SUBCUTANEOUS IMMUNOTHERAPY (SCIT) IS THE PREFERRED FIRST LINE METHOD OF ALLERGEN

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ALLERGIC RHINITIS IS A SIGNIFICANT PUBLIC HEALTH CONCERN

- Prevalence of AR has continued to rise over the last 50 years
- Worldwide, 10-30% of the population and up to 50% of children
- 6th leading cause of chronic illness in the US → Over 50 million Americans
- Allergic rhinitis accounts for:
  - 11.1 million office visits
  - 3.5 million lost workdays
  - 2 million missed school days
- 36% of patients report impairment in at-work performance due to AR
- Overall productivity impairment due to AR ~40%, similar to other chronic diseases (Depression, COPD, Arthritis)
- Excess of $18 billion in annual costs

CDC 2017; WHO WHITE BOOK ON ALLERGY 2011-2012; NATIONAL AMBULATORY MEDICAL CARE SURVEY: 2010; NATHAN RA. ALLERGY ASTHMA PROC; VANDENPLAS O. JACI IN PRACTICE 2018 (JUL - AUG;6(4):1274-1286.E9)

SCIT IS SUPERIOR TO SLIT

- Long history of use
- SCIT leads to disease modification
- SCIT leads to disease prevention
- SCIT is effective
- SCIT is cost effective
- SCIT has better compliance than SLIT
- SCIT is safe
- SCIT is tailored to the patient

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OVER 100 YEARS OF PUBLICATIONS

- First SCIT article, Lancet 1911 “Prophylactic inoculation against hay fever”
  - Used eye drops made of Timothy grass pollen extract to elicit reactions, noted at very low dilutions in allergic patients
  - Patients given subcutaneous immunotherapy, demonstrating an increase in resistance to pollen extract
- SLIT therapy introduced in the 1970s

NOON L. LANCET 1911

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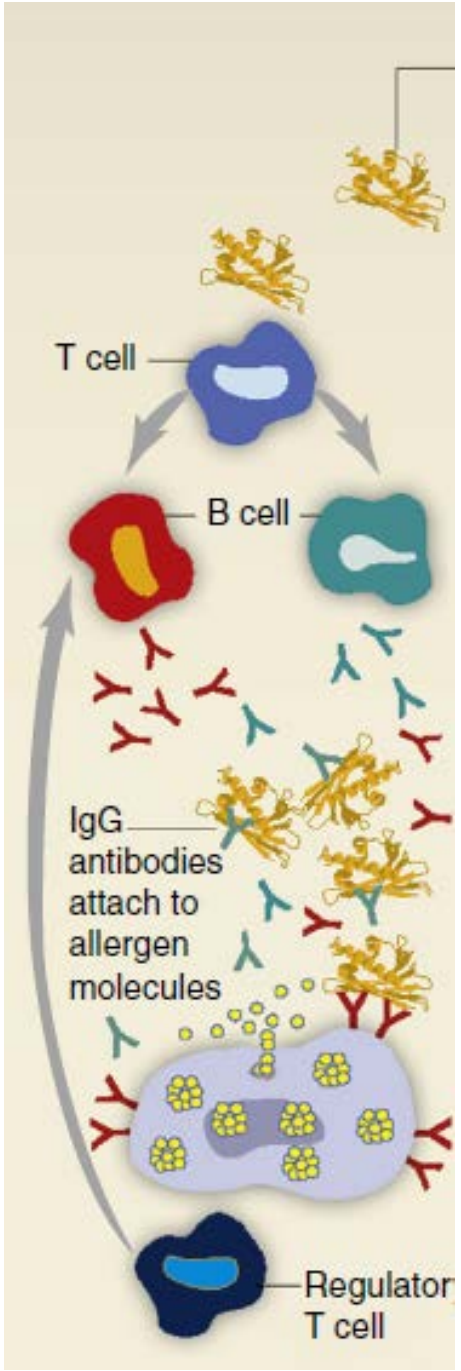
SCIT LEADS TO DISEASE MODIFICATION

- SCIT results in immunologic tolerance characterized by:
  - Decreases in the sensitivity of end organs
  - Changes in the humoral and cellular immunity
- Successful SCIT → generation of regulatory T cells, occurring within days or weeks
  - Continued SCIT → immune deviation from Th2 to Th1 cytokine response
- Specific IgE levels initially increase then decrease
- Increase in allergen-specific IgG (especially IgG 4) levels → blocks IgE-dependent histamine release and IgE-facilitated antigen presentation



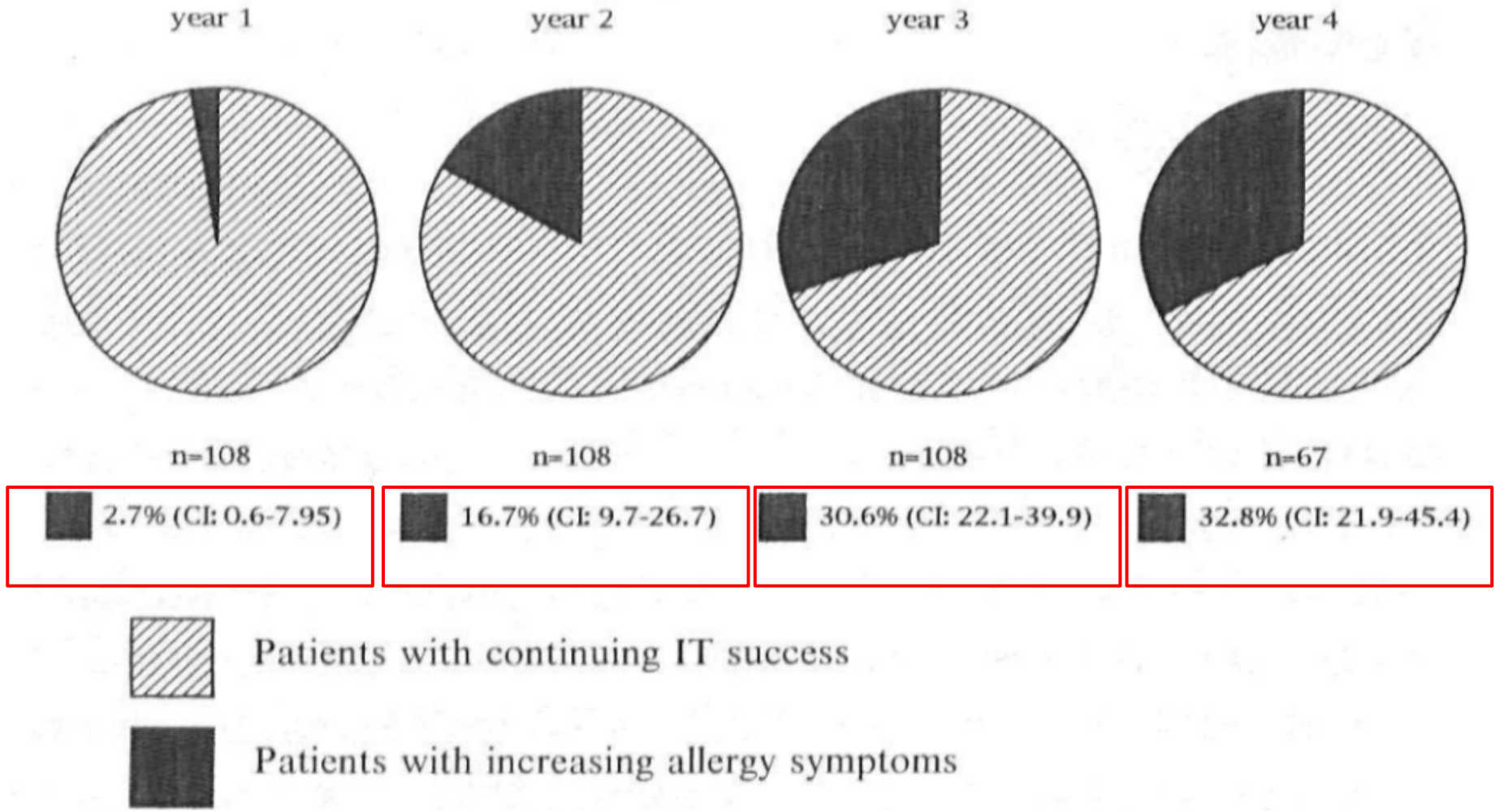
HAMID QA. JACI 1997 99:254-60, IIB. LARSEN J. DRUG DISCOVERY TODAY 2016 JAN;21(1):26-37.

