

Comparative Efficacy and Safety of Sublingual vs Subcutaneous Immunotherapy in Bronchial Asthma

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- I** Efficacy of SCIT and SLIT
- II** Comparative Efficacy of SCIT vs SLIT
- III** Safety of SCIT and SLIT

Bronchial Asthma

- The pathophysiology of asthma is **very complex** and includes several disease variants.
- Asthma is a **heterogeneous disease**, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

GINA 2014 update

- Asthma is not exclusively associated with allergy/atopy.
- However, more than 50 % of the asthmatic population is allergic/atopic.

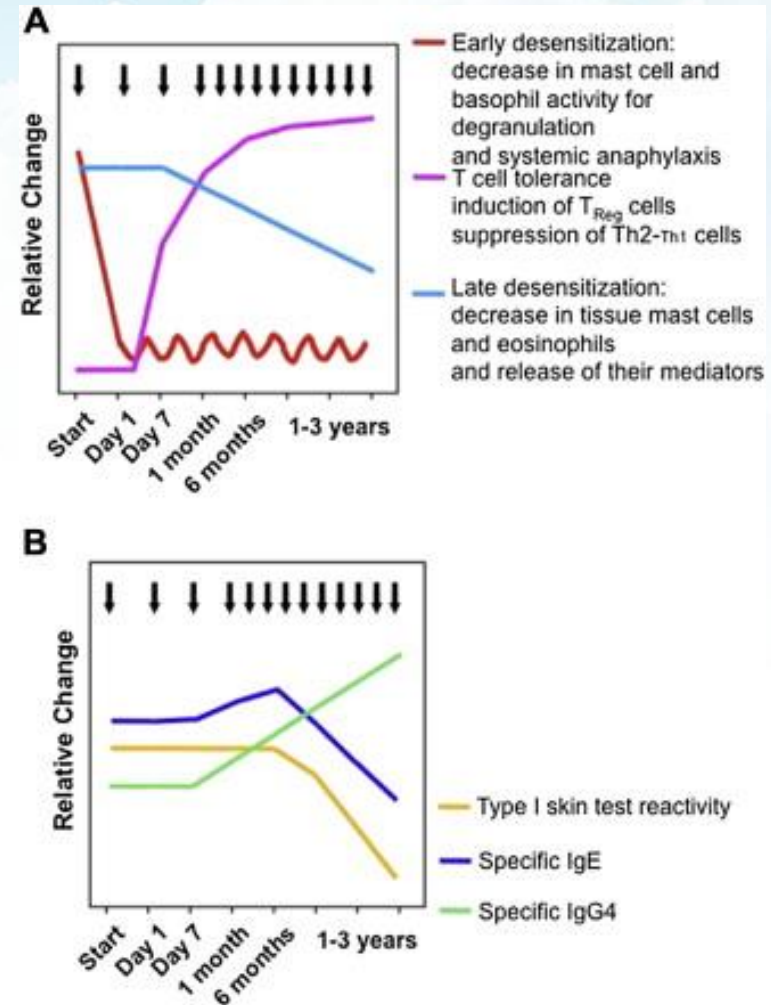
Management of Asthma

- Current Pharmacotherapy can effectively control symptoms and the inflammatory process.
- Limitation of current pharmacotherapies
 - Long-term side effects, compliance, and cost.
 - Varying responses to individual drugs
 - They do not affect the underlying immune response.
Thus, they are limited to blunting the progression of the disease, which relapses on ceasing the treatment.
- Allergen-specific immunotherapy (AIT)
 - the only etiology-based treatment capable of disease modification
 - the only **real curative modality** in allergic asthma



Multiple Mechanisms of AIT

- Induction of both rapid desensitization and long-term allergen-specific immune tolerance
- Induction of peripheral tolerance by the generation of regulatory T cells
 - IL-10 and TGF-beta secretion
 - Regulatory T cells and particularly IL-10 also have an influence on B cells, **suppressing IgE production** and inducing the production of **blocking type IgG4 antibodies**



Jutel M, et al. Allergol Int 2013;62:425-33

Burks AW, et al. J Allergy Clin Immunol 2013;131:1288-96

Allergy Immunotherapy (AIT)

- AIT involves the repeated administration of allergen preparations in order to induce clinical and immunologic tolerance to the offending allergen.

Two most commonly prescribed routes

- ➔ Subcutaneous immunotherapy (SCIT)
- ➔ Sublingual immunotherapy (SLIT)

Jutel M, et al. Curr Treat Options Allergy 2014;1:213-9

AIT for Allergies

→ SCIT

- Noon and Freeman in 1911
- The U.S. FDA has approved in treating seasonal and perennial allergic rhinitis (AR) and allergic asthma.



→ SLIT

- First randomized study in 1986
- placing drops or tablets with the allergen extract under the tongue for local absorption



SLITone



Lais

Indication for IT

- Allergen-specific immunotherapy is typically used for:
 - Patients whose allergic asthma symptoms **cannot be controlled** by medication and environmental control
 - Patients who **cannot tolerate** medications
 - Patients who **do not comply with long term** medications
- Factors considered for the selection of route include vaccine availability or approval, geographic location, cost, and the patient's characteristics or the physician's or patient's preference.

Calderon MA, et al. J Allergy Clin Immunol 2011;127:30-8



I. Efficacy of SCIT and SLIT



Allergen AIT for Asthma

Comparison 1. Allergen immunotherapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	27	1064	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.99, -0.44]
1.1 Mite immunotherapy	9	304	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-1.27, -0.29]
1.2 Pollen immunotherapy	14	547	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-0.99, -0.33]
1.3 Other immunotherapy	5	213	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.92, 0.26]
2 Symptomatic deterioration	22	1112	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.41, 0.65]
2.1 Mite immunotherapy	12	460	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
2.2 Pollen immunotherapy	3	220	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.90]
2.3 Animal dander immunotherapy	4	107	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.92]
2.4 Other immunotherapy	3	325	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.65]
3 Asthma medication scores	14	608	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.13, -0.48]
3.1 Mite immunotherapy	8	242	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.61, -0.52]
3.2 Pollen immunotherapy	6	245	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.16, -0.21]
3.3 Other immunotherapy	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.62, 0.10]
4 Increased asthma medication	16	564	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.58, 0.76]
5 Lung function parameters	16		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Peak Expiratory Flow	8	406	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.45, 0.53]
5.2 FEV1	6	174	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.83, 0.57]
5.3 Thoracic Gas Volume	2	81	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
6 Deterioration in lung function	7	253	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.10]
7 Nonspecific BHR indices	15	471	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.71, -0.14]
7.1 LogPD20 Methacholine	9	348	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.66, -0.00]
7.2 LogPC20 Histamine	4	76	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.37, 0.28]
7.3 LogPC35 Acetylcholine	1	21	Std. Mean Difference (IV, Random, 95% CI)	-1.29 [-2.28, -0.31]
7.4 DeltaFEV1% Cold air	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.31, 0.26]
8 Increased nonspecific BHR	5	121	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.33, 0.72]
9 Allergen specific BHR indices	15	436	Std. Mean Difference (IV, Fixed, 95% CI)	-0.66 [-0.87, -0.45]
9.1 LogPD20 Mite	5	115	Std. Mean Difference (IV, Fixed, 95% CI)	-1.14 [-1.62, -0.65]
9.2 LogPD20 Pollen	2	107	Std. Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.09, -0.30]
9.3 LogPD20 Animal dander	6	153	Std. Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.95, -0.27]
9.4 LogPD20/PC100 Other allergens	2	61	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.70, 0.33]
10 Increased allergen specific BHR	16	430	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.41, 0.63]

-0.72

-0.80

-0.66

Allergen-specific immunotherapy for respiratory allergies: From meta-analysis to registration and beyond

Moisés A. Calderón, MD, PhD,^a Thomas B. Casale, MD,^b Alkis Togias, MD,^c Jean Bousquet, MD, PhD,^{d,e} Stephen R. Durham, MD,^a and Pascal Demoly, MD, PhD^d *London, United Kingdom, Omaha, Neb, Bethesda, Md, and Montpellier and Villejuif, France*

- The clinical efficacy of SCIT in asthma was demonstrated by a Cochrane meta-analysis.

