Unconventional Immunotherapy: Updates on Rush and SLIT

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UT SOUTHWESTERN MEDICAL CENTER

Disclosures

- Research Grants
  - NIH
- Honoraria
  - UpToDate, Genentech
- Consulting
  - Aimmune (DSMB)
- Organizations:
  - Joint Task Force on Practice Parameters
  - AAAAI BOD

Objectives

- By attending this lecture the participant should be able to:
  - Differentiate rush protocols from cluster or conventional immunotherapy
  - Discuss advantages and disadvantages of rush immunotherapy
  - Describe common reactions seen during rush immunotherapy and methods to reduce them
  - Discuss updates in SLIT

Rush Immunotherapy (RIT) Definition

- Rush immunotherapy is an accelerated immunotherapy build-up schedule that entails administering incremental doses of allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved

Allergen immunotherapy: A practice parameter third update
J Allergy Clin Immunol 2011;127:S1-55.

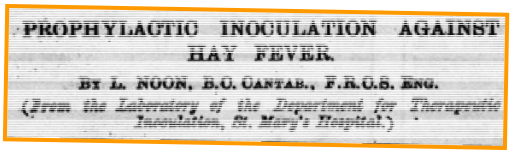
Cluster Immunotherapy (CIT) Definition

- Cluster immunotherapy is an accelerated build-up schedule that 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).

Allergen immunotherapy: A practice parameter third update
J Allergy Clin Immunol 2011;127:S1-55.

The Origins of Accelerated IT Schedules

Leonard Noon (1878-1913)



PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

BY L. NOON, B.C. CANTAB., F.R.C.S. ENG.

(From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)

Noon L, Cantab BC Lancet 1911,i:1572.

History of Rush Immunotherapy

- "Leisurely" Desensitization 1909
  - Developed by Noon and Freeman
  - "…inoculations were given weekly merely because our out-patients were in the habit of coming every week."
  - "This plan has worked fairly well, and is still perhaps the method in most general use."

Freeman J. Lancet 1930;i:744-7.

John Freeman (1877-1962)

"RUSH" INOCULATION,

WITH SPECIAL REFERENCE TO HAY-FEVER TREATMENT.

By JOHN FREEMAN, D.M., B.Ch. Oxf.,

DIRECTOR OF THE DEPARTMENT OF CLINICAL BACTERIOLOGY, ST. MARY'S HOSPITAL.

Freeman J. Lancet 1930;i:744-7.

Intensive Desensitization (Cluster)

- "Intensive Desensitization" 1924
  - "Later when desensitizing horse asthmatics or other animal sensitives to horse dandruff, &c., I fell into the way of inoculating these patients every day with gradually increasing doses (a 10% to 20% increase). There was no off season with these people, and they were usually in a great hurry to go and hunt, or look after their dogs, or retrieve their cats…
  - "This intensive method proved so convenient, that in 1926 I gave it to a number of hay-fever patients, and have used it increasingly ever since"

Freeman J. Lancet 1930;i:744-7.

Rush Desensitization

- "Rush Desensitization"
  - Injections q 1.5-2 hrs during a 14 hr day
  - Build-up over several days
  - Dose increased by 10-20%
  - Done in hospital setting with nurse and "constant supervision of the doctor"
- Initial cases of RIT
  - Dust asthma
  - Fish-sensitive
  - Horse asthma
  - Grass hay-fever

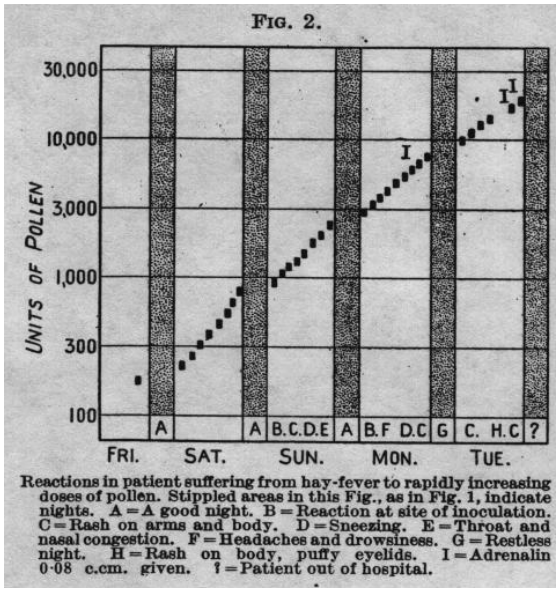
Freeman J. Lancet 1930;i:744-7.

Case of GH

- Young gymnastic instructress with uncomplicated hay-fever
- "Early in June she arrived in a desperate state, a mental and physical wreck, and quite unable to carry on her work."
- "She was taken into hospital and put through a "rush" course of pollen inoculations…"

Freeman J. Lancet 1930;i:744-7.

G.H. Pollen Rush



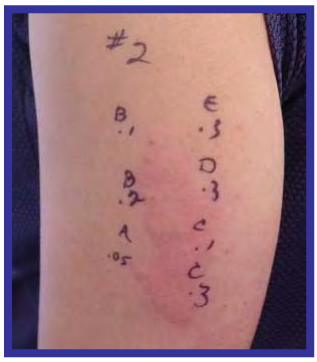
Reactions in patient suffering from hay-fever to rapidly increasing doses of pollen. Stippled areas in this Fig., as in Fig. 1, indicate nights. A = A good night. B = Reaction at site of inoculation. C = Rash on arms and body. D = Sneezing. E = Throat and nasal congestion. F = Headaches and drowsiness. G = Restless night. H = Rash on body, puffy eyelids. I = Adrenalin 0·08 c.cm. given. † = Patient out of hospital.

Case GH Outcome

- In four days the dose increased from 160 units to 17,000 units
- She left the hospital and afterwards and "rolled in a hayfield without being able to get a sneeze out of it"
- "She was cured- for that year at any rate."

Freeman J. Lancet 1930;i:744-7.