SCIT LEADS TO SUPERIOR DISEASE MODIFICATION

- Review comparing SCIT and SLIT studies: “The greater effect of SCIT on immunologic and tissue threshold markers is striking”
  - Specific IgG4 rose significantly in the SCIT arm
    - Never equaled or exceeded by SLIT
  - Significant decreases in SPT observed only with SCIT
  - Nasal or bronchial challenge improved only with SCIT
  - Increased $CD4^{+}CD25^{+}$ T cells observed only with SCIT
- No studies in which immunologic results were significant only with SLIT

NELSON H. JACI IN PRACTICE 2014 MAR-APR;2(2):144-9.

SCIT HAS LONG LASTING EFFECTS



EBNER C. ALLERGY 1994 JAN;49(1):38-42

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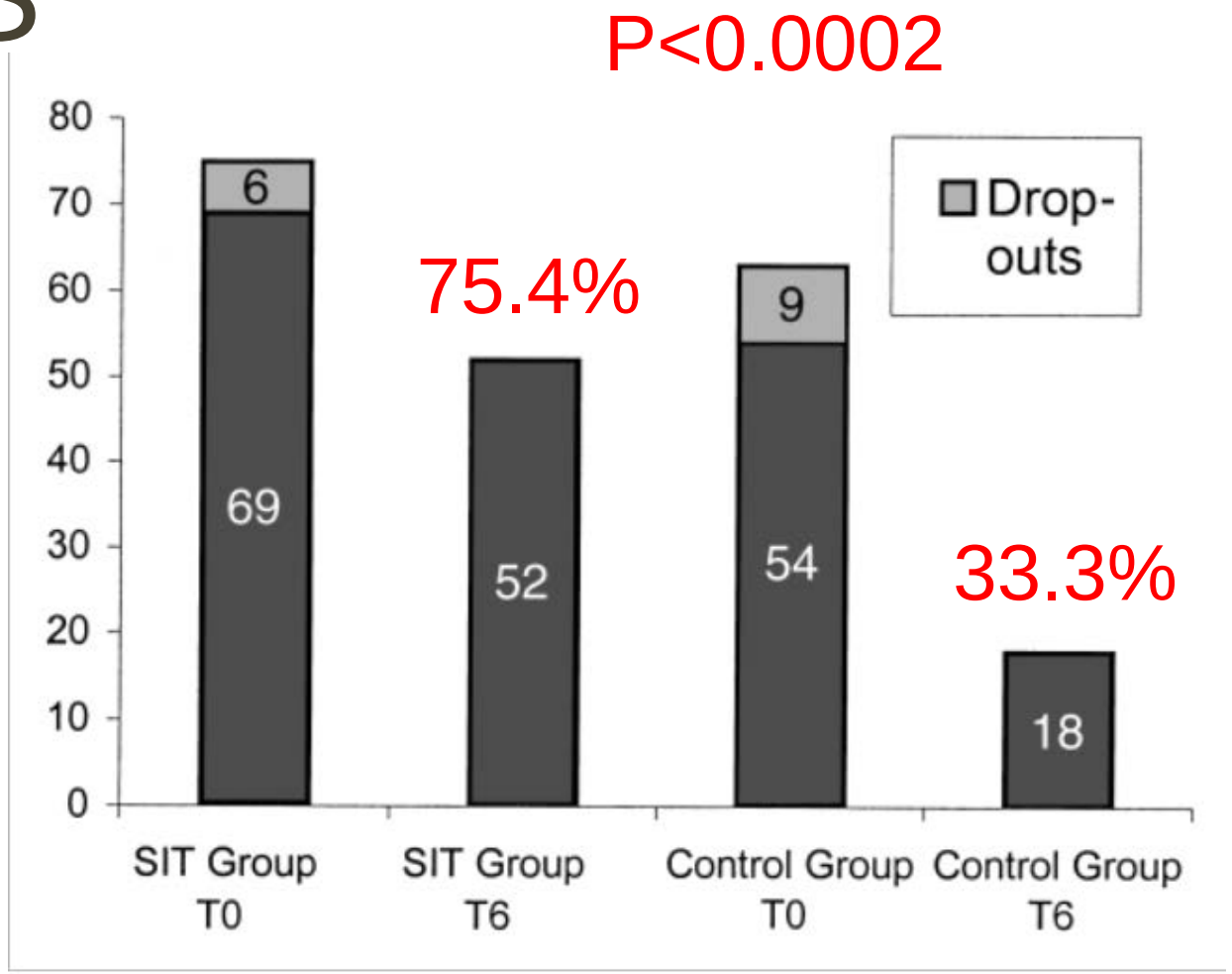
SCIT PREVENTS NEW SENSITIZATIONS