Abramson MJ, et al. Cochrane Database Syst Rev. 2003;(4):CD001186

TABLE II. Summary of meta-analyses for SCIT and SLIT

Disease	Authors (y)	RCTs included (No. of participants)	Symptom scores SMD (95% CI) I ² (heterogeneity) No. of studies	Medication scores SMD (95% CI) I ² (heterogeneity) No. of studies	Cochrane Review
SCIT					
Asthma	Abramson et al (2003) ¹⁶	75 (3506) Adults and children	-0.72 (-0.99, -0.44) I ² = 74.1% 28 Studies	-0.80 (-1.13, -0.48) I ² = 65.5% 15 Studies	Yes
Rhinitis	Calderon et al (2007) ¹⁷	51 (2871) Adults	-0.73 (-0.97, -0.50) I ² = 63.2% 15 Studies	-0.57 (-0.82, -0.33) I ² = 64.0% 13 Studies	Yes

Calderon MA, et al. J Allergy Clin Immunol 2011;127:30-8

Comparison 1. Allergen immunotherapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	34	1284	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.83, -0.35]
1.1 Mite immunotherapy	12	408	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.96, -0.00]
1.2 Pollen immunotherapy	18	663	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.87, -0.35]
1.3 Other immunotherapy	5	213	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.92, 0.26]
2 Symptomatic deterioration	22	1112	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.41, 0.65]
2.1 Mite immunotherapy	12	460	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
2.2 Pollen immunotherapy	3	220	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.90]
2.3 Animal dander immunotherapy	4	107	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.92]
2.4 Other immunotherapy	3	325	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.65]
3 Asthma medication scores	20	869	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.80, -0.27]
3.1 Mite immunotherapy	12	424	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.04, -0.18]
3.2 Pollen immunotherapy	8	324	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.91, -0.13]
3.3 Other immunotherapy	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.62, 0.10]
4 Increased asthma medication	17	636	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.79]
5 Lung function parameters	20		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Peak Expiratory Flow	11	524	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.33, 0.61]
5.2 FEV1	7	199	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.96, 0.31]
5.3 Thoracic Gas Volume	2	81	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
6 Deterioration in lung function	7	253	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.10]
7 Nonspecific BHR indices	18	576	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.59, -0.11]
7.1 LogPD20 Methacholine	12	453	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
7.2 LogPC20 Histamine	4	76	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.37, 0.28]
7.3 LogPC35 Acetylcholine	1	21	Std. Mean Difference (IV, Random, 95% CI)	-1.29 [-2.28, -0.31]
7.4 DeltaFEV1% Cold air	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.31, 0.26]
8 Increased nonspecific BHR	5	121	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.33, 0.72]
9 Allergen specific BHR indices	19	564	Std. Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.79, -0.43]
9.1 LogPD20 Mite	6	148	Std. Mean Difference (IV, Fixed, 95% CI)	-0.98 [-1.39, -0.58]
9.2 LogPD20 Pollen	5	202	Std. Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.84, -0.27]
9.3 LogPD20 Animal dander	6	153	Std. Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.95, -0.27]
9.4 LogPD20/PC100 Other allergens	2	61	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.70, 0.33]
10 Increased allergen specific BHR	16	430	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.41, 0.63]
11 Local reactions	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Per patient	14	396	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.70]
12 Systemic reactions	37		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Per patient	37	1784	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.91, 3.13]
13 Asthma symptom scores (adequate allocation concealment)	9	362	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.08, -0.26]
13.1 Mite immunotherapy	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.53, 1.22]
13.2 Pollen immunotherapy				
13.3 Other immunotherapy				

-0.59

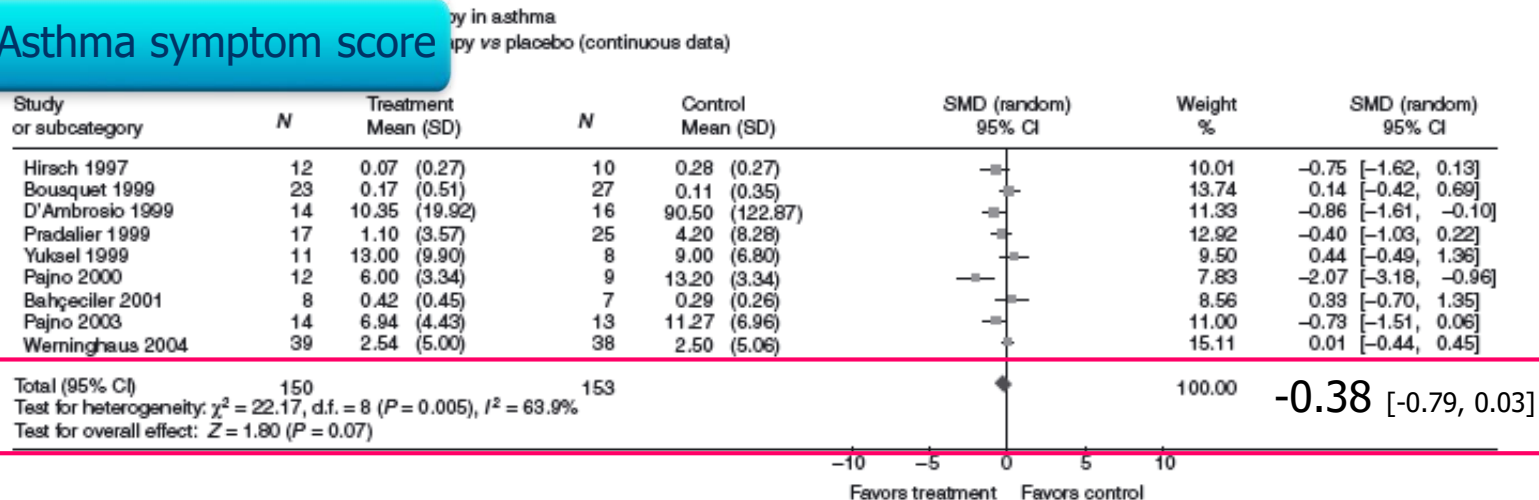
-0.53

-0.35

-0.61

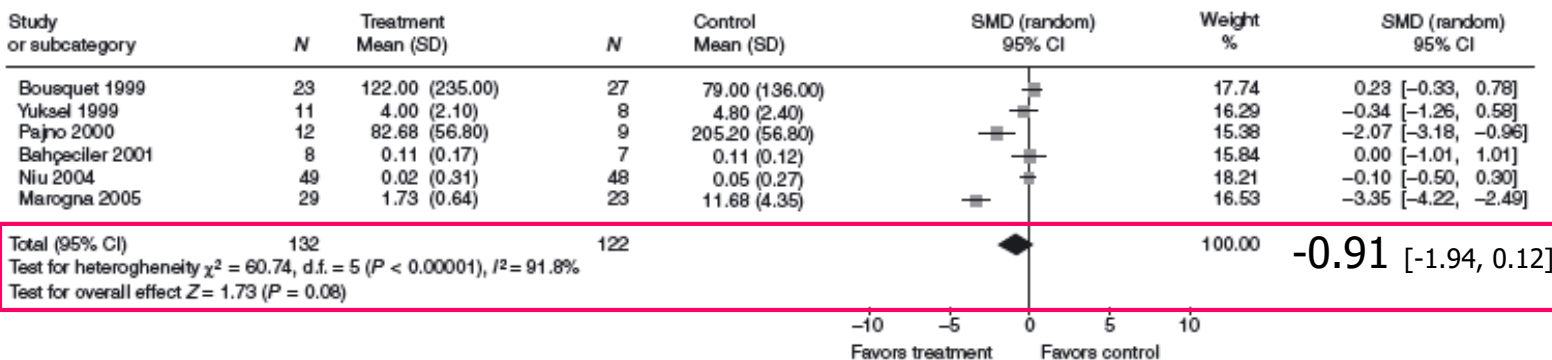
Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

Asthma symptom score



Medication use score

Review: Efficacy of sublingual immunotherapy in asthma
 Comparison: 02 Allergen sublingual immunotherapy vs placebo (continuous data)
 Outcome: 08 Reduction of medication use to asthma



Efficacy of AIT

TABLE II. Summary of meta-analyses for SCIT and SLIT

Disease	Authors (y)	RCTs included (No. of participants)	Symptom scores SMD (95% CI) I ² (heterogeneity) No. of studies	Medication scores SMD (95% CI) I ² (heterogeneity) No. of studies	Cochrane Review
SCIT					
Asthma	Abramson et al (2003) ¹⁶	75 (3506) Adults and children	-0.72 (-0.99, -0.44) I ² = 74.1% 28 Studies	-0.80 (-1.13, -0.48) I ² = 65.5% 15 Studies	Yes
Rhinitis	Calderon et al (2007) ¹⁷	51 (2871) Adults	-0.73 (-0.97, -0.50) I ² = 63.2% 15 Studies	-0.57 (-0.82, -0.33) I ² = 64.0% 13 Studies	Yes
SLIT					
	Calamita et al (2006) ²⁰	25 (1706) Adults and children	-0.38 (-0.79, 0.03)* I ² = 63.9% 9 Studies	-0.91 (-1.94, 0.12)* I ² = 91.8% 6 Studies	No
	Penagos et al (2008) ²¹	9 (441) Children	-1.14 (-2.10, -0.18) I ² = 94.4% 9 Studies	-1.63 (-2.83, -0.44) I ² = 95.4% 7 Studies	No
Asthma	Olaguíbel et al (2005) ²²	5 (193) Children	-1.42 (-2.51, -0.34) I ² = NR 6 Studies	NR	No
	Compalati et al (2009) ²³ (only HDM)	9 Adults and children	-0.95 (-1.74, -0.15) I ² = 93% 9 Studies (476 participants)	-1.48 (-2.70, -0.26) I ² = 96% 7 Studies (397 participants)	No
Rhinitis	Wilson et al (2005) ¹⁸	22 (979) Adults and children	-0.42 (-0.69, -0.15) I ² = 73.5% 21 Studies	-0.43 (-0.63, -0.23) I ² = 43.8% 17 Studies	Yes
	Penagos et al (2006) ¹⁹	10 (484) Children	-0.56 (-1.01, -0.10) I ² = 81.1% 10 Studies	-0.76 (-1.46, -0.06) I ² = 85.5% 7 Studies	No
	Olaguíbel et al (2005) ²²	6 (232) Children	-0.44 (-1.22, 0.35) I ² = NR 6 Studies	NR	No
	Compalati et al (2009) ²³ (only HDM)	8 Adults and children	-0.95 (-1.77, -0.14) I ² = 92% 8 Studies (382 participants)	-1.88 (-3.65, -0.12) I ² = 95% 4 Studies (175 participants)	No

HDM, House dust mite; I², I squared (for heterogeneity); NR, not reported; RCT, randomized controlled trial; SMD, standardized mean difference.

*P value = not significant.

Efficacy of AIT for Allergic Respiratory Disease

Symptom score

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I ² †
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon, ^{E1} 2007	15	Adults	597	466	-0.73 (-0.97 to -0.50)	63%
Asthma	Abramson, ^{E2} 2010	34	Adults and children	727	557	-0.59 (-0.83 to -0.35)	73%
SLIT							
Rhinitis	Wilson, ^{E3} 2003	21	Adults and children	484	475	-0.42 (-0.69 to -0.15)	73%
Rhinitis	Penagos, ^{E4} 2006	10	Children	245	239	-0.56 (-1.01 to -0.10)	81%
Rhinitis	Radulovic, ^{E5} 2011	49	Adults and children	2333	2256	-0.49 (-0.64 to -0.34)	81%
Asthma	Calamita, ^{E6} 2006	9	Adults and children	150	153	-0.38 (-0.79 to 0.03)	64%
Asthma	Penagos, ^{E7} 2008	9	Children	232	209	-1.14 (-2.10 to -0.18)	94%
Conjunctivitis	Calderon, ^{E8} 2011	36	Adults and children	1725	1674	-0.41 (-0.53 to -0.28)	59%
House dust mites	Compalati, ^{E9} 2009	8	Adults and children	194	188	-0.95 (-1.77 to -0.14)	92%
Grass allergens	Di Bona, ^{E10} 2010	19	Adults and children	1518	1453	-0.32 (-0.44 to -0.21)	56%

Medication score

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I ² †
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon, ^{E1} 2007	13	Adults	549	414	-0.57 (-0.82 to -0.33)	64%
Asthma	Abramson, ^{E2} 2010	20	Adults and children	485	384	-0.53 (-0.80 to -0.27)	67%
SLIT							
Rhinitis	Wilson, ^{E3} 2003	17	Adults and children	405	398	-0.43 (-0.63 to -0.23)	44%
Rhinitis	Penagos, ^{E4} 2006	7	Children	141	138	-0.76 (-1.46 to -0.06)	86%
Rhinitis	Radulovic, ^{E5} 2011	38	Adults and children	1737	1642	-0.32 (-0.43 to -0.21)	50%
Asthma	Calamita, ^{E6} 2006	6	Adults and children	132	122	-0.91 (-1.94 to 0.12)	92%
Asthma	Penagos, ^{E7} 2008	7	Children	192	174	-1.63 (-2.83 to -0.44)	95%
Conjunctivitis	Calderon, ^{E8} 2011	13	Adults and children	560	478	-0.10 (-0.22 to 0.03)	34%
House dust mites	Compalati, ^{E9} 2009	4	Adults and children	89	86	-1.88 (-3.65 to -0.12)	95%
Grass allergens	Di Bona, ^{E10} 2010	17	Adults and children	1428	1358	-0.33 (-0.50 to -0.16)	78%

*Effect size (SMD): poor, <-0.20; medium, -0.50; high, >-0.80.

†Heterogeneity (I²) = 0% to 40%, might not be important; 30% to 60%, 100%, considerable heterogeneity.

Systematic Review

- **142 studies** were included in the review with these populations: adults only (52%), children only (24%), and adults and children (22%).
- RCTs published **from January 1967 to May 2012**
- All included studies were randomized controlled trials.
 - Efficacy and safety of SCIT: n = 74
 - Efficacy and safety of SLIT: n = 60
 - Comparisons of SCIT versus SLIT: n = 8
- Follow-up varied and ranged from one pollen season to 6 years.
- The strength of evidence ratings are classified into four broad ratings:

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

SCIT Versus Placebo or Standard Therapy: Asthma Outcomes

Primary Outcome	Results	No. of RCTs, No. of Patients (n)	Strength of Evidence
Asthma symptom score	17–84% greater improvement vs. controls	16 RCTs, n = 1,178	High
Use of asthma medications	Decreased in 42% of studies vs. controls	12 RCTs, n = 1,062	High
Combined asthma symptom and medication score	Significant improvement in 83% of studies vs. placebo	6 RCTs, n = 196	Low

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.

SLIT Versus Placebo or Standard Therapy: Asthma Outcomes

Primary Outcome	Results	No. of RCTs, No. of Patients (n)	Strength of Evidence
Asthma symptom score	Significant improvement across all studies vs. controls	13 RCTs, n = 625	High
Use of asthma medications	Evidence is unavailable or does not permit a conclusion		Insufficient
Combined asthma symptom and medication score	Evidence is unavailable or does not permit a conclusion		Insufficient

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.

SLIT Versus Placebo or Standard Therapy: Asthma Plus Rhinitis/Rhinoconjunctivitis Outcomes

Primary Outcome	Results	No. of RCTs, No. of Patients (n)	Strength of Evidence
Asthma plus rhinitis/ rhinoconjunctivitis symptoms	Significantly improved in 80% of studies vs. controls	5 RCTs, n = 308	Moderate
Use of asthma plus rhinoconjunctivitis medications	Significant improvement in 47% of studies vs. controls	38 RCTs, n = 2,724	Moderate
Asthma plus rhinitis/ rhinoconjunctivitis symptom and medication score	Significant improvement in 68% of studies vs. controls	19 RCTs, n = 1,462	Moderate

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.

Lin SY, et al. JMA 2013;309:1278-88

Efficacy of SCIT and SLIT

- Both SCIT and SLIT are of **proven value in asthma**.
- Numerous double-blind, placebo-controlled trials have confirmed that **SCIT and SLIT are effective in reducing symptom scores and medication use, improving quality of life in asthma, and inducing favorable changes in specific immunologic markers.**
- Overall, moderate-to-high (somewhat weaker in children) evidence was found for the efficacy of both SCIT and SLIT for the treatment of allergic asthma.

Burks AW, et al. J Allergy Clin Immunol 2013;131:1288-96

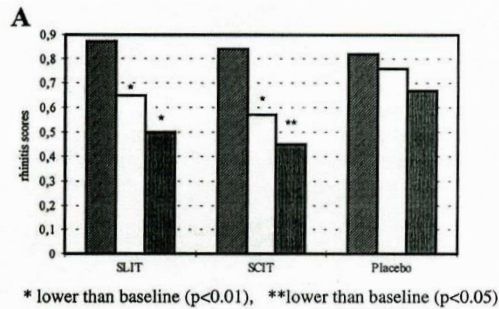
II. Comparative Efficacy of SCIT vs SLIT



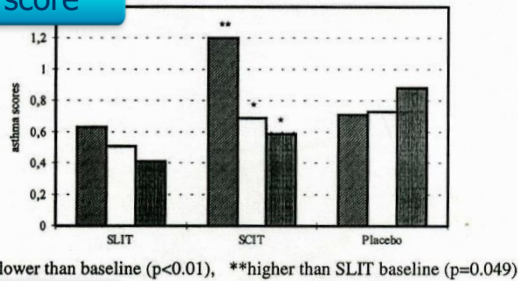
Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma—a placebo controlled study

Dilsad Mungan, Zeynep Misirligil, and Lütü Gürbüz

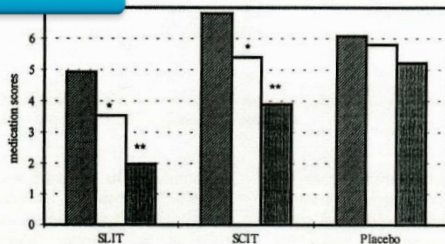
- Randomized study of 36 patients with AR and asthma due to HDM allergy



Asthma score



Medication score



*lower than baseline (SLIT: p<.001, SCIT: p<.01)
*lower than baseline and first 6 months (SLIT: p<.001, p<.01, SCIT: p<.01, p<.05, respectively).

■ 0: Baseline □ 1: First 6 months ■ 2: Second months

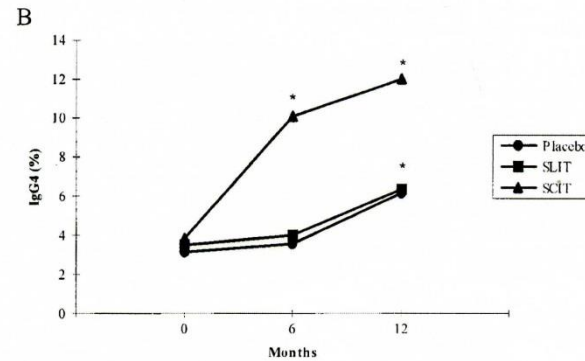
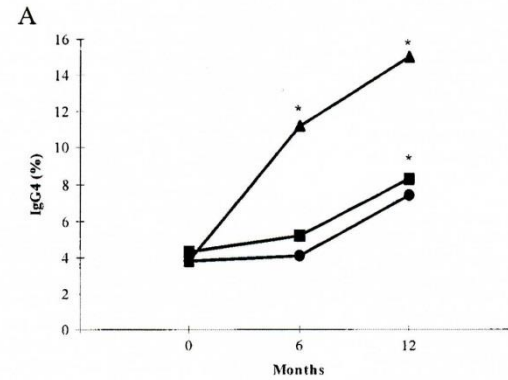


Figure 2. Specific IgG4 levels (A) *D. pteronyssinus* and (B) *D. farinae*. SLIT = sublingual immunotherapy and SCIT = subcutaneous immunotherapy.

Mungan D, et al. Ann Allergy Asthma Immunol 1999;82:485-90

Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy

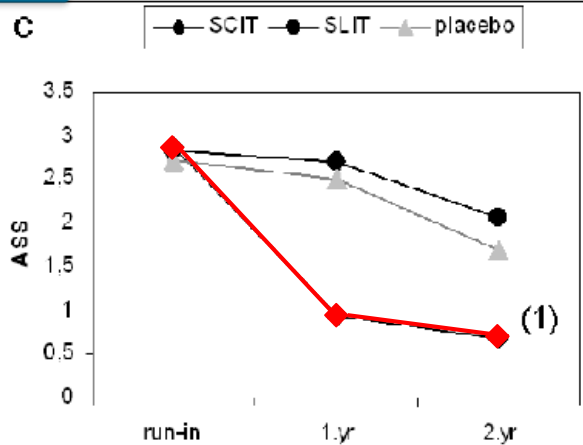
Ayfer Yukselen,¹ Seval Güneser Kendirli,² Mustafa Yilmaz,² Derya Ufuk Altintas² and Gulbin Bingol Karakoc²

- 1-year study randomizing children to HDM SCIT or SLIT
- 1-year open-label extension
- 30 patients

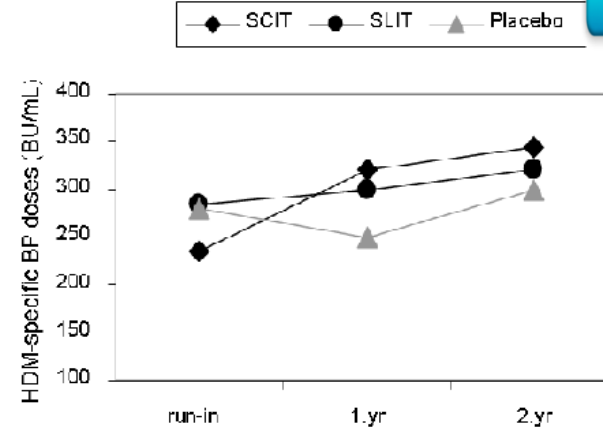
Yukselen A, et al. Asian Pac J Allergy Immunol 2013;31:233-41



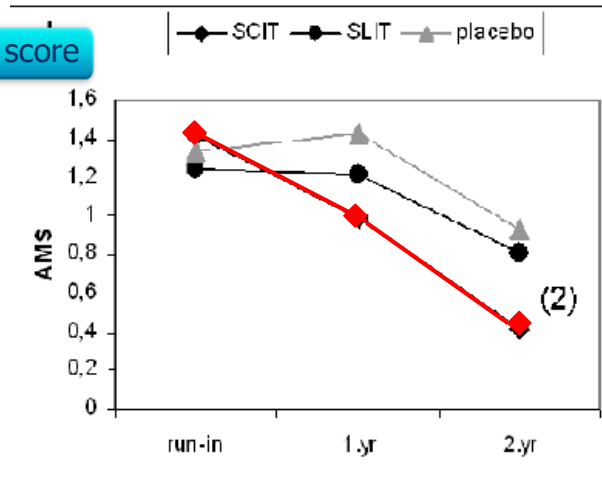
Asthma score



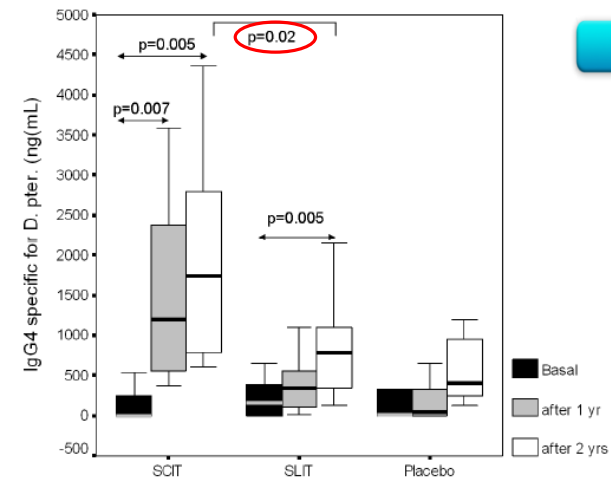
Specific bronchial provocation



Medication score



Dp-specific IgG4



Symptoms and medication usage related to asthma decreased significantly in the SCIT group when compared with the SLIT group.

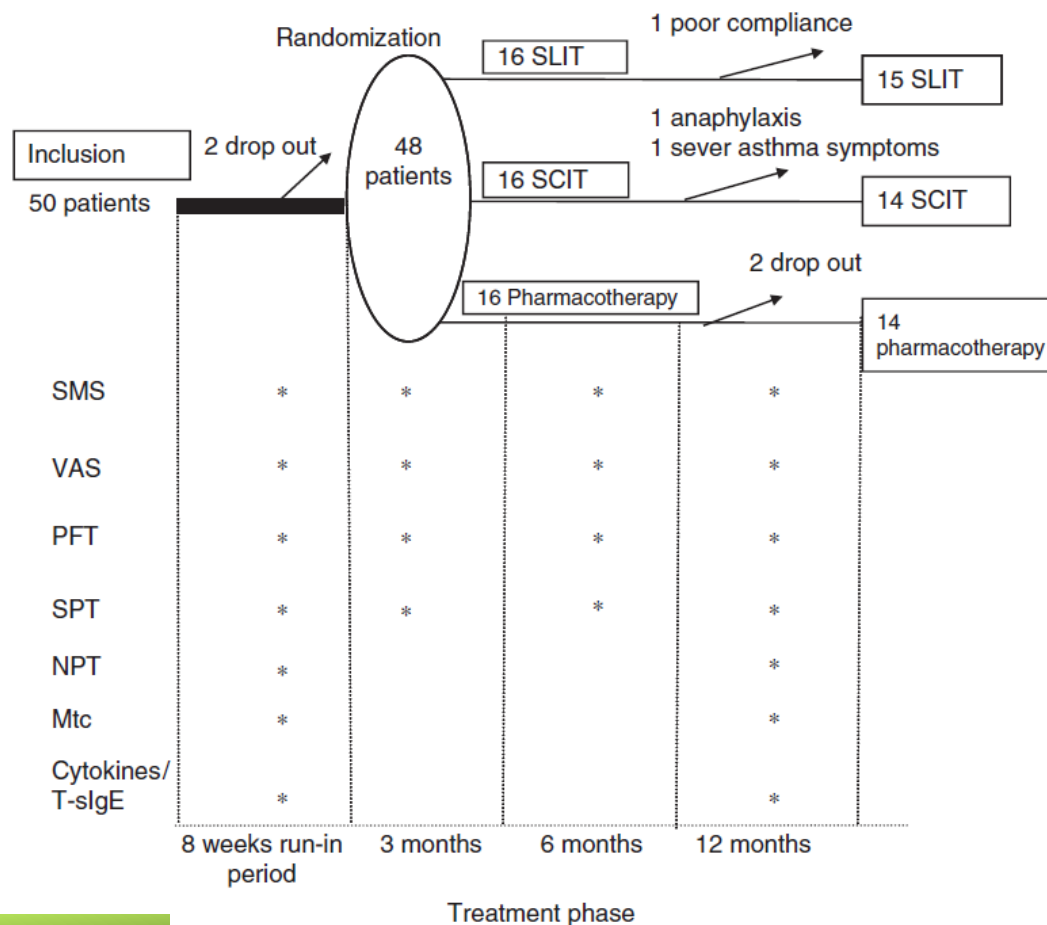
Yukselen A, et al. Asian Pac J Allergy Immunol 2013;31:233-41

Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial

A. O. Eifan^{1,2}, T. Akkoc¹, A. Yildiz¹, S. Keles¹, C. Ozdemir¹, N. N. Bahceciler¹ and I. B. Barlan¹

¹Division of Pediatric Allergy and Immunology, Marmara University Medical Faculty, Istanbul, Turkey and ²Allergy & Clinical Immunology Section, NHLI, Imperial College, Faculty of Medicine, London

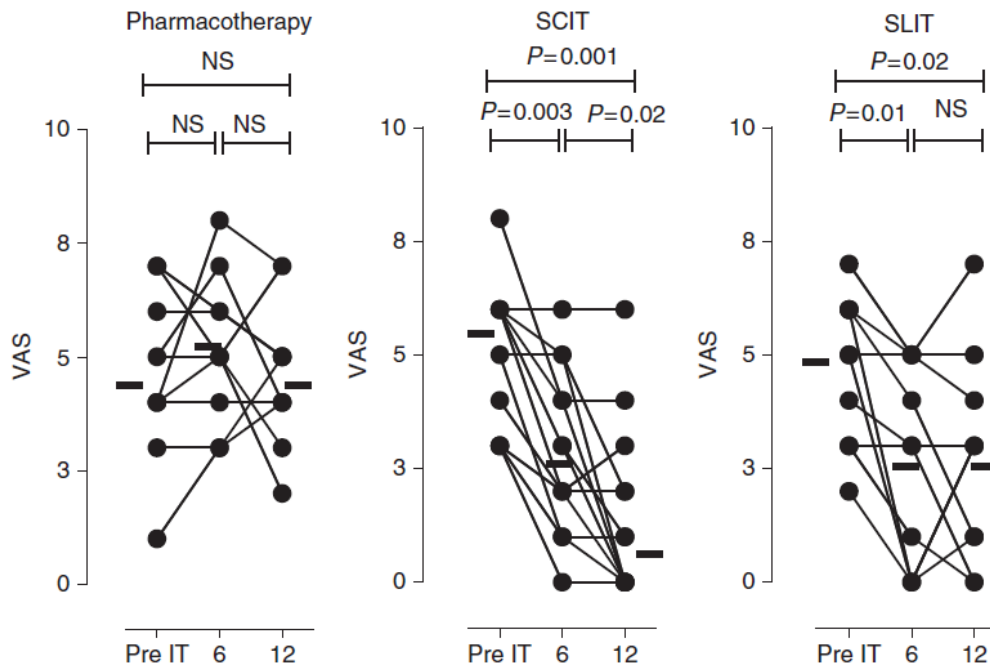
- 48 children mono-sensitized to HDM
- Prospective, randomized, controlled, open labelled, three parallel group trial



Eifan AO, et al. Clin Exp Allergy 2010;40:922-32

Table 3. Primary outcomes of SCIT, SLIT and pharmacotherapy

	Pharmacotherapy		SLIT		vs pharmacotherapy		SCIT		vs SCIT	
	T0	T1	T0	T1	P^{***}	†	T0	T1	P^{***}	†
TRSS	1.56±1.05 1.78 (0-3)	2.9±0.7 2.8 (2-4)	1.3±0.9 2 (0-3)	1.5±1.0 1.5 (0-3)	0.03	47	1.8±0.9 1 (1-4)	1.2±0.9 1 (0-3)	0.01	67
TASS	0.95±0.62 1 (0-2)	2.5±1.6 2.7 (0-4)	1.4±1.5 1 (0-5)	0.2±0.4 0 (0-1)	0.02	100	0.9±0.7 1 (0-2)	0.4±0.6 0.2 (0-2)	0.04	93
TSS	2.5±1.3 3 (0-4)	5.4±1.7 5.5 (3-8)	2.8±2.2 3 (0-7)	1.4±1.5 1.3 (0-4)	0.01	77	2.8±1.3 3 (1-6)	1.6±1.5 1 (0-4)	0.01	81
TMS	2.5±1.5 2 (0-4)	2.8±1.1 2 (2-4)	2.8±1.2 2 (0-4)	1.2±0.9 1.6 (0-2)	0.03	20	2.4±1.4 2 (0-4)	1.7±1.4 2 (0-4)	0.26	0
VAS	4.9±1.9 5 (1-8)	4.6±1.5 5 (2-7)	4.9±1.5 5 (2-7)	2.7±2.1* 3 (0-7)	0.02	40	5.5±1.7 6 (3-9)	1.5±1.8** 1 (0-6)	0.001	80

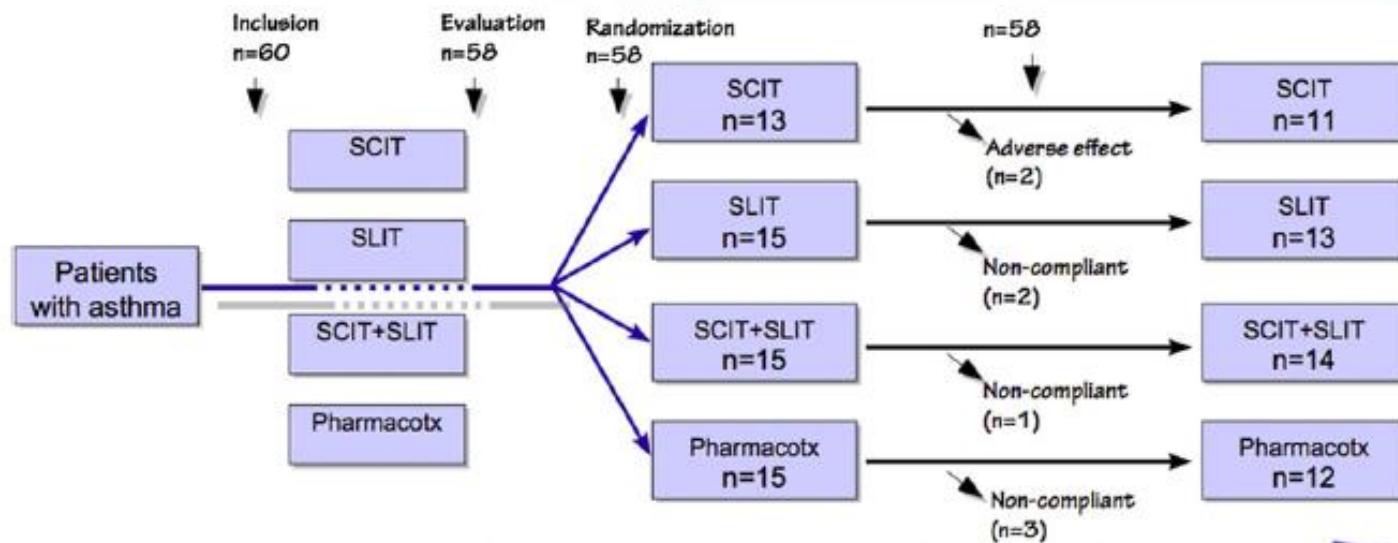


No statistical difference between the SLIT and the SCIT group was observed.

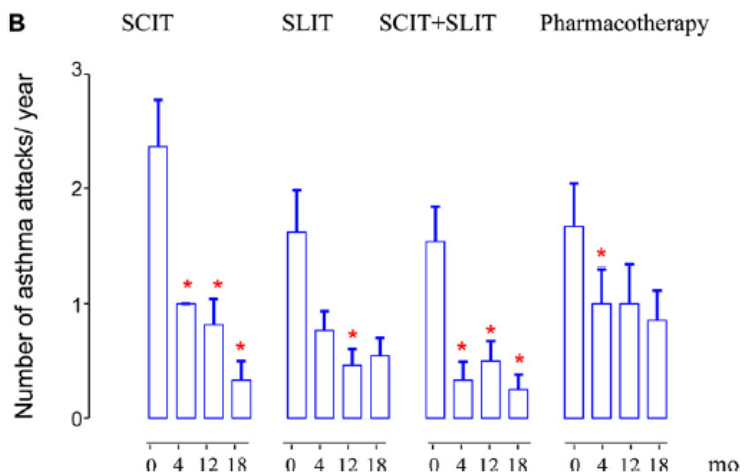
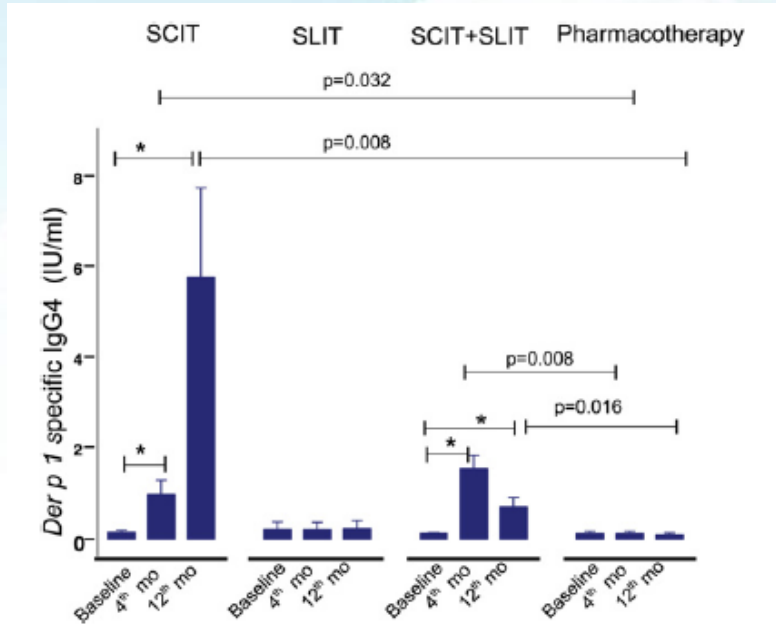
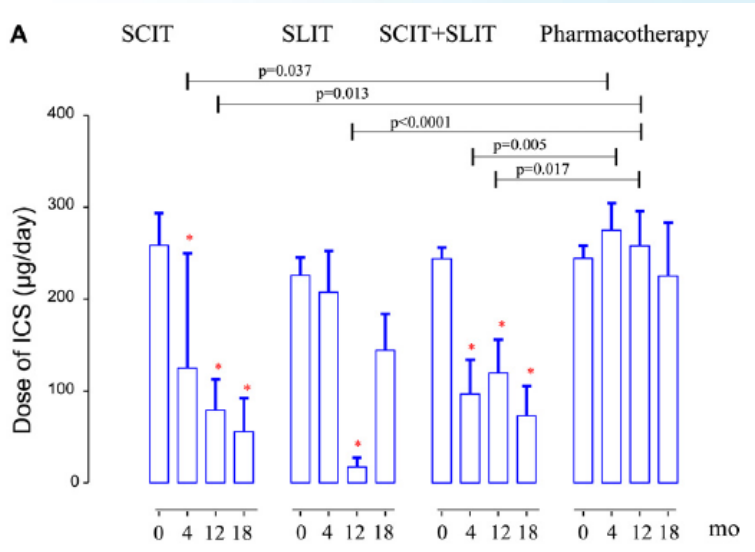
A novel approach in allergen-specific immunotherapy: Combination of sublingual and subcutaneous routes

Sevgi Keles, MD,^a Elif Karakoc-Aydiner, MD,^a Ahmet Ozen, MD,^b Ayse Gul Izgi, MS,^a Ayzer Tevetoglu, MS,^a Tunc Akkoc, PhD,^a Nerin N. Bahceciler, MD,^a and Isil Barlan, MD^a *Istanbul, Turkey*

- 51 HDM –sensitized children with mild-to-moderate asthma
- Prospective, randomized, controlled study



Keles S, et al. J Allergy Clin Immunol 2011;128:808-15

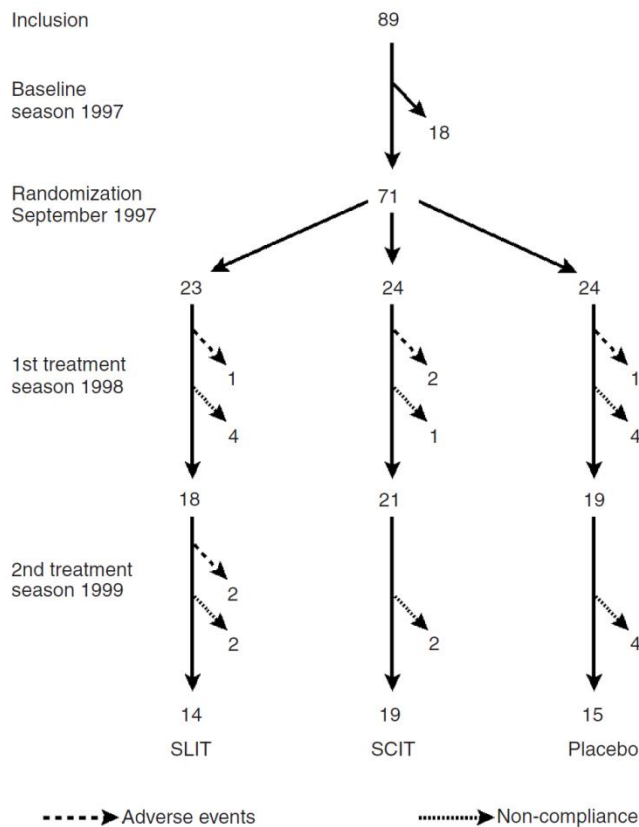


SCIT and SCIT+SLIT groups had earlier and more sustained decreases in asthma attack and ICS dosage.

Keles S, et al. J Allergy Clin Immunol 2011;128:808-15

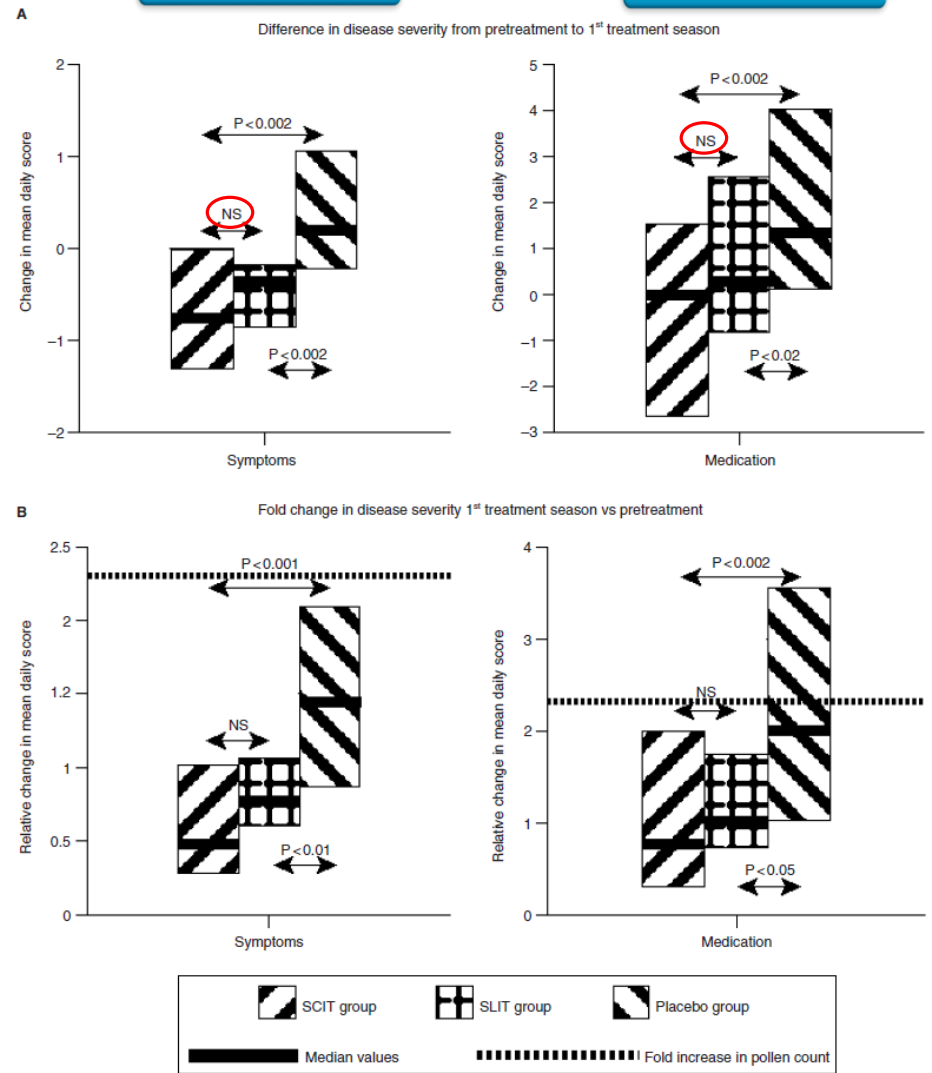
Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study

- Clinical efficacy was estimated in 58 rhinoconjunctivitis patients



Allergy symptom

Medication score



No statistical difference between two groups

Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study

T. QUIRINO, E. IEMOLI, E. SICILIANI, S. PARMIANI* and F. MILAZZO

Servizio di Allergologia Ospedale 'L. Sacco' and *Neo Abellò S.p.A., Milan, Italy

- 10 matched pairs of allergic subjects

Table 5. Mean values and statistics of symptoms and drugs scores of the SLIT treated patients versus the injective therapy treated patients for years 1992 and 1993 (Mann-Whitney *U*-test)

	Average value		<i>P</i>
	Injective	SLIT	
1992			
Symptom score	574	501.5	0.3845
Drug score	239.6	245	0.5967
Total score	813.6	746.5	0.9397
1993			
Symptom score	278	250.5	0.5795
Drug score	119.6	115.1	0.6774
Total score	397.6	365.6	0.8206

Table 8. Mean values and statistics of immunoglobulins at times T0, T1, T2 (i.e. before, after 6 months, after 12 months) of treatment (ANOVA)

Immunoglobulins	Average \pm SD			
	T0	T1	T2	T0-T1-T2
SLIT IgEs	15.29 \pm 4.94 (SEM = 1.49)	14.96 \pm 5.53 (SEM = 1.91)	15.49 \pm 4.64 (SEM = 1.40)	<i>P</i> = 0.317 (ns)
Total IgGs	16.91 \pm 4.57 (SEM = 1.38)	14.91 \pm 3.83 (SEM = 1.16)	16.64 \pm 5.87 (SEM = 1.77)	<i>P</i> = 0.393 (ns)
IgG4	13.64 \pm 4.80 (SEM = 1.45)	12.0 \pm 2.97 (SEM = 0.89)	14.64 \pm 6.10 (SEM = 1.84)	<i>P</i> = 0.429 (ns)
SCIT IgEs	12.76 \pm 7.02 (SEM = 2.12)	11.68 \pm 5.39 (SEM = 1.63)	14.55 \pm 5.22 (SEM = 1.57)	<i>P</i> = 0.190 (ns)
Total IgGs	17.27 \pm 4.63 (SEM = 1.40)	31.64 \pm 16.42 (SEM = 4.95)	28.27 \pm 13.90 (SEM = 4.19)	<i>P</i> < 0.001 ***
IgG4	11.45 \pm 4.97 (SEM = 1.5)	21.64 \pm 14.38 (SEM = 4.49)	22.82 \pm 11.51 (SEM = 3.47)	<i>P</i> < 0.001 ***

Quirino T, et al. Clin Exp Allergy 1996;26:1253-61

SCIT Versus SLIT

Primary Outcome	Results	No. of RCTs, No. of Patients (n)	Strength of Evidence
Improves asthma symptom score	SCIT may improve asthma symptoms more effectively than SLIT	4 RCTs, n = 171	Low
Improves rhinitis/ rhinoconjunctivitis symptoms	SCIT is superior to SLIT for improving allergic nasal and/or eye symptoms	6 RCTs, n = 412	Moderate
Decreases use of asthma plus rhinoconjunctivitis medications	There are no consistent differences between SCIT and SLIT	5 RCTs, n = 219	Low
Improves asthma plus rhinitis/rhinoconjunctivitis symptom and medication score	SCIT is favored in 1 of 2 studies	2 RCTs, n = 65	Low

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.

Comparative Efficacy

- The comparative efficacy of SLIT and SCIT in patients with allergic respiratory diseases has been evaluated in several underpowered trials.
 - The published data show **little or no statistical difference between SCIT and SLIT** with respect to symptom scores and medication scores.
 - The lack of significant difference between the 2 treatments does not indicate equivalent efficacy.
 - To detect minor differences, larger groups are necessary.

Calderon MA, et al. J Allergy Clin Immunol 2011;127:30-8

- **SCIT may improve asthma symptoms more effectively than SLIT** (low strength of evidence).

Keles S, et al. J Allergy Clin Immunol 2011;128:808-15

Efficacy of Multi-allergen SCIT vs SLIT

SCIT or SLIT	Author/ Journal	Allergen	No. of Patients	Results
SCIT	Pfarr et al. Allergy 2013	Mixed grass and birch extract SCIT	285	A significant reduction in rhinoconjunctivitis symptom and medication scores
SLIT	Amar SM, et al. J Allergy Clinical Immