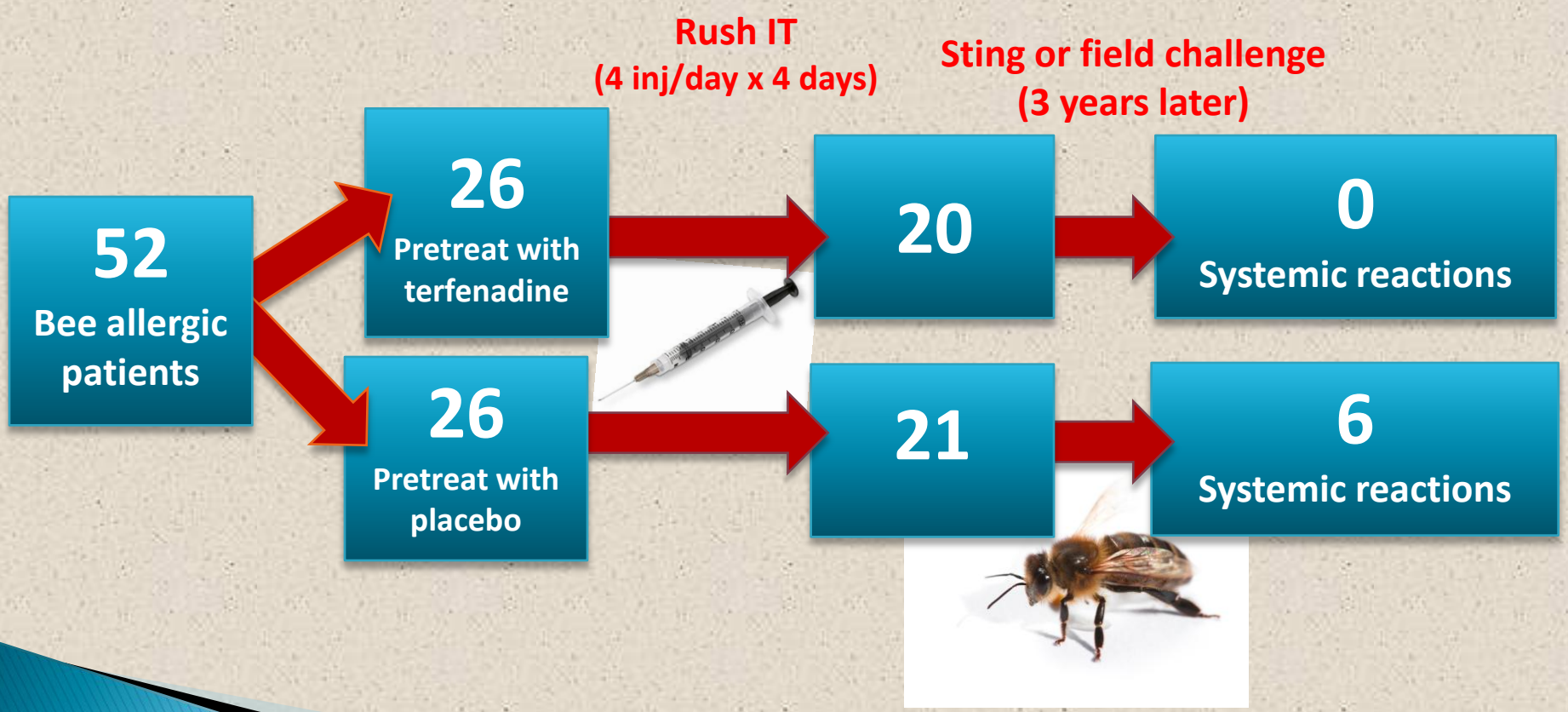
Premedication with montelukast reduces local reactions of allergen immunotherapy

- **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

- Does premedication alter the efficacy of IT?