Rush Immunotherapy



Rush Immunotherapy Terminology

- Ultra-rush
  - Typically reaches maintenance in 1 day
- Rush
  - Typically reaches maintenance in 2-3 days
- Modified Rush
  - 1 day of frequent injections (5-8) to reach 80-90% target maintenance
  - Followed by conventional build-up over few weeks to reach maintenance

Rush Immunotherapy (RIT)

- Aerollergens
  - Pollens
    - trees, grasses, ragweed
  - Dust mites
  - Molds (*Alternaria*)
  - Animal danders (cat and dog)
  - Aeroallergen mixes
- Other Allergens
  - Venoms
  - Latex
- Subcutaneous and sublingual methods

Aeroallergen Rush Immunotherapy Basics

- 1-2 day build-up schedule typically with multiple injections (5-8) given in a single day
- **Most Rush protocols do not achieve maintenance after Rush build-up**
- Maintenance dose achieved in 4-8 weeks after Rush build-up

Multi-Aeroallergen RIT

US experiences

Multi-Allergen RIT in Children

- 1 day (6 hr) RIT protocol in 22 asthmatic children
  - Starting dose 0.3cc 1;100,000
  - Final dose 0.2cc 1:100 (wt/vol/substance)
- Premedication 2 days before and day of RIT
  - Astemizole 10 mg
  - Ranitidine 150 mg bid
  - Prednisone 30 mg bid

Sharkey P, Portnoy J. Ann Allergy Asthma Immunol 1996;76:175-80.

KU Medical Center Protocol

Table 1. Schedule for Administration of 1-Day Rush Immunotherapy

Time	Volume, mL	Dilution
09:00	0.30	1:100,000
09:30	0.10	1:10,000
10:00	0.30	1:10,000
10:30	0.05	1:1000
11:00	0.15	1:1000
12:00	0.30	1:1000
13:00	0.05	1:100
14:00	0.10	1:100
***Total**	**0.20**	**1:100**

* Total is the cumulative dose given over 6 hours.

Systemic reactions: 23%

Sharkey P, Portnoy J. Ann Allergy Asthma Immunol 1996;76:175-80.

Multi-Allergen RIT in Adults

- 1 day 4 hr RIT protocol in a university-based allergy clinic in 65 adults (37% with asthma) with multi-aeroallergen sensitivity
- Premedication 1 day before and morning of RIT
  - Prednisone 40 mg
  - Cetirizine 10 mg
  - Ranitidine 300 mg
  - Montelukast 10 mg/zafirlukast 40mg

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

Initial UT Southwestern 4-hour RIT Protocol

Time (minutes)	Concentration (Vol:Vol)	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
180	1:10	0.2
240	Undiluted concentrate	0.05

Systemic reactions during RIT: 38%

88% of reactions

All patients observed 2 hrs after final dose

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

Systemic reactions: 7.2% all mild

All patients observed 90 minutes after final dose

M. L. Alvares, et al. J Allergy Clin Immunol 2012;129:AB194[Abstract].

Recommended IT 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	1:10 v:v	0.35
4	1:1 v:v (concentrate)	0.05
5	1:1 v:v	0.1
6	1:1 v:v	0.2
7	1:1 v:v	0.3
8	1:1 v:v	0.4
9	1:1 v:v	0.5
11	1:1 v:v	0.5
14	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 9 weeks with weekly post-RIT build-up (4 weeks with twice weekly build-up)

Joshi S, et al. J Allergy Clin Immunol 2017;139:AB150[Abstract].

Low Dose Modified RIT

N=893 patients

Table 3 Dosing schedule for patients receiving 2–3 hr RAV procedure

	Volume (mL)	Dilution
RAV Procedure Dosing, Time (min)		
0	0.025	1:1,000,000
15	0.25	1:1,000,000
30	0.025	1:100,000
45	0.25	1:100,000
60	0.025	1:10,000
75	0.25	1:10,000
90	0.025	1:1000
105	0.1	1:1000

Systemic reactions: 2%

Very low final target dose

Smits WL et al. Allergy Asthma Proc 2007;28:305–312.

Conventional vs. Cluster vs Rush

Ann Allergy Asthma Immunol 117 (2016) 542–545

Contents lists available at ScienceDirect

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Annals

Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy

Andrew W. Winslow, MD [*]; Joseph C. Turbyville, MD [†]; J. Wesley Sublett, MD [†]; James L. Sublett, MD [†]; Stephen J. Pollard, MD [†]

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[†] Family Allergy & Asthma, Louisville, Kentucky

Winslow AW et al. Ann Allergy Asthma Immunol 2016;117:542-5.

Aeroallergen Immunotherapy Rapid Build Schedules

Cluster[1]			2-Day Rush[2]			
Visit	Concentration	Dosing	Concentration	Day 1	Concentration	Day 2
1	1:10,000/1:1,000	.1,.2,.4/.1	1:100,000	.25	1:10	.10
2	1:1,000/1:100	.2,.4/.1	1:100,000	.50	1:10	.25
3	1:100/1:10	.2,.4/.07	1:10,000	.25	1:10	.50
4	1:10	.1,.15,.25	1:10,000	.50	1:1	.10
5	1:10	.35/.5	1:1,000	.25	1:1	.25
6	1:1	.07,.1	1:1,000	.50	1:1	.50
7	1:1	.15,.2	1:100	.10		
8	1:1	.3, .4	1:100	.25		
9	1:1	.5	1:100	.50		
			1:10	.10		
			1:10	.25		
			1:10	.50		

[1] Premedication (90 min. prior): Prednisone 20 mg, Montelukast 10 mg, H-1 Antihistamine
[2] Premedication (90 min. prior): Prednisone 40 mg, Montelukast 20 mg, H-1 Antihistamine, H-2 Antihistamine

Conventional IT build-up with 30-40 injection visits to reach maintenance

Table 1
Summary of Systemic Reaction Incidence by Build-up Method

Variable	Standard[a]	Cluster[a]	Rush[a]	Total
Injections, No. (%)	2,398,491 (94)	144,760 (5.7)	6,372 (0.2)	2,549,643 (100)
Patients, No. (%)	9,229 (77)	2,576 (21.5)	177 (1.5)	11,982 (100)
SRs, No. (%)	307 (74.7)	83 (20.2)	21 (5.1)	411 (100)
Per-patient incidence, %	2.8	2.5	11.9	
Per-injection incidence, %	0.01	0.06	0.33	

[a]Includes build-up and maintenance after build-up immunotherapy.