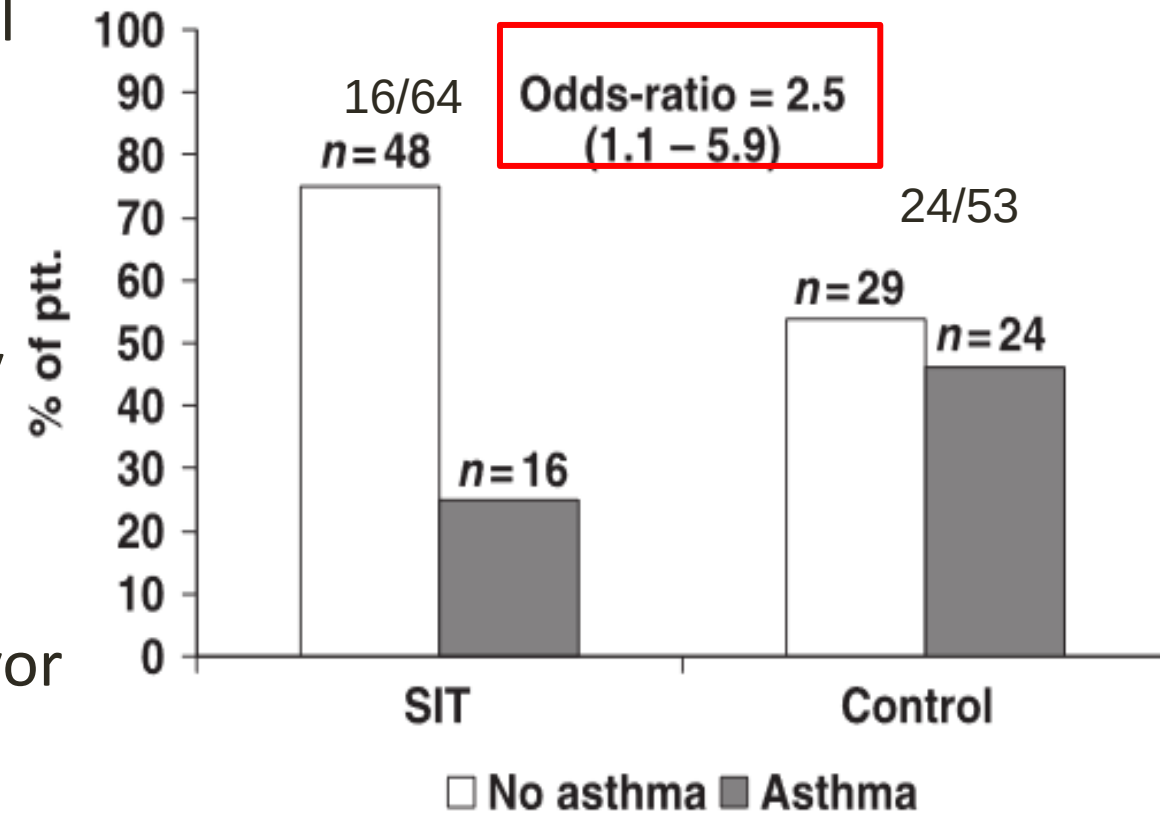
- 134 children (5-8y) with mild-intermittent asthma monosensitized to dust mite
  - 75 SCIT / 63 control
  - SCIT for 3 years and followed for 6 years
- 123 completed the study
  - 75.4% (52/69) in SCIT group vs 33.3% (18/54) in control group showed no new sensitization



PAJNO G. CLIN AND EXPERIMENTAL ALLERGY 2001 SEP;31(9):1392-7

SCIT PREVENTS PROGRESSION TO ASTHMA

- 205 children (ages 6-14) with grass and/or birch pollen allergy randomized to 3y SCIT vs control
  - 147 (ages 16-25) participated in 10 year follow up
  - 117/147 no asthma at baseline
- Continued significant improvements in rhinoconjunctivitis and conjunctival sensitivity
- Significantly fewer patients had developed asthma by clinical symptoms
- OR for no-asthma 4.6 95% CI (1.5–13.7) in favor of SCIT
  - Longitudinal treatment effect (P = 0.0075)



JACOBSEN L. ALLERGY 2007 AUG;62(8):943-8.

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SCIT IS EFFECTIVE

"This review has shown that **specific allergen injection immunotherapy** in suitably selected patients with seasonal allergic rhinitis **results in a significant reduction in symptom scores and medication use"** when compared to placebo

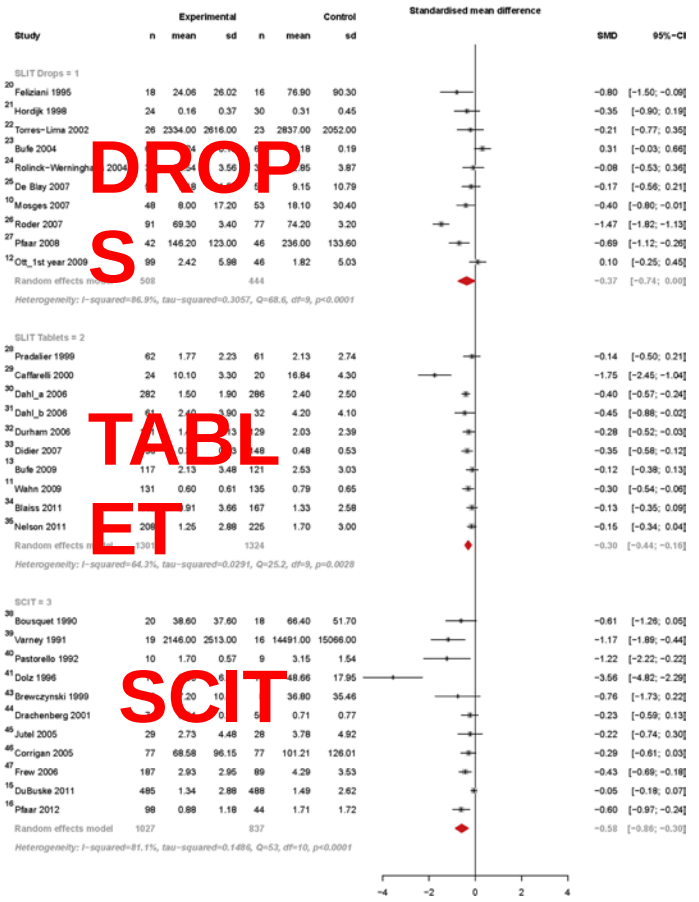
- Allergen injection immunotherapy for seasonal allergic rhinitis, Cochrane Review 2007

CALDERON MA. COCHRANE DATABASE SYST REV 2007 (1):CD001936..