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

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)

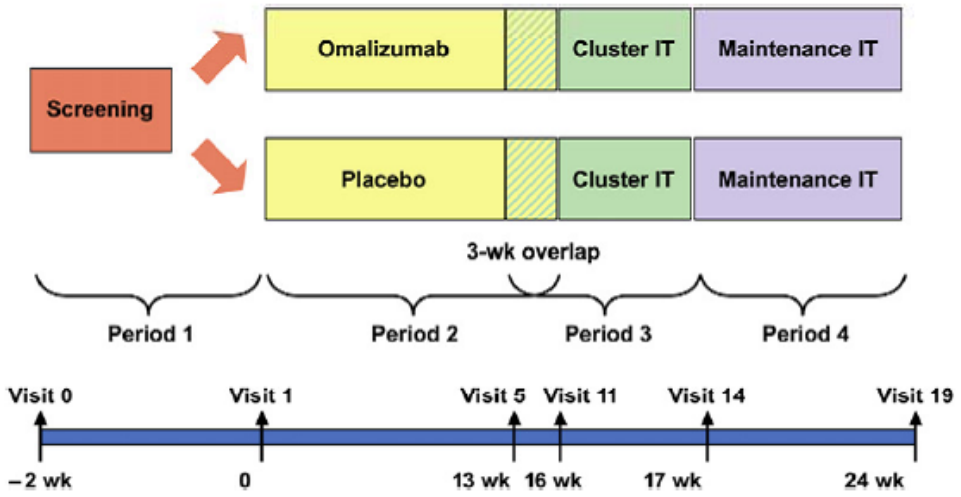


FIG 1. Study design.

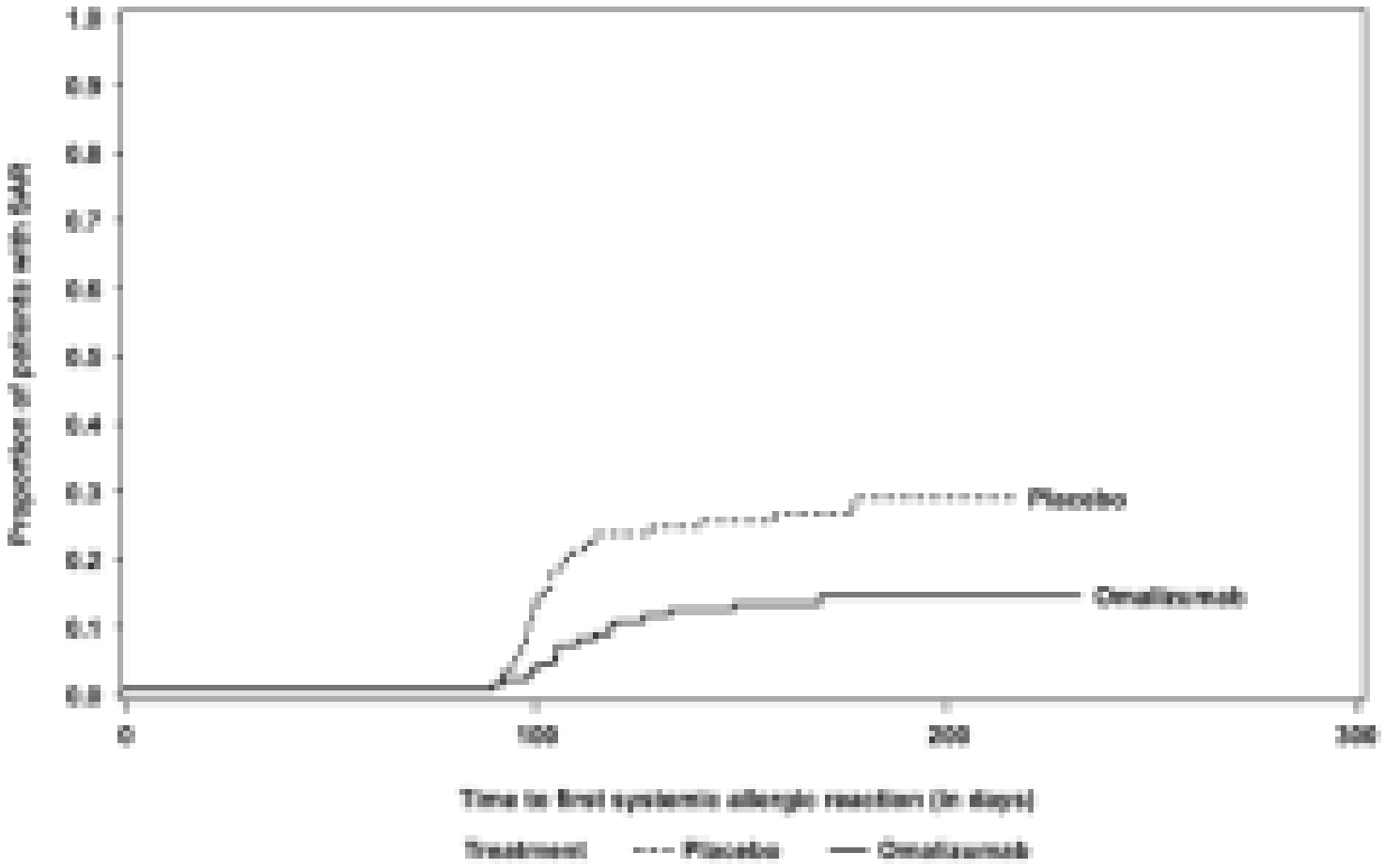
Massanari et al, J Allergy Clin Immunol. 2010;125(2):383-9

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



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

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.