Antigen	Recommended Dose[†]	Maintenance Dose[‡]
Cat	1,000-4,000 BAU	1,000 BAU
Dog	15 mcg Can f 1	About 13 mcg Can f 1
Dust Mite	500-2,000 AU	1,000 AU
Tree	1:100-1:200 W/V	About 1:200 W/V
Pasture Grass	1,000-4,000 BAU	1,000 BAU
Bermuda	300-1,500 BAU	100 BAU
Ragweed	6-12 AgE	3-6 AgE

[†]Cox, Linda, et al. "Allergen immunotherapy: a practice parameter third update."*Journal of Allergy and Clinical Immunology* 127.1 (2011): S1-S55.
[‡]Family Allergy and Asthma dosing

Similar Reaction Severity with Accelerated Protocols

Systemic Reaction Severity Versus Aeroallergen Build-Up Method				
Grade	Standard° (n=307)	Cluster° (n=83)	Rush° (n=21)	**Total$^{\Delta}$ (n=411)**
1	38%	51%	62%	**42%**
2	46%	37%	29%	**43%**
3	13%	11%	4%	**12%**
4	3%	1%	4%	**3%**
5	0%	0%	0%	**0%**

°Percentages for Standard, Cluster, and Rush denote percentage of World Allergy Organization Grade 1-5 systemic reactions observed for each respective method of immunotherapy build-up

$^{\Delta}$Percentages for Total denote percentage of World Allergy Organization Grade 1-5 systemic reactions observed across all methods of immunotherapy build-up

Premedication for RIT

Pre-medication with H1, H2, prednisone for multiple aeroallergen RIT

Characteristic	Placebo (n=11)	Active (n=11)	P value
Reaction grade	3.0 +/- 0.5	1.3 +/- 0.6	.038
Systemic rxns	8 (73%)	3 (27%)	.047
Local rxns	8 (73%)	3 (27%)	.047
# completing RIT	7 (64%)	10 (91%)	.311

Portnoy J et al. Ann Allergy 1994;73:409-18.

Pre-Medication of RIT with omalizumab

- Initially RIT protocol used maintenance dosage (12 mcg Amb a 1) as target for final dose
  - 10/17 had allergic reactions
    - 5/7 (OM + IT)
    - 3/3 (IT)
- DSMB recommended modifying protocol to end at 1.2 mcg Amb a 1 ($1/10^{th}$ maintenance dosage)

Casale T et al. J Allergy Clin Immunol 2006;117:134-40.

Pre-Medication of RIT with omalizumab

	OM + IT (n = 36)	OM (n = 37)	IT (n = 39)	PL (n = 37)
Wheezing	0	0	3	0
Flushing†	5	1	16	3
Urticaria†	3	2	11	0
Angioedema	1	0	3	1
Mean drop of BP ≥ 15 mm	4	4	3	3
Lightheadedness	2	2	7	2
Itching†	5	5	12	1
Abdominal pain	0	0	3	0
Nausea	0	0	2	0
Any reaction†	12 (33.3%)	11 (29.7%)	22 (56.4%)	7 (18.9%)
Anaphylaxis†	2 (5.6%)	1 (2.7%)	10 (25.6%)	1 (2.7%)

Casale T et al. J Allergy Clin Immunol 2006;117:134-40.

Rush Immunotherapy for Stinging Insect Hypersensitivity

Rush Immunotherapy for Stinging Insects

- Numerous studies have evaluated safety and efficacy of venom RIT
- Protocols vary considerably
  - Conventional
  - Cluster
  - Rush
  - Ultra-Rush

Risk of Reactions to Venom RIT

- Summary Statement 21: Choose a buildup dose schedule for optimal safety and convenience. Maintenance dose and protection can be achieved with equal safety using conventional (achieving 100-mg maintenance dose in 4 months) or modified rush (8 weeks) regimens. **The risk of systemic reaction is similar using rush regimens** (2-3 days) but may be slightly greater using ultrarush regimens (4-8 hours). (Strong recommendation; B evidence)

Stinging insect hypersensitivity practice parameter second update
Ann Allergy Asthma Immunol 118 (2017) 28e54.

Cluster vs. Rush vs. Ultra-rush VIT

- Retrospective review of different RIT protocols in 1055 venom allergic pts treated at University of Münster, Germany
- From 1992-1997 they changed their protocol in a stepwise fashion to less injections and fewer days
- 933 wasp VIT; 122 bee VIT
- 3 cohorts
  - Cohort 1 (n=317): 20 injections in 7-9 days
  - Cohort 2 (n=335): 10-14 injections in 3-6 days
  - Cohort 3 (n=403): 9 injections in 2 days
- No premedication
- Out-pt setting?

Brehler R et al. J Allergy Clin Immunol 2000;105:1231-5.

TABLE I. Treatment protocols for up-dosing of VIT

	VIT dose (μg of venom)					
Day	Cohort 1		Cohort 2			Cohort 3
1	0.001	0.001	0.001	0.001	0.001	0.01
	0.004	0.01	0.01	0.01	0.1	0.1
			0.1	0.1	1	1
					10	10
					20	20
						40
						80
2	0.008	0.1	1	1	40	100
	0.02	1	5	10	60	100
	0.04	2	10	20	80	
	0.08	4		40		
3	0.2	8	20	60	100	
	0.4	10	40	80	100	
	0.8	20	60			
			80			
4	1	40	100	100		
	2	60	100	100		
	4	80				
	8					
5	10	100				
	20	100				
	40					
6	60					
	80					
7	100					
	100					
Cumulative	431.553	425.111	416.111	411.111	411.11	351.11

Cluster vs. Rush vs. Ultra-rush VIT

- Total Adverse reactions
  - 7-9 day RIT: 22.4%
  - 3-6 day RIT: 13.7%* p= 0.0027 (7-9 vs. 3-6d)
  - 2 day: 10.7%* p = 0.001 (3-6d vs. 2d)
- Most of systemic reactions attributed to anxiety
  - Dizziness, dyspnea, headache, tickle in throat
  - No difference between wasp and bee VIT
- Treatment
  - Oral AH: 7.1%
  - IV AH: 2.9%
  - IV steroids 0.8%
  - No epinephrine required
- No difference in need for IV Rx across cohorts

Brehler R et al. J Allergy Clin Immunol 2000;105:1231-5.

Comparison of Systemic Reactions to VIT Protocols

- Review of systemic reactions to VIT
  - Conventional/Cluster
    - 11.2%
  - Rush VIT
    - 25.6%
  - Ultra Rush VIT
    - 11.3%

Sturm G et al. J Allergy Clin Immunol 2002;110:928-33.

Randomized Comparison of Ultra Rush vs. RIT vs Conventional VIT

Table 2: Demographic and clinical data of the 76 patients enrolled in the study.

Group	N =	Treatment	Vespula/Apis	Sex (M/F)	Age (range)	Age (mean)	Local large reactions*	Systemic allergic reactions§	Grade§ (I) (II) (III) (IV)
A	27	Ultrarush	18/9	19/8	16–76	39.1	1	26	(3) (3) (12) (8)
B	25	Rush	16/9	16/9	18–68	40.3	1	24	(5) (4) (13) (2)
C	24	Slow Conventional	16/8	16/8	19–69	38.6	2	22	(2) (6) (10) (4)
Total	76	—	50/26	51/25	16–76	39.3	4	72	(10)(13)(35)(14)

*It is defined as a swelling exceeding a diameter of 10 cm which lasts longer than 24 h.
§Classified according to Müller [9]: grade I: urticaria, pruritus, and malaise; grade II: angioedema, chest tightness, nausea, vomiting, abdominal pain, and dizziness; grade III: dyspnoea, wheeze, stridor, dysphagia, and hoarseness; grade IV: hypotension, collapse, loss of consciousness, incontinence, and cyanosis.