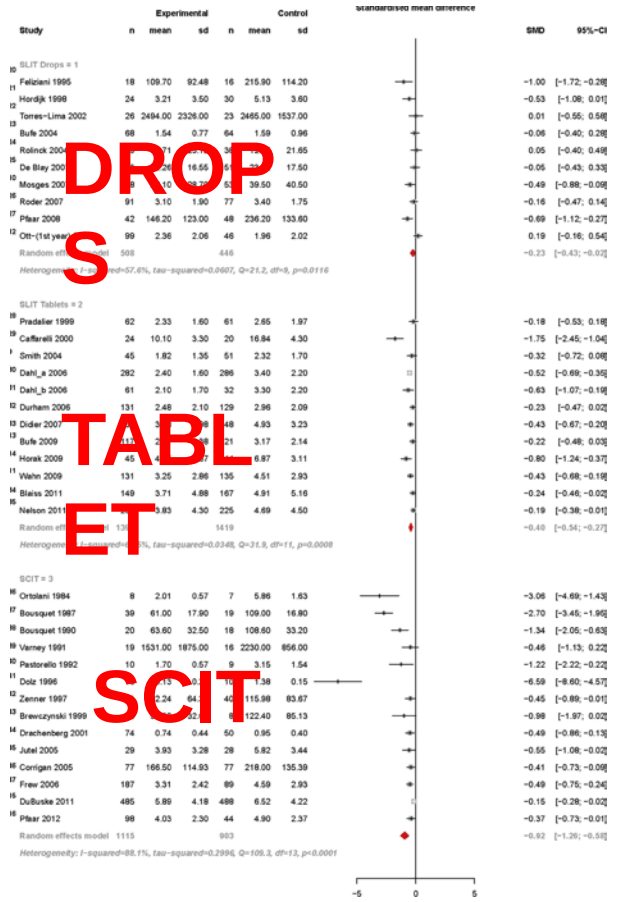
SCIT IS MORE EFFECTIVE THAN SLIT

- Meta-analysis of 36 RCT (3014 patients; 2768 controls)
- Compared the Standard Mean Difference (SMD) between the 2 groups
- Symptom score
  - **SCIT: SMD, −0.92**; 95%CI, −1.26 to −0.58
  - SLIT drops: SMD, −0.25; 95% CI, −0.45 to −0.05
  - SLIT tablets: SMD, −0.40; 95%CI, −0.54 to −0.27
- Medication score
  - **SCIT: SMD, −0.58**; 95% CI, −0.86 to −0.30
  - SLIT drops: SMD, −0.37; 95% CI, −0.74 to −0.00
  - SLIT tablets: SMD, −0.30; 95% CI, −0.44 to −0.16)

Symptom Score



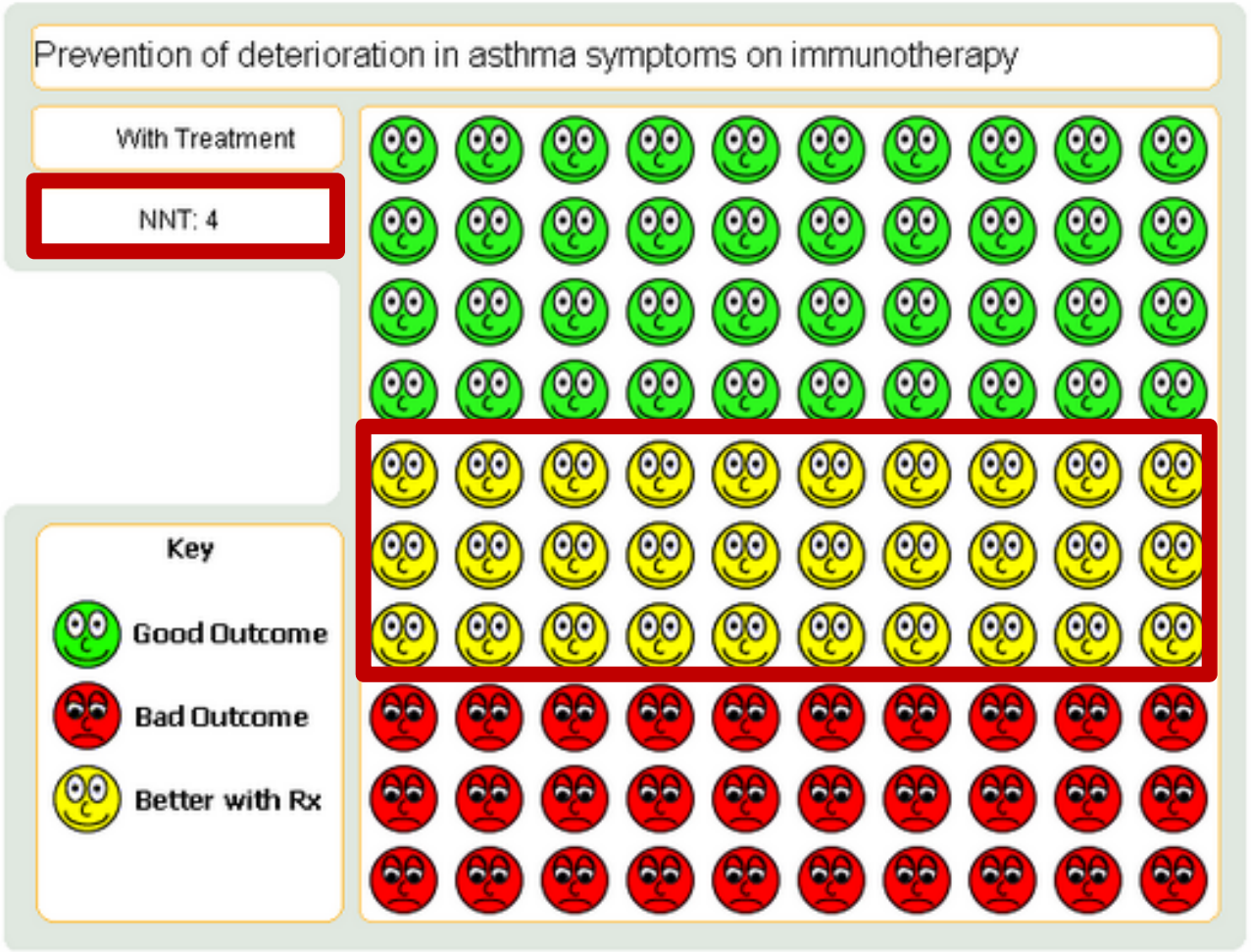
Medication Score



DI BONA. JACI 2012 NOV;130(5):1097-1107.E2

SCIT IS EFFECTIVE FOR ASTHMA

- Reduced asthma symptoms
- Reduced use of asthma medications
- Improved bronchial hyper-reactivity
- Benefit possibly comparable to inhaled steroids
- For every 100 asthma patients treated with SCIT
  - **30 patients** will be **<u>prevented</u>** from having an attack (worse symptoms)
- NNT = 4



ABRAMSON MJ. COCHRANE DATABASE SYST REV 2010 (8):CD00118

SLIT IS NOT EFFECTIVE FOR ASTHMA

“Therefore, this meta-analysis does not demonstrate a definitive result regarding the efficacy of SLIT for asthma treatment”

- Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method, Allergy 2006.