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

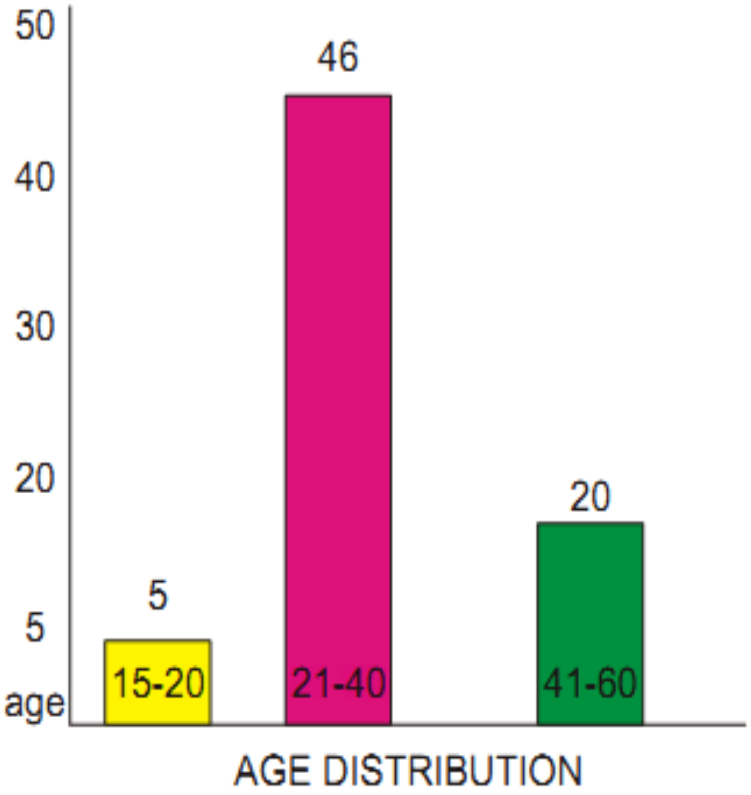
A) combined Omalizumab (Anti-IgE) + Cluster Immunotherapy - (9)

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)