Patella V et al. J Allergy 2012;1-8.

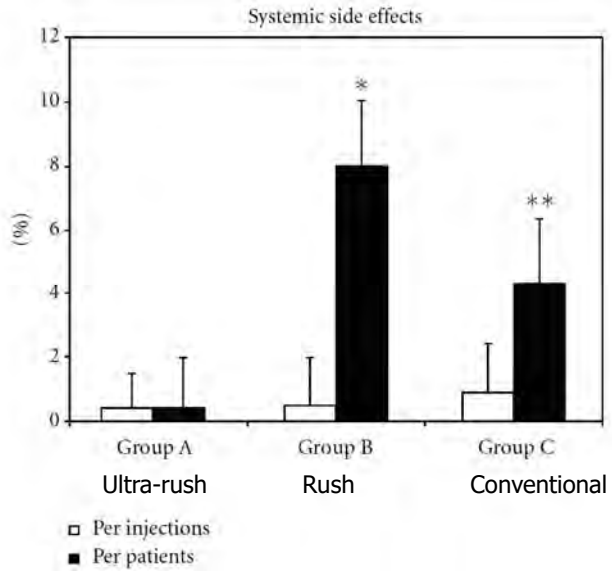
Randomized Comparison of Ultra Rush vs. RIT vs Conventional VIT

Table 1: Protocol of incremental treatment for ultrarush*, rush§, and slow conventional therapy*.

Group A			Group B				Group C		
μg/dose	Cumulative μg/dose	Minute	μg/dose	Cumulative μg/dose	Day	Hour	μg/dose	Cumulative μg/dose	Week
0.001	0.001	0	0.01	0.01	1	0	0.02	0.02	1
0.01	0.011	15	0.1	0.11		2	0.04	0.06	2
0.04	0.051	30	1	1.11		4	0.08	0.14	3
0.05	0.11	45	2	3.11		6	0.2	0.34	4
0.1	0.21	60	3	5.11	2	0	0.4	0.74	5
0.4	0.61	75	3.5	9.61		2	0.8	1.54	6
0.5	1.11	90	3.5	13.11		4	2	3.54	7
1	2.11	105	10	23.11	3	0	4	7.54	8
4	6.11	120	15	38.11		2	8	15.54	9
5	11.11	135	15	53.11		4	10	25.54	10
10	21.11	150	20	73.11	4	0	20	45.54	11
40	61.11	165	25	98.11		2	40	85.54	12
50	111.101	180	25	123.11		4	60	145.54	13
			30	153.11	5	0	80	225.54	14
			35	188.11		2	100	325.54	15
			35	223.11		4			

Patella V et al. J Allergy 2012;1-8.

Systemic Reactions Lower in Ultra Rush than Rush and Conventional VIT



What About Bee VIT?

Original Paper

Allergy and Immunology

Int Arch Allergy Immunol 2011;156:90–98
DOI: 10.1159/000322258

Received: August 10, 2010
Accepted after revision: October 22, 2010
Published online: March 30, 2011

Three Days Rush Venom Immunotherapy in Bee Allergy: Safe, Inexpensive and Instantaneously Effective

Arnon Goldberg Ayala Yogev Ronit Confino-Cohen

The Allergy and Clinical Immunology Unit, Meir Medical Center, Kfar Saba, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

179 patients underwent VIT

20 patients (hypereactive group) had failed conventional VIT due to systemic reactions

Table 1. Conventional VIT protocol: concentrations, volumes and doses of venom administered at weekly intervals

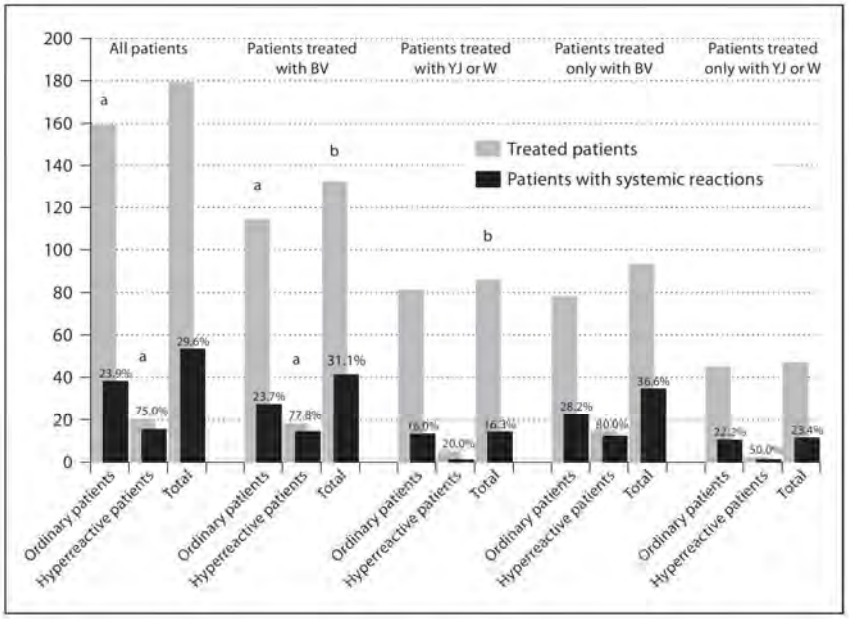
1 µg/ml	0.05, 0.1, 0.2, 0.4 ml (0.05, 0.1, 0.2, 0.4 µg)
10 µg/ml	0.05, 0.1, 0.2, 0.4 ml (0.5, 1, 2, 4 µg)
100 µg/ml	0.02, 0.05, 0.07, 0.1, 0.2, 0.4, 0.6, 0.8, 1 ml (2, 5, 7, 10, 20, 40, 60, 80, 100 µg)

Table 2. Rush VIT protocol: concentrations, volumes and doses of venom administered at 15-min intervals

Day 1	
1 µg/ml	0.05, 0.1, 0.2, 0.4, 0.8 ml (0.05, 0.1, 0.2, 0.4, 0.8 µg)
10 µg/ml	0.2, 0.5, 1 ml (2, 5, 10 µg)
100 µg/ml	0.2, 0.2 ml (20, 20 µg)
Day 2	
100 µg/ml	0.2, 0.3, 0.5 ml (20, 30, 50 µg)
Day 3	
100 µg/ml	1 ml (100 µg)