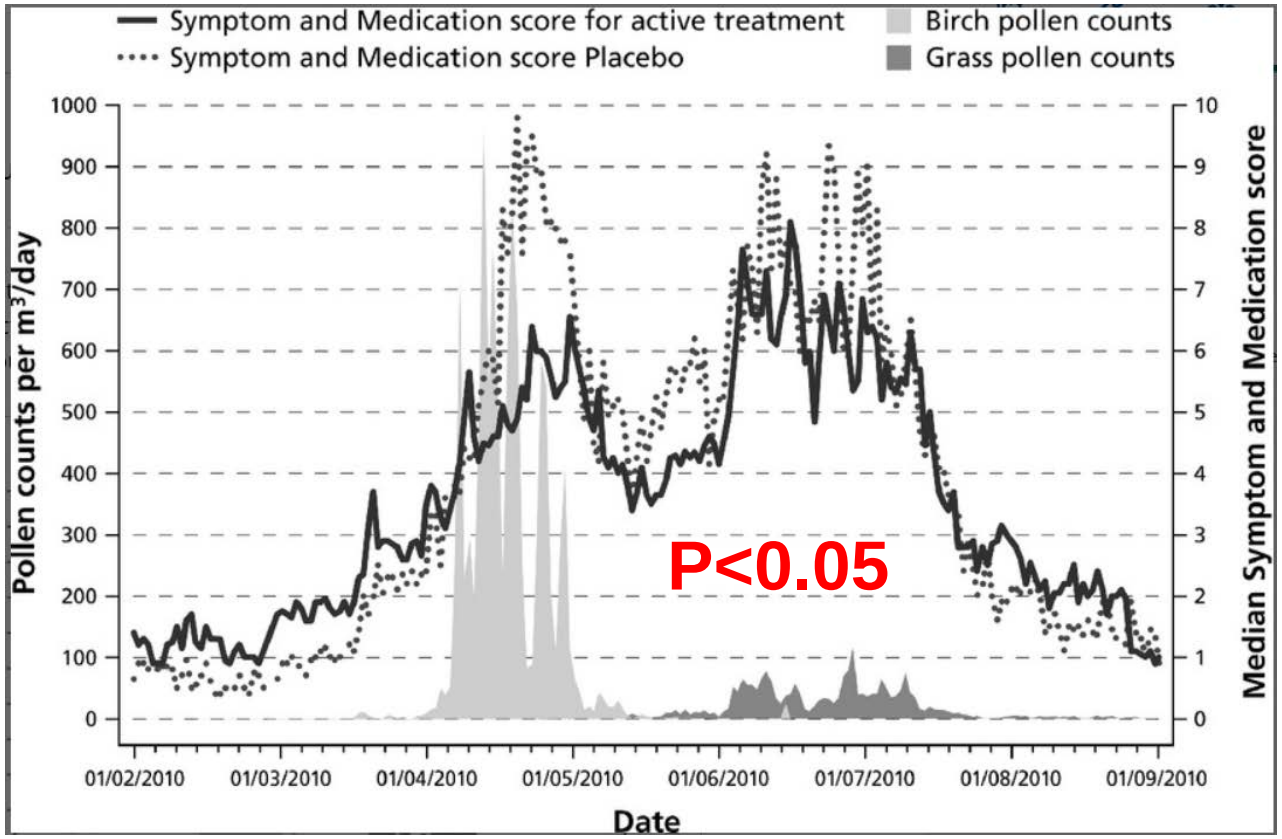
“Lack of data for important outcomes such as **exacerbations** and **quality of life** and **use of different unvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion**. Very few serious adverse events have been reported, but most studies have included **patients with intermittent or mild asthma**, so we **cannot comment on the safety of SLIT for those with moderate or severe asthma**.”

- Sublingual therapy for asthma, Cochrane Review 2015

CALAMITA Z. ALLERGY 2006 OCT;61(10):1162-72, NORMANSELL R. COCHRANE REVIEW 2015 AUG 28;(8):CD011293.

SCIT IS EFFECTIVE IN POLYSENSITIZED PATIENTS

- Polysensitization is more prevalent than monosensitization
  - Europe: 16-20% monosensitized vs 13-25% polysensitized
  - US: 16% monosensitized vs 40% polysensitized
- Combined treatment for grass/birch
  - Significant reduction in median symptom medication score for SCIT 5.70 vs placebo 7.07
  - Significant improvement in rhinitis quality-of-life scores
  - Increase in both birch and grass IgG4



CALDERON MA. JACI 2012 APR;129(4):929-34; PFAAR O. ALLERGY 2013 OCT;68(10):1306-13

SLIT IS NOT EFFECTIVE IN POLYSENSITIZED PATIENTS

"Clinical efficacy [of slit] may be reduced with the addition of multiple allergens, **limiting SLIT use in polysensitized individuals"**

- Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract, JACI 2009

"**No studies** found efficacy of multiple allergens administered as a mixture, there is a need for further investigations **to determine efficacy and optimal formulations and regimens for multiallergen SLIT"**

- Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update, Ann Allergy Asthma Immunology 2017

AMAR SM. JACI 2009 JUL;124(1):150-156.E1-5; GREENHAWT M. ANN ALLERGY ASTHMA IMMUNOLOGY 2017 118:276-282

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SCIT IS COST EFFECTIVE

- Florida Medicaid study matched 2771 SCIT with 11,010 controls
- SCIT patients had significantly lower 18-month median per-patient:
  - Total health care: $1625
  - Outpatient exclusive SCIT: $1519
  - Outpatient inclusive SCIT: $795
  - Pharmacy: $208
- Difference in total health care costs was evident **3 months after SCIT initiation** and **increased through study**
  - $248 → $1625

Table 3. Differences in Health Care Costs[a] Between IT-Treated Patients and Matched Controls During 18-Month Follow-up

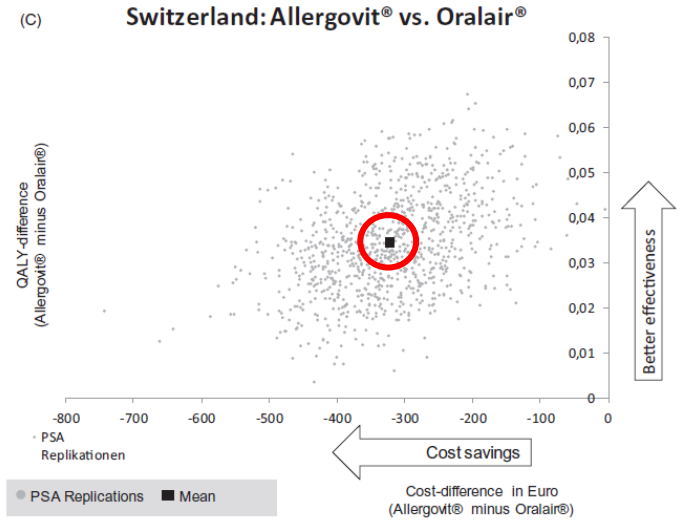
Cost category	Study time points				Between-group differences
	3 mo	6 mo	12 mo	18 mo	
Total health care costs, $					
IT-treated patients	790	1,347	2,345	3,247	$P < .001$ at all time points
Matched controls	1,038	1,874	3,406	4,872	
Inpatient costs, $					
IT-treated patients	1,770	3,057	2,918	3,901	Nonsignificant at all time points
Matched controls	2,573	2,754	4,682	4,414	
Outpatient costs exclusive of IT, $					
IT-treated patients	239	416	772	1,107	$P < .001$ at all time points
Matched controls	644	1,107	1,903	2,626	
Outpatient costs inclusive of IT, $					
IT-treated patients	465	805	1,358	1,829	$P < .001$ at all time points
Matched controls	635	1,086	1,887	2,594	
Pharmacy costs, $					
IT treated patients	272	465	829	1,108	$P < .001$ at all time points
Matched controls	316	533	936	1,316	

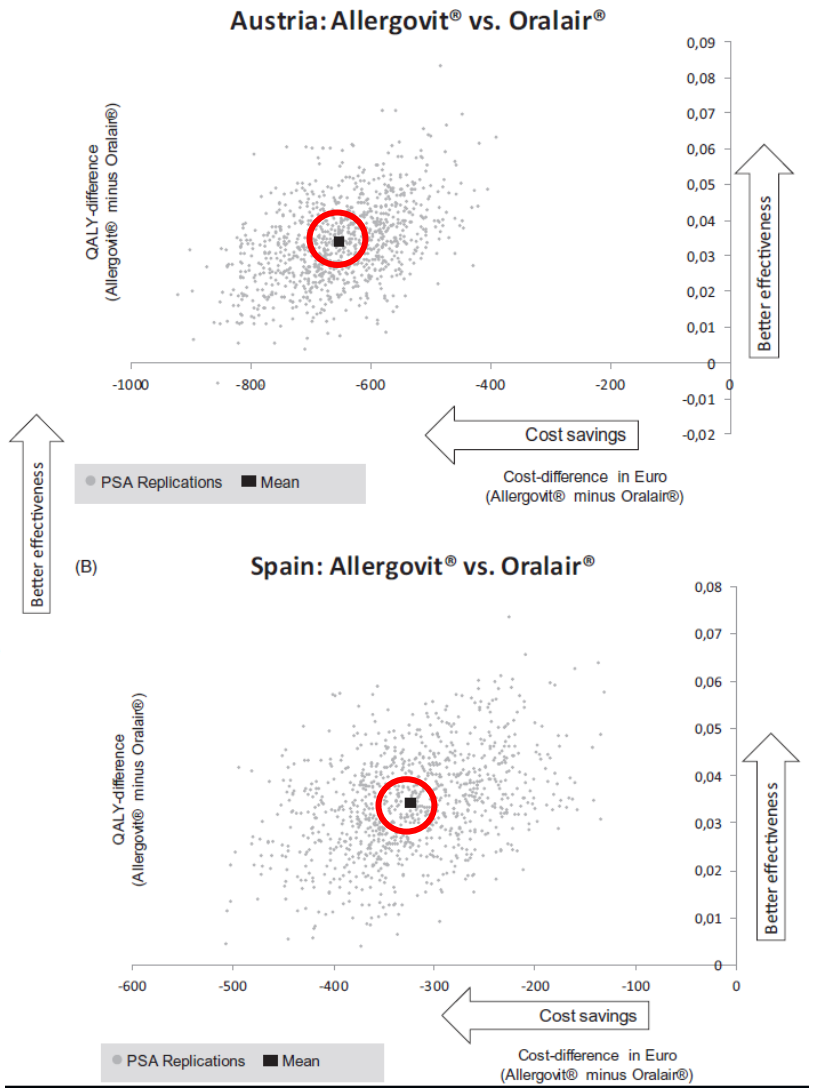
Abbreviation: IT, immunotherapy.
[a] All costs are median and per patient.

HANKIN CS. ANN ALLERGY ASTHMA IMMUNOL. 2010 JAN;104(1):79-85

SCIT IS MORE COST EFFECTIVE THAN SLIT

- SCIT (Allergovit) vs SLIT (Oralair) for 3yr treatment over 9yr period
- Total per-patient cost of treatment
  - Austria €1,368 vs €2,012
  - Spain €2,229 vs €2,547
  - Switzerland €1,901vs €2,220
- SCIT with superior effectiveness in symptom-score based quality-adjusted life years (QALY)
  - SCIT 8.02 vs SLIT 7.98 vs Medication 7.90





BRUGGENJURGEN B J. MED ECON. 2018 APR;21(4):374-381

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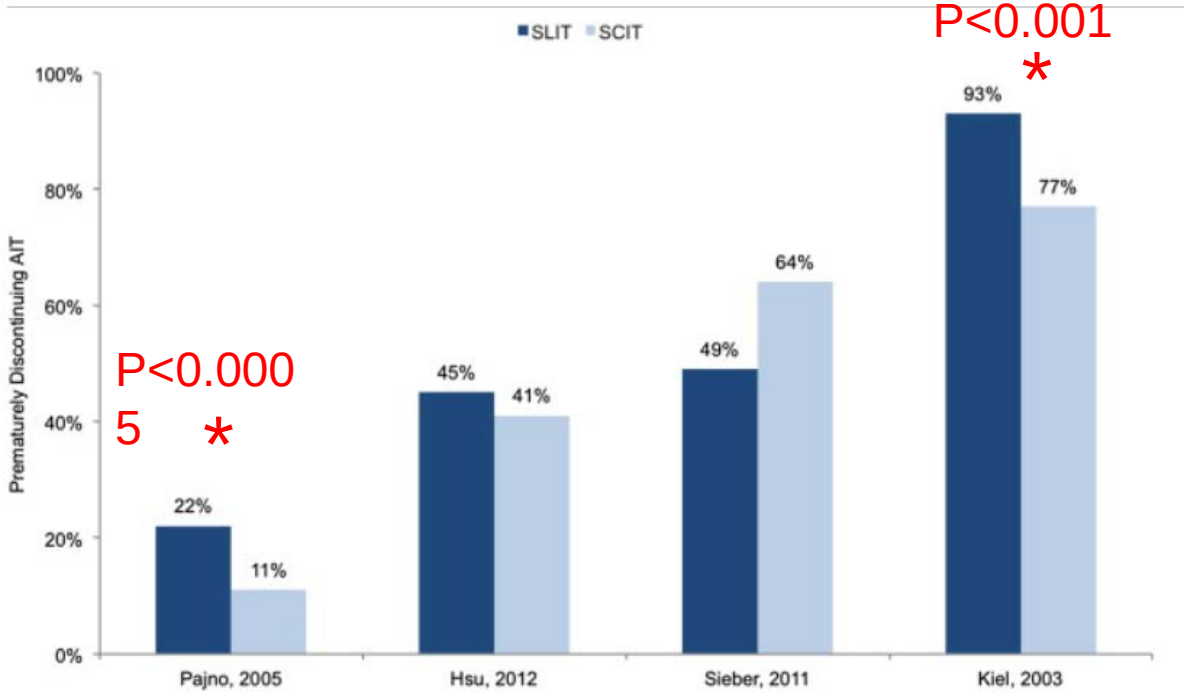
MORE PATIENTS ADHERE TO SCIT THAN SLIT

- Data from Italian manufacturers: less than 15% of patients initiating SLIT reach the 3rd yr of treatment
  - 43.7% → 27.7 % → 13.2 %
- Pajno 1998-2003: SCIT (n=1186) vs SLIT (n=806) → 22% of patients treated with SLIT prematurely discontinued treatment during the first 3 years vs 11% SCIT
- Kiel: Retrospective study of 6486 Dutch pharmacy claims SCIT (n=2796) vs SLIT (n=3690) → 93% of patients treated with SLIT discontinued treatment before 3 years vs 77% SCIT