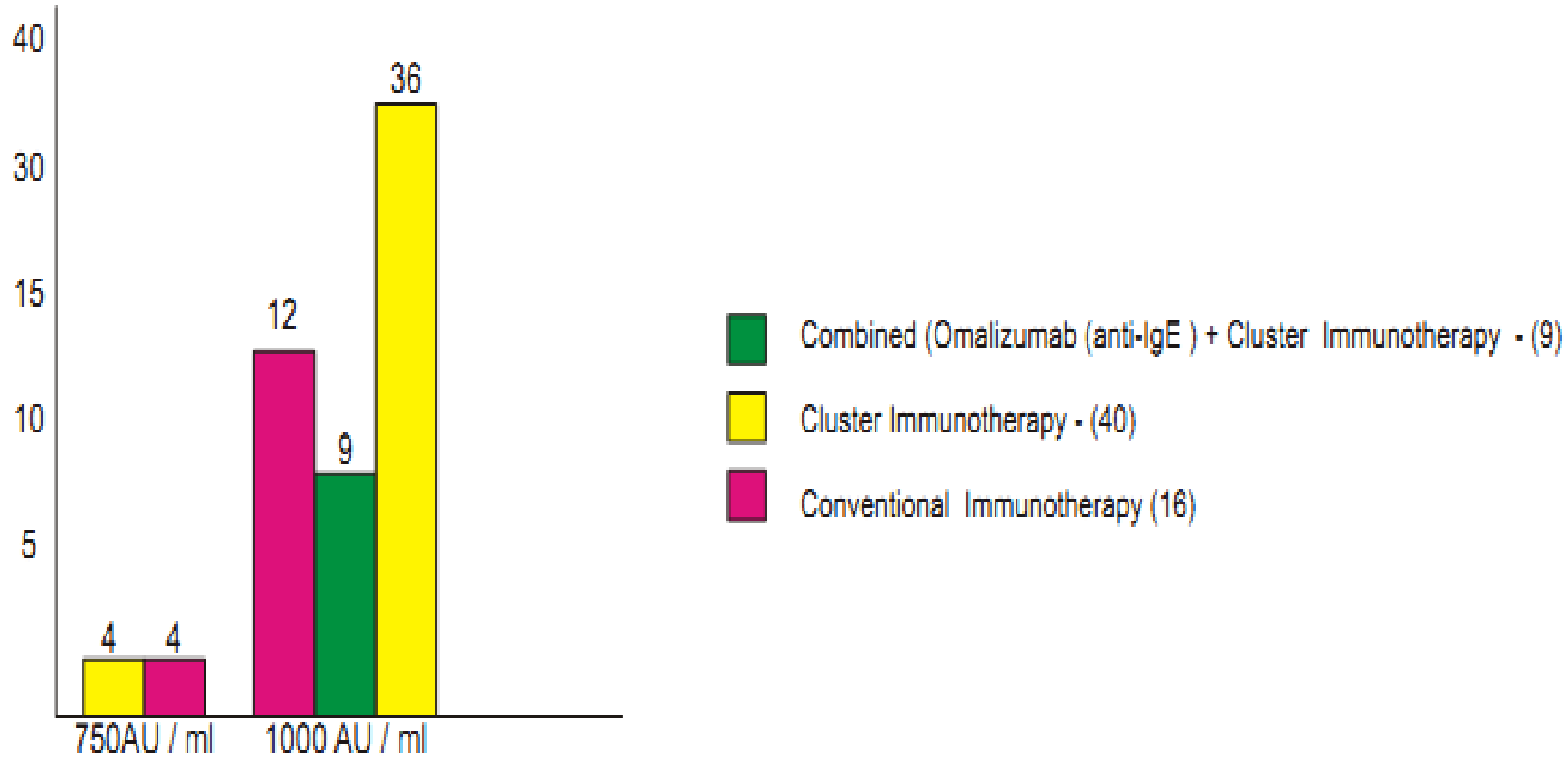


AGE DISTRIBUTION

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

SEX DISTRIBUTION

- **RESULTS -**



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

Comparison studies

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

Comparison studies

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