	RVIT (n = 179)	CVIT (n = 75)
Male/female	146/33 (82/18)	59/16 (79/21)
Age		
Mean ± SD, years	33.0 ± 15.0	34.1 ± 18.8
3–10 years	12 (7)	8 (11)
11–20 years	66 (37)[a]	11 (15)[a]
21–40 years	61 (34)	30 (40)
41–60 years	36 (21)	18 (24)
≥61	4 (2)[b]	8 (11)[b]
Severity of SR that prompted VIT		
Mild (grade 1)	37 (21)	13 (17)
Moderate (grade 2)	112 (63)	53 (71)
Severe (grade 3)	30 (17)	9 (12)
Venoms administered for immunotherapy		
BV only	93 (52)	36 (48)
BV + YJ	24 (13)	12 (16)
BV + W	1 (0.6)	1 (1)
BV + YJ + W	14 (8)	10 (13)
YJ only	33 (18)	11 (15)
YJ + W	14 (8)	5 (7)

Figures in parentheses are percentages. RVIT = Rush venom immunotherapy; CVIT = conventional venom immunotherapy; SR = systemic reaction. [a] p = 0.0003; [b] p = 0.007.



Systemic reactions similar in bee VIT RIT vs. conventional
All "ordinary" patients reached maintenance after VIT; 89% hyperactive group reached maintenance

What About VIT in Kids?

Original Article

Rush Venom Immunotherapy in Children

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TABLE II. Patient characteristics

	All	RVIT, n = 84	CVIT, n = 43	*P* value
Male (%)	97 (76.4%)	60 (71.4%)	37 (84%)	.07
Age	10.56 ± 4.23 (2-17.5)	10.9 ± 4.4 (3-17)	9.9 ± 3.9 (2-17.5)	.1
Severity of the original systemic reaction				
Grade 1	4 (3.1%)	2 (2.4%)	2 (4.6%)	.1
Grade 2	114 (89.8%)	78 (92.8%)	36 (83.7%)	
Grade 3	9 (7.1%)	4 (4.8%)	5 (11.6%)	

CVIT, Conventional venom immunotherapy; *RVIT*, rush venom immunotherapy.

J Allergy Clin Immunol Pract 2017 (in press).

Rush VIT and Conventional VIT in Children with Similar Reactions

TABLE III. Venom immunotherapy characteristics

	RVIT, n = 84	CVIT, n = 43	*P* value
Venoms administered			
BV only	70 (83.3%)	30 (69.7%)	.015
YJ only	2 (2.3%)	3 (7%)	
Wasp only	0	1 (2.3%)	
BV+YJ	4 (4.7%)	5 (11.6%)	
BV+Wasp	1 (1.1%)	4 (9.3%)	
YJ+Wasp	2 (2.3%)	0	
BV+YJ+Wasp	5 (5.9%)	0	
Achieved 100 mcg maintenance dose with the initial protocol	83 (98.8%)*	39 (90.7%)†	.04
Time to maintenance dose (d)	3.1 ± 0.6	153.3 ± 91	<.001
Systemic reactions during the build-up phase			
All	16 (19%)	10 (23.2%)	.6
Grade 1	13 (81.3%)	8 (80%)	1
Grade 2	3 (18.7%)	2 (20%)	
Grade 3	0	0	

J Allergy Clin Immunol Pract 2017 (in press).

What About Rush VIT in Mastocytosis?

ORIGINAL ARTICLES | EUR ANN ALLERGY CLIN IMMUNOL | VOL 47, N 6, 192-196, 2015

M. VERBURG, J.M. OLDHOFF, R.J.B. KLEMANS, A. LAHEY-DE BOER, M.S. DE BRUIN-WELLER, H. RÖCKMANN, C. SANDERS, C.A.F.M. BRUIJNZEEL-KOOMEN, S.G.M.A. PASMANS, A.C. KNULST

Rush immunotherapy for wasp venom allergy seems safe and effective in patients with mastocytosis

3 day RIT Protocol

Table 3 - Safety and efficacy of IT in our study population.

							sIgE		Tryptase			
No	Age	Sex	Type mastocytosis	BM	SRS	IC[1] t = 0	t = 0	t = IT	t = 0	t = IT	Duration IT (years)	Symptoms IT
1	59	m	CM	-	4	0.0001	20.4	5.3	28	22	5	-
2	54	f	CM	nd	4	0.0001	> 100	29.3	5	6.3	4	-
3	71	m	CM	nd	4	0.0001	11	5	nd	nd	19	-
4	67	m	CM	nd	4	nd	26	nd	nd	26	3	-
5	64	f	CM+SM	pos	4	0.0001	6	1.3	13	31,7	6	Numbness hand/feet/tongue
6	39	m	CM	neg	4	0.0001	3.8	nd	12.5	nd	0.1	Nausea, headache
7	56	f	SM	pos	4	0.01	0.4	< 0.35	38	31	3	-
8	41	f	CM	neg	4	0.01	< 0.35	< 0.35	22.3	20.1	2	-
9	67	m	CM+SM	pos	4	0.01	1.17	nd	nd	43	7	Urticaria, oedema, erythema, dyspnea, drop blood pressure

All had severe symptoms with wasp stings
Patient #9 reacted to last dose on Day #2 of RIT but tolerated rest of protocol

***Table 1** - Safety and efficacy according to protocol followed during up-dosing phase.*

Author	C/R	SSE	Re-stung	SS Re-stung
Bonnadonna[9]	15 C	2	13	2
Gonzalez de Olano[11]	10 C	1	5	1
Total	25 C	3	18	3
Gonzalez de Olano[11]	5R	2	4	1
Total	5R	2	4	1
Our data	9R	1	2	0
Oude Elberink[7]	2 nd	1	2	0
Müller[6]	1 nd	0	0	-
Fricker[10]	4 nd	0	3	1

C/R: conventional/rush immunotherapy; nd: not determined; SSE: systemic side effects; SS: systemic symptoms.

Fire Ant Rush Immunotherapy

- 59 patients treated with 2 day protocol up to 0.3 cc of 1:100 wt/vol
  - Day 8 received 2 hourly injections of 0.25 cc of 1:100
  - Day 15 received 0.5 cc of 1:100 wt/vol
  - Day 22 received 2 sting challenges 2 hours apart
  - Premedication (active vs. placebo) randomized and blinded
    - Terfenadine 60 mg , ranitidine 150 mg, prednisone 30 mg bid
- 3 (5.2%) had mild systemic reactions during protocol
  - 2 placebo, 1 active p=0.87

Tankersley M et al. J Allergy Clin Immunol 2002; 109:556-62.

Patient Selection

Patient Selection

- Patient Factors Favoring RIT/Cluster
  - Unable to commit time to long build-up schedules
  - Desire for more rapid relief
  - Upcoming allergy season
  - Economics

Patient Selection

- Patient Factors Against RIT/Cluster
  - Desire for safest form of immunotherapy
  - Economics

Summary

- Any patient who is considered a candidate for immunotherapy is a candidate for cluster or RIT

Exception: patients on beta-blockers

Editorial

Rush Venom Immunotherapy: Ready for Prime Time?

David B.K. Golden, MD *Baltimore, Md*

"The report in this issue, along with accumulated evidence to date, suggests that if we would just try it, we might conclude that **rush VIT is not just for special circumstances, but is indeed ready for prime time in our daily practice**."

Golden DBK. J Allergy Clin Immunol Pract 2017;5:804-5.

Rush Immunotherapy Summary

- Majority of studies on RIT for inhalant allergies do not restrict patient selection
- RIT reaction rates for aeroallergens higher than conventional and vary by protocol, severe reactions are similar
- Ultra-rush VIT may have lower reaction rate than conventional VIT and provides rapid protection
- Using pre-medication and appropriate RIT protocols, RIT can be accomplished safely
- RIT sets apart allergists from other quasi-"allergists"

"The 'rush' method of desensitization offers many advantages when used alone or in combination with other systems. To get successful and safe results, however, it is just as necessary as ever to be cautious."

Freeman J. Lancet 1930;i:744-7.

Update on SLIT

New Practice Parameter on SLIT

Ann Allergy Asthma Immunol 118 (2017) 276–282

Contents lists available at ScienceDirect

ELSEVIER

Annals

Practice Parameter

Sublingual immunotherapy

A focused allergen immunotherapy practice parameter update

Matthew Greenhawt, MD, MBA, MSc; John Oppenheimer, MD; Michael Nelson, MD, PhD; Hal Nelson, MD; Richard Lockey, MD; Phil Lieberman, MD; Anna Nowak-Wegrzyn, MD; Anju Peters, MD; Charlotte Collins, JD; David I. Bernstein, MD; Joann Blessing-Moore, MD; David Khan, MD; David Lang, MD; Richard A. Nicklas, MD; Jay M. Portnoy, MD; Christopher R. Randolph, MD; Diane E. Schuller, MD; Sheldon L. Spector, MD; Stephen A. Tilles, MD; Dana Wallace, MD

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 1: Only use FDA-approved SLIT products** for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B)
- **Summary Statement 2: The physician should be aware that SLIT may not be suitable in patients with certain medical conditions**, particularly those that may reduce the patient's ability to survive a systemic reaction or the resultant treatment of the systemic reaction. (Strength of Recommendation: Strong; Evidence: D)
  - Unique SLIT contraindications: EoE; Concerns with oral inflammation

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 3: Use FDA-approved SLIT products very cautiously in the pregnant or breastfeeding patient** because there are insufficient data regarding the safety of initiating or continuing SLIT during either pregnancy or breastfeeding. (Strength of Recommendation: Weak; Evidence: C)
- **Summary Statement 4: Do not assume dosing equivalence between SLIT tablets and extracts of the same allergen.** There are no direct comparisons between the same allergen extract administered as a SLIT tablet vs as an aqueous SLIT extract, and it is unknown whether equal efficacy and/or safety exists when using similar doses of the 2 preparations. Each formulation has to have its own safety profile established. (Strength of Recommendation :Weak; Evidence: C)

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 5: Administer the patient's first dose of SLIT in a medical facility** under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. The patient should be observed in the clinic or medical facility for 30 minutes after the administration of the SLIT dose. (Strength of Recommendation: Strong; Evidence: D)

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 6: Prescribe epinephrine (either an autoinjector or other form for self-injection) to patients receiving SLIT tablets.** Patients should be trained how to use the device, instructed on how to recognize and manage adverse reactions and missed doses, and advised on when to contact their physician or other health care professional. Recommendations for when to withhold the SLIT tablet dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. (Strength of Recommendation: Strong; Evidence: D)

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 7: Reduce a patient's SLIT dose if they have missed treatment for more than 7 days.** (Strength of Recommendation: Weak; Evidence: D)
- **Summary Statement 8: Schedule patients receiving SLIT therapy for regular follow-up care** with a specialist trained in the evaluation of patients with allergic conditions to monitor efficacy and safety and as a strategy for optimizing adherence. (Strength of Recommendation: Moderate; Evidence: D)

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

SLIT Parameter Summary Statements

- **Summary Statement 9:** Currently, the only FDA-approved products for SLIT in the United States are the 5-grass (Oralair), Timothy grass (Grastek), and ragweek (Ragwitek) tablets, indicated for the treatment of allergic rhinitis. Although alternative regimens and preparations for SLIT have been proposed and may be used off-label in the United States (eg, use of liquid SCIT extract for sublingual delivery or use of specific sublingual drops or other sublingual tablets), these products and formulations do not have FDA approval at present and have not been systematically studied in a rigorous manner in US populations. Use of such products or formulations as prescribed SLIT therapy is currently off-label, at a practitioner's discretion and liability, and is without recommendation for any current particular indication in the US populations. **Therefore, off-label use of aqueous SLIT extracts or any other non-FDA-approved SLIT formulation is not endorsed.** (Strength of Recommendation: Strong; Evidence: D)

Greenhawt M et al. Ann Allergy Asthma Immunol 118 (2017) 276e282.

28 Other Questions on SLIT

eTable 1
Suggested Guidelines for the Practicing Allergist Regarding the Use of FDA-Approved SLIT Products