SENNA G. JACI 2010; 126(3):668–9; COX L . J ALLERGY CLIN: IN PRACTICE 2014 MAR-APRIL;2(2): 156-60

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SCIT IS SAFE IN CHILDREN AND DURING PREGNANCY

- SCIT can be initiated in **children less than 5** if indicated
- SCIT (at maintenance) **can be continued pregnant** patients
- **No evidence of an increased risk** of prescribing or continuing SCIT for a mother while breastfeeding and **no risk** for the breast-fed child

COX L. JACI 2011 JAN;127

SLIT LIMITATIONS IN PEDIATRICS AND PREGNANCY

- Only 2 FDA-approved SLIT products for children
  - Grastek (age 5) and Oralair (age 10)
- Use FDA-approved SLIT products **very cautiously** in the pregnant or breastfeeding patient → **insufficient data** regarding the **safety of initiating or continuing SLIT** during either pregnancy or breastfeeding

GREENHAWT M. ANN ALLERGY ASTHMA IMMUNOLOGY 2017; 118:276-282

SLIT IS NOT AN ALTERNATIVE FOR SCIT

- "Both patients had respiratory—that is, **systemic**—side effects. In the first patient, they even progressed from large local reactions with SCIT to **respiratory reactions with SLIT, thus increasing in severity**"
  - Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy, JACI 2009
- **SLIT tablet contraindications**: severe, unstable, or uncontrolled asthma; **any history of a severe systemic reaction to any form of immunotherapy**; a history of eosinophilic esophagitis (EoE); or hypersensitivity to any of the inactive ingredients of the preparation."
  - Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update

COCHARD M. JACI 2009 AUG;124(2):378-9; GREENHAWT M. ANN ALLERGY ASTHMA IMMUNOLOGY 2017; 118:276-282

SLIT LIMITATIONS

SLIT LIMITATIONS

- **Only use FDA-approved SLIT products** for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition
- FDA approved SLIT products:
  - Grastek (Ages 5-65) – Timothy Grass
    - Start 12 weeks prior to grass season (March through September)
  - Oralair (Ages 10-65) – 5-grass mix (sweet vernal, orchard, perennial rye, timothy, Kentucky blue grass)
    - Start 4 months prior to grass season (March through September)
  - Ragwitek (Ages 18-65) – Ragweed
    - Start 12 weeks prior to ragweed season (August through October)
  - Odactra (Ages 18-65) – Dust mite (DF and DP)
    - Year Round

Januar

December

May

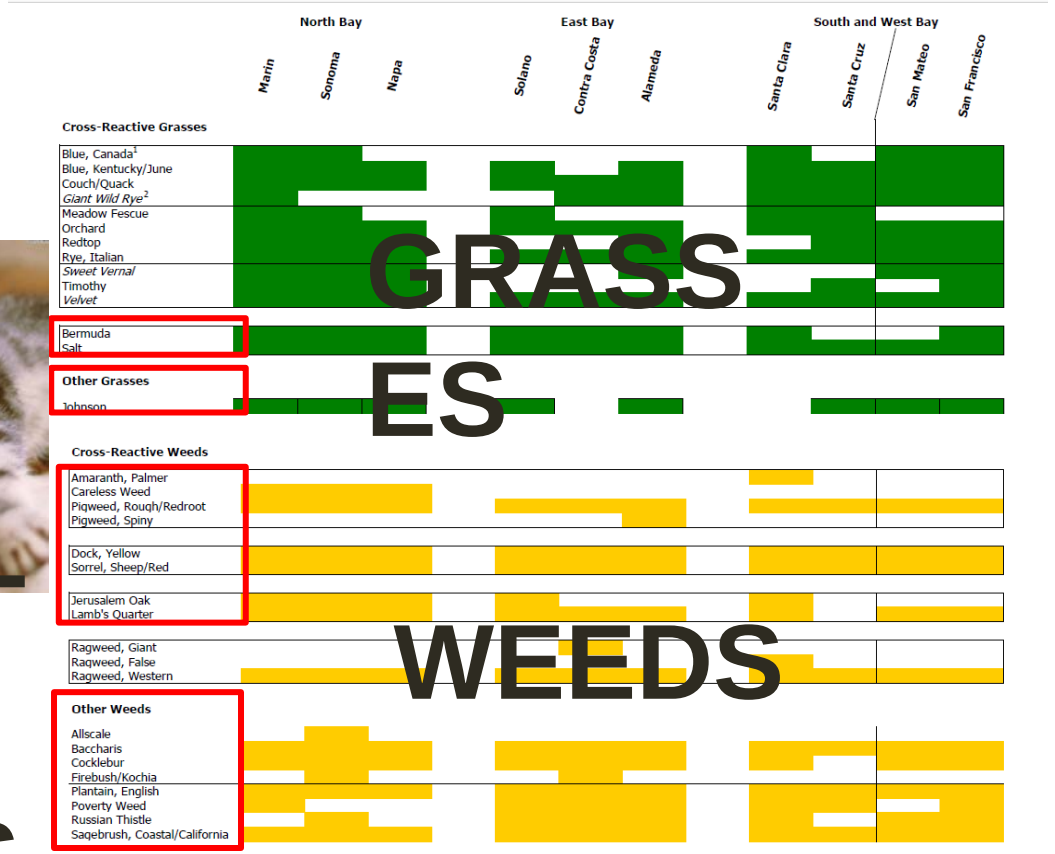
GREENHAWT M. ANN ALLERGY ASTHMA IMMUNOLOGY 2017; 118:276-282; BAUER CS. JACI 2015SEP;134(3):765-765.E2

MISSING ALLERGENS

TREES

ANIMALS

MOLDS



GRASSES

WEEDS

COX L. JACI 2011 JAN;127(1 SUPPL):S1-55; BAUER CS. JACI 2014 SEP;134(3):765-765.E2;IMAGE: HTTPS://WALLPAPER-HOUSE.COM/GROUP/KITTENS-AND-PUPPIES-WALLPAPER/INDEX.PHP

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SCIT IS TAILORED TO THE PATIENT

- Standardized extracts with effective dose ranges
- Wide range of extracts: pollens (trees, grasses, weeds), animals, and molds which can be tailored to the patient based on their sensitizations
- Many ways to build-up SCIT based on patient preference and tolerance
  - Rush and Ultra-Rush schedules to reach maintenance faster
- Maintenance dosing every 4-6 weeks, tailored to patient symptoms
- Administered in a monitored setting
  - Allows for patient evaluation at each visit to assess safety
  - Allows for dosing adjustments during high-pollen season
  - Allows for dosing adjustments based on prior reactions
  - Billable procedure with each administration