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

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

 **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)**		

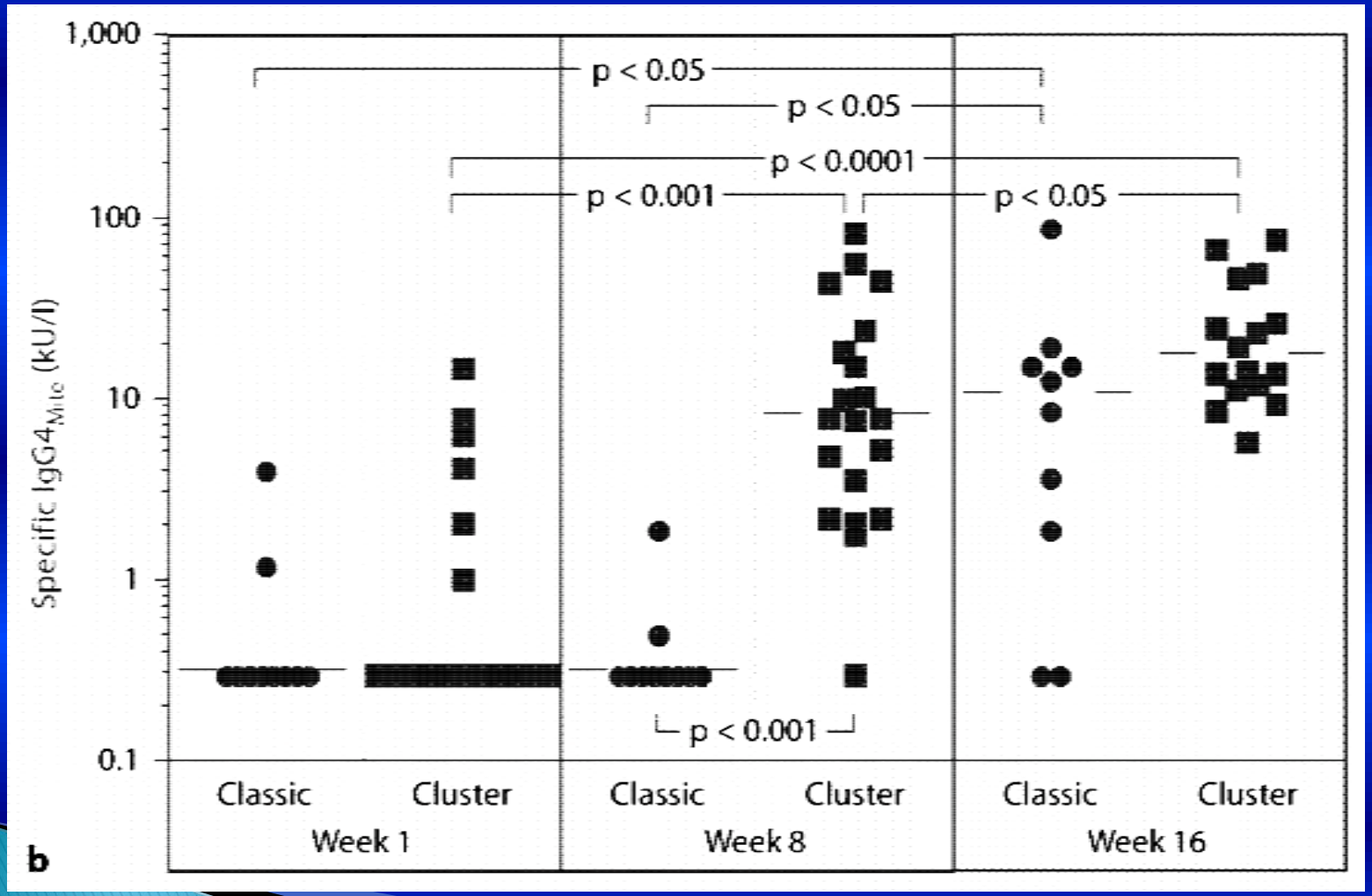
- Did not assess clinical efficacy
- Maintenance dose unclear to me, unstandardized extracts

Prospective studies

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

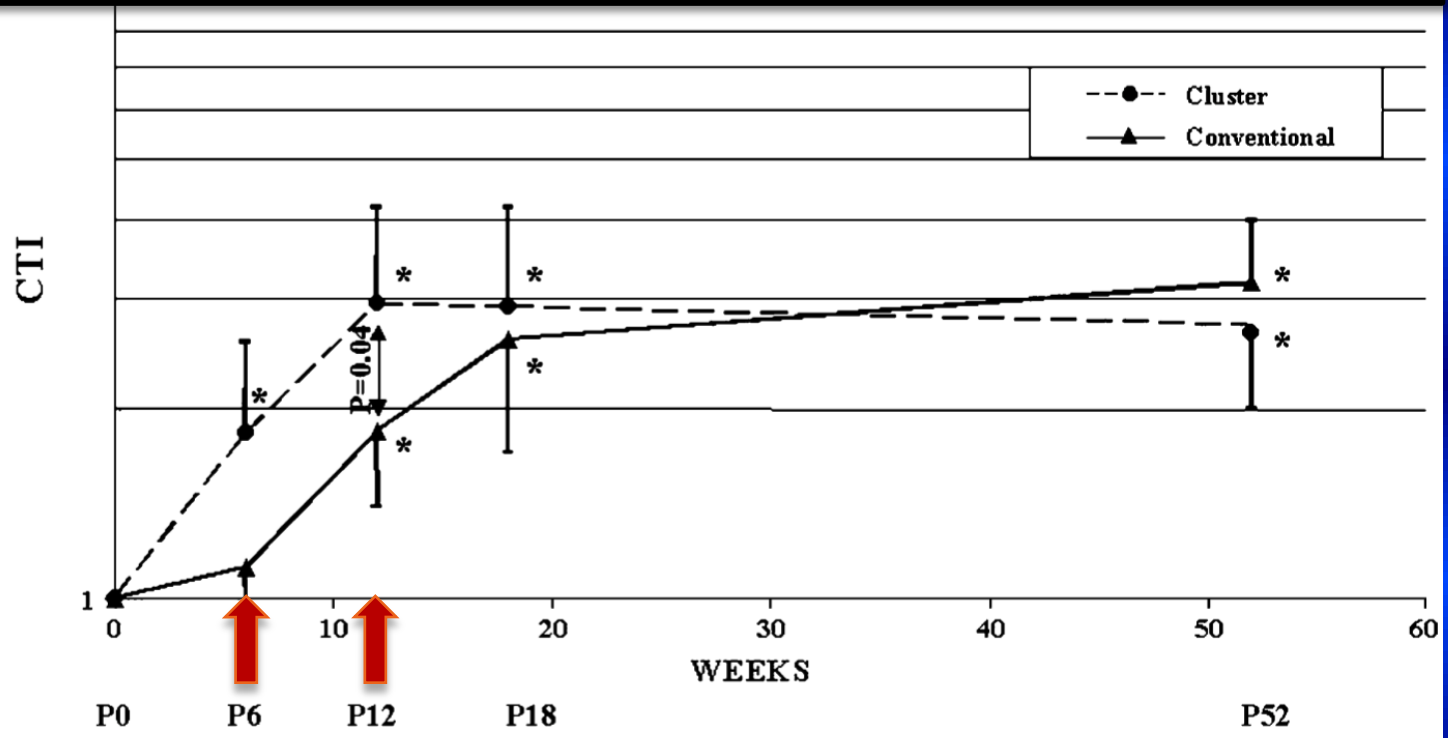
Immunogenicity



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)

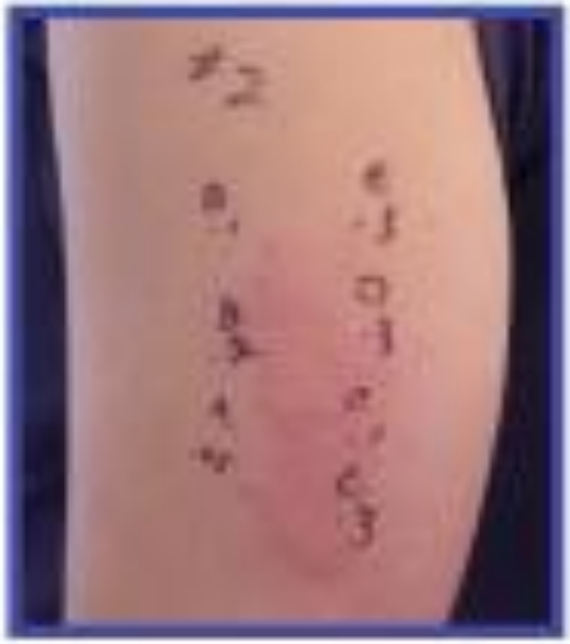
Cluster IT Disparities U.S. vs. Europe

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

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

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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

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

Reduced SR and Severe SR with Premedication and Preventive Measure

Table 1. Systemic Reactions According to Immunotherapy Schedule, Premedication, and Prevention Measures in Dust Mite and Pollen Allergic Patients With Allergic Rhinitis With or Without Asthma*

Treatment regimen	Allergen	SR per patient, %	SR per injection, %	Asthma reactions, %	Anaphylaxis, %
Group A: 3-day RIT, 290 patients	Dust mite, 290 patients	36	3.8	30.6	5.1
	Pollen, 74 patients	31.3	3.1	9.7	5.8
Group B: RIT plus premedication†	Dust mite, 160 patients	16.2	2.0	13.7	1.8
	Pollen, 102 patients	14.7	3.1	5.8	5.8
Group C: RIT plus premedication and preventive measure‡	Dust mites, 479 patients	7.3	0.8	6.8	3.2
	Pollen 200 patients	7.5	2.3	2.5	3.3
Group D: step protocol with premedication and preventive measure§	Dust mites, 223 patients	5.1	0.6	5.0	3.1
	Pollen, 78 patients	2.6	2	0	3

Table from Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol. 2006 Aug;97(2):126-37

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.

Mild reaction at 55, severe at 150 minutes

"29-year-old woman who began developing pruritus on her neck 55 minutes after the third-to-last injection of the protocol. The next injection was held, but she developed urticaria that was treated with cetirizine and prednisone. Ninety minutes after the onset of her symptoms, the patient acutely worsened and became hypotensive. She was treated with 2 doses of epinephrine, 0.5 mg, administered intramuscularly with prompt resolution of

her hypotension. Her course after RIT was uneventful, and she reached a maintenance dose of 0.5 mL of concentrate."

Harvey SM et al. Ann Allergy Asthma Immunol 2004;92:414-9.

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

NATIONAL ALLERGY CENTRE

Tel : *25884136*
25880057
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