Question no.	Question or concern	Expert suggestion and rationale
16	Administration in conjunction with SCIT (using different allergens, eg, perennial allergens)	Although using multiple allergens in SCIT has not been associated with increased risks, combining SCIT and SLIT has not been well studied.
17	Increased risks of SLIT when using multiple allergen, multiple tablet treatment	The limited studies on SLIT are mixed, with some studies demonstrating no increased risk,[10] but one case study indicating increased risk.[11] Reduced efficacy has also been a concern with the use of multiple SLIT tablets.
18	Use of concurrent thyroid medication, first-generation antihistamines, tricyclics, á-adrenergic blockers, and/or cardiac glycosides or diuretics	The FDA indicates that it may not be suitable to start SLIT in a patient taking one of these medications, in that, were anaphylaxis to occur, these medications could potentiate or inhibit the effect of epinephrine. On the basis largely of the favorable experience with SCIT, it is recommended that the patient and physician determine, before initiating SLIT, whether the benefits of treatment outweigh the risks.
19	Must use of monoamine oxidase inhibitors be stopped?	The risk of adverse effects of epinephrine administration is theoretically greater if the patient is taking a monamine oxidase inhibitor. Therefore, the allergist should discuss an alternative medication with the prescribing physician. Consider monoamine oxidase inhibitors a relative contraindication to the use of SLIT.
20	Must use of β-blockers be stopped?	A patient taking a β-blocker may be less responsive to the beneficial effect of epinephrine when this drug is administered for the treatment of anaphylaxis. Therefore, the concomitant use of β-blockers and allergen immunotherapy should be carefully considered from an individualized risk-benefit standpoint, and the patient's preferences should be incorporated into the medical decision-making process.[2,4,5,7]
21	Must use of angiotensin-converting enzyme inhibitors be stopped?	Although there is a theoretical risk of more severe or unresponsive anaphylaxis when the patient is taking an ACE inhibitor, there is no evidence that ACE inhibitors infer any increased risk for inhalant immunotherapy. Therefore, we see no reason to stop using these medications when SLIT is initiated.[2,7]
22	Does use of NSAIDS need to be stopped?	It is not advised that use of NSAIDs needs to be stopped for SLIT.
23	Do antihistamines help with GI symptoms attributable to SLIT?	There is no known benefit of antihistamines for reducing the GI symptoms that develop with SLIT.
24	Can antihistamines be taken before SLIT administration? Will this help with oral symptoms of SLIT?	Use of antihistamines does not need to be stopped and may reduce local oral symptoms. On the other hand, intermittent use of antihistamines potentially increases the risk of adverse reactions in SCIT.[1,2,7]
25	Concurrent GI infection and the administration of SLIT	Although there are limited published data[8] on risks associated with GI infections, for moderate to severe GI infections, we recommend that SLIT be discontinued until improvement occurs.[2,5]

(continued on next page)

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Adverse Effects in SLIT Trials

Product	# Patients	Treatment-Related Adverse Events	Study
Timothy grass tab	439	73% vs. 28% PBO Oral pruritus/throat irritation 34-29% Epi for 1 subject with flush/chest discomfort	Nelson 2010
Timothy grass tab	345	70% vs. 25% PBO Oral pruritus/throat irritation 39-37% 4% with urticaria Epi for 1 subject with lip AE/cough/dysphagia Epi for PBO pt with pharyngitis	Blaiss 2010
Timothy grass tab	1501	59% vs. 24% PBO Oral pruritus/throat irritation 18-23% 2 subjects with systemic rxns, no Rx	Maloney 2014
5-grass tab	473	55% vs. 22% PBO Oral pruritus/throat irritation most common No systemic rxns reported, no Epi	Cox 2012
Ragweed tab	565	64% vs. 28% PBO Oral pruritus/throat irritation 19-27% No systemic rxns reported Epi for 1 subject with subj pharyngeal swelling	Nolte 2013
Ragweed liq	429	12 vs. 3% PBO Oral pruritus 2% No systemic, No Epi needed for treatment-related	Creticos 2013

Grading Reactions in SLIT

Table 2
World Allergy Organization Grading System for SLIT Local Reactions[a]

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

Each local AE can be early (<30 minutes) or delayed.
• See Table I for the MedDRA code that applies to exactly report and describe the AE.

Rhinitis, sinusitis, and upper airway disease

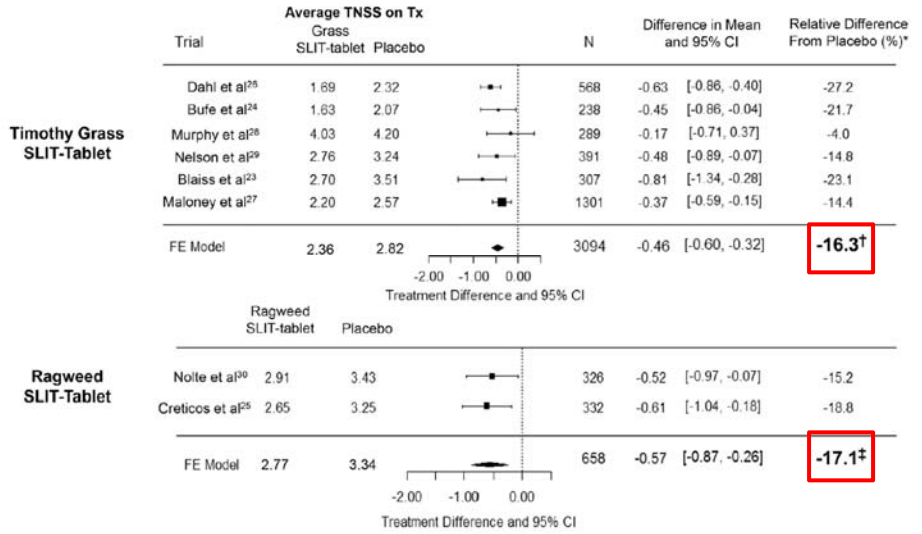
Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses

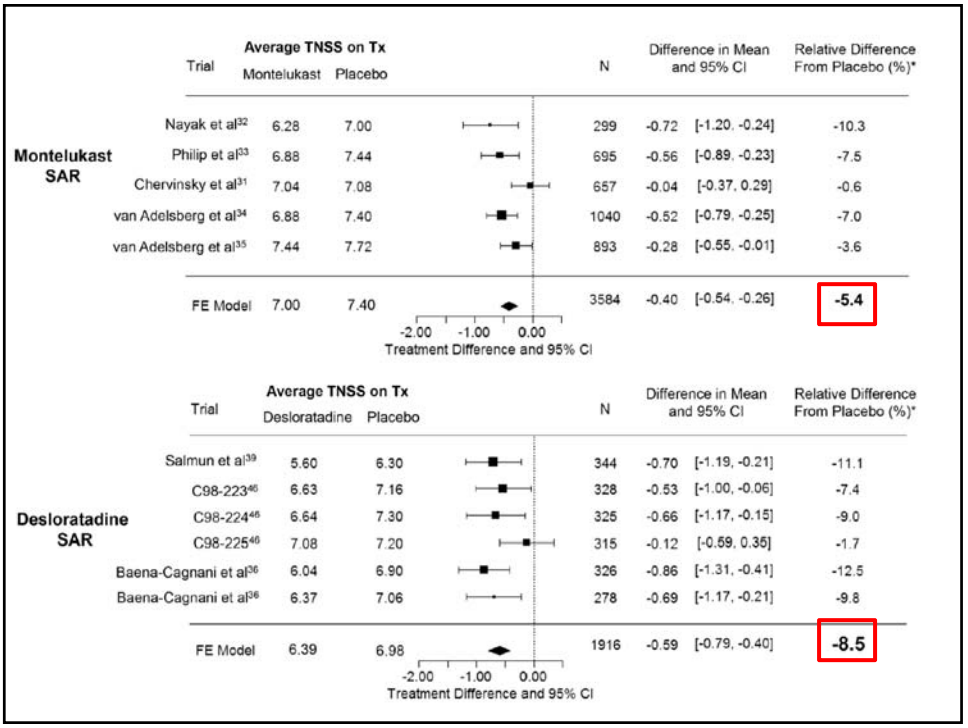
Stephen R. Durham, MD,[a] Peter S. Creticos, MD,[b] Harold S. Nelson, MD,[c] Ziliang Li, PhD,[d] Amarjot Kaur, PhD,[d] Eli O. Meltzer, MD,[e] and Hendrik Nolte, MD, PhD[d]
London, United Kingdom, Baltimore, Md, Denver, Colo, Kenilworth, NJ, and San Diego, Calif

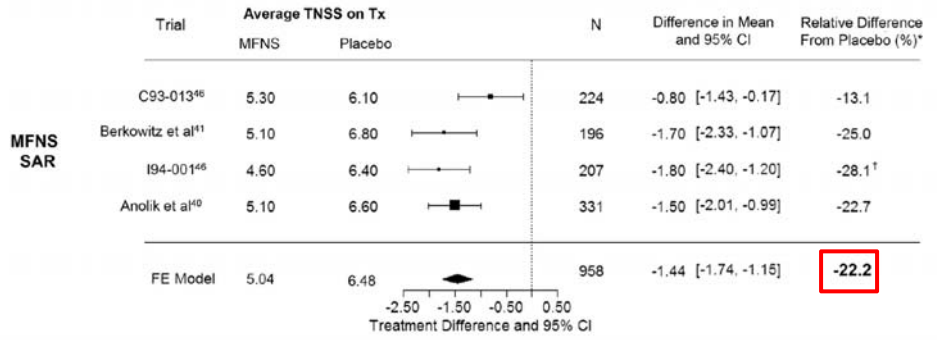
- Comparison of pooled data from Merck sponsored trials to compare effects seen with antihistamines, leukotriene antagonists, nasal steroids, and SLIT tablets
- Evaluated seasonal (SAR) vs perennial (PAR) trials

Durham SR et al. J Allergy Clin Immunol 2016;138:1081-8.

Seasonal Allergic Rhinitis (SAR)

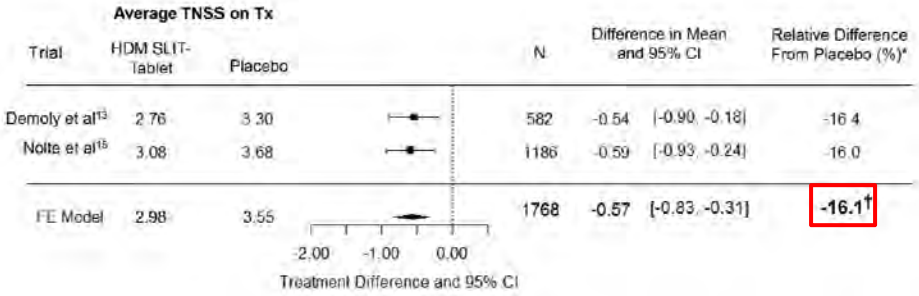


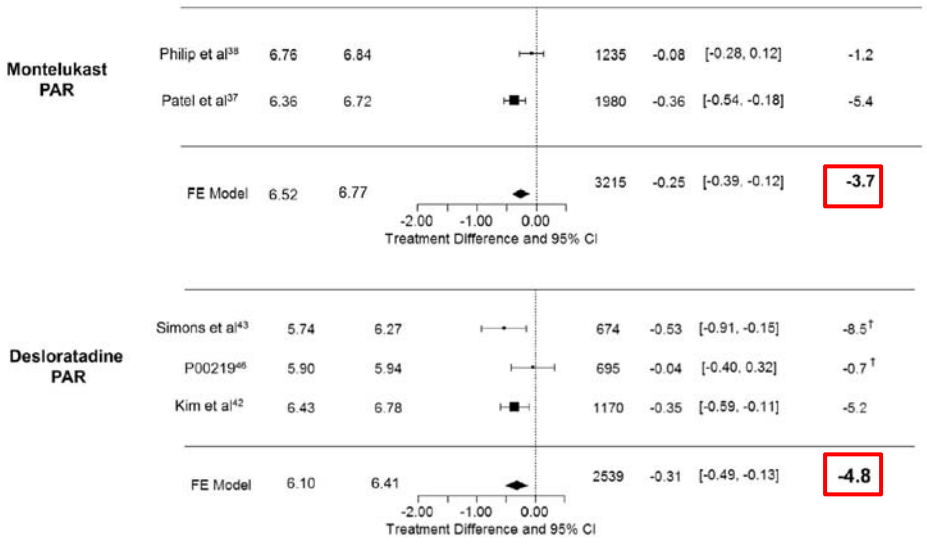


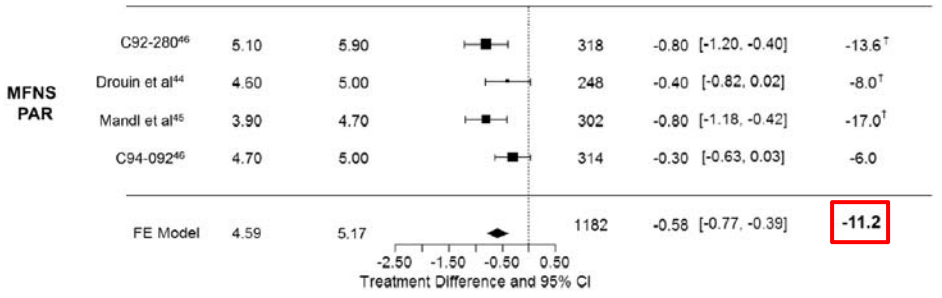


For seasonal allergic rhinitis, rank order effect size for symptom reduction was:
Nasal corticosteroid > SLIT > Antihistamine > Montelukast

Perennial Allergic Rhinitis







For perennial allergic rhinitis, rank order effect size for symptom reduction was:
SLIT > Nasal corticosteroid > Antihistamine > Montelukast

True comparator studies are needed to determine accurate clinical comparisons

SLIT Summary

- FDA approved SLIT tablets are safe and effective for allergic rhinitis
- Another therapeutic option for patients with predominantly single allergen sensitivity
- Insurance coverage and expense are significant roadblocks