EPSTEIN T. JACI IN PRACTICE 2014 MAR-APR;2(2):161-7; COX L. JACI 2011JAN;127(1 SUPPL):S1-55

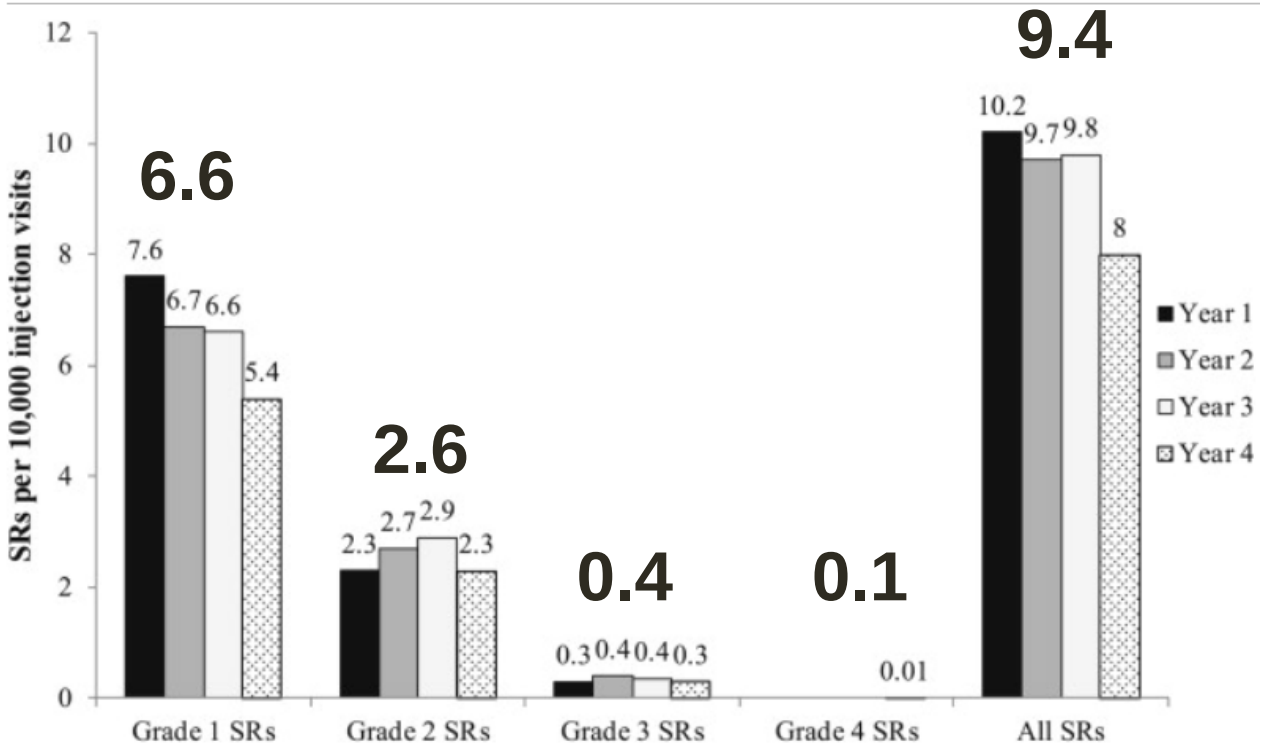
SLIT IS NOT THE PREFERRED THERAPY

- Long history
  - 100+ years vs 45 years
- SCIT leads to disease modification
  - Superior immunologic responses in comparison studies with SLIT
- SCIT leads to disease prevention
- SCIT is effective
  - Effective for asthma treatment, no data for SLIT
  - Superior symptom and medication scores in comparison studies with SLIT
- SCIT is cost effective when compared to medication
  - More cost effective than SLIT in comparison studies
- SCIT has better compliance than SLIT
- SCIT is safe for use in children and pregnant/breastfeeding patients
- SCIT is tailored to the patient

SCIT IS STILL SUPERIOR TO SLIT

SCIT SAFETY CONTINUES TO IMPROVE

- Reaction Rate: 9.4/10,000 injection visits
- Grade 1 (Urticaria, Upper respiratory symptoms): 6.6/10,000 injection visits
- Grade 2 (Asthma reactions with decreased lung function +/- GI symptoms): 2.6/10,000 injection visits
- Grade 3 (Anaphylaxis with severe airway compromise or upper airway obstruction): 0.4/10,000 injection visits
- Grade 4 (Adopted 2011 – respiratory failure or hypotension +/- LOC): 0.01/10,000 injection visits



EPSTEIN T. JACI IN PRACTICE 2014 MAR-APR;2(2):161-7

LOCAL REACTIONS DO NOT LEAD TO DISCONTINUATION

- Analysis of 381 charts of patients who had stopped SCIT
  - Only 5.5% stated local reactions from SCIT as reason for discontinuation
- Survey of 249 SCIT patients
  - 96.6% would not stop allergen immunotherapy because of local reactions
  - 81.9% deemed local reactions not to be bothersome

COOP CA. ANN ALLERGY ASTHMA IMMUNOL. 2008 101(1):96-100; MORE DR. ANN ALLERGY ASTHMA IMMUNOL. 2002; 88: 391–394

SCIT FATALITY RATES ARE DECLINING

- Before 2002: 3.4 fatal reactions per year (1 in 2.5 million injection visits)
- Between 2008-2012: 1 fatality (1 in 23.3 million injection visits)

1 in 149,000

EPSTEIN T. JACI IN PRACTICE 2014 MAR-APR;2(2):161-7; BARLOW T. FORBES 2011

SCIT	SLIT
• Established effective dose ranges	• Non-standardized dosing ranges
• Efficacy proven for pollen, animal allergens, dust mite, and mold/fungi • Multi-allergen therapy	• FDA-Approved products include grass (timothy grass, sweet vernal, orchard, perennial rye, Kentucky blue grass), ragweed and dust mites • No data for non-standardized allergy drops
• Customize dose amount (build-up and maintenance) to patient	• One standard dose (FDA-Approved products)
• Customize dosing interval to patient	• Daily dosing • Missed dose (1-7 days) → contact health provider
• Safe to use in children 5 and under	• 2 FDA-approved products for children: Grastek (age 5) and Oralair (age 10). Others are 18+
• Ok to continue maintenance during pregnancy and breastfeeding	• Use cautiously due to insufficient data on initiating or continuing during pregnancy or breastfeeding

• Medical conditions that reduce the patient's ability to survive systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy	• Contraindicated in:
	  • EoE
	  • Severe/unstable or uncontrolled asthma
	  • History of severe systemic reaction to any form of IT
	  • History of severe local reaction to SLIT

SCIT	SLIT
• N/A	• Hold doses 24h after dental cleaning, 10-14 days after dental extraction and with oral lesions until healed
• Improves outcomes in patients with allergic asthma	• Lack of data to draw clinical conclusion per Cochrane Review 2015
• Prevents new onset of allergen sensitivities in monosensitized patients	• Conflicting data and use of non FDA-approved SLIT products
• Prevents progression from allergic rhinitis to asthma	• Conflicting data and use of non FDA-approved SLIT products
• More cost-effective in comparison studies	---
• Higher adherence in comparison studies with SLIT	---
• Managed by board-certified Allergists and administered in clinic in observed setting • Billable procedure (95165)	• Can be managed by PCP and ENT in addition to allergists. • Taken at home, unable to bill aside from initial administration • Risk of overdosing error at home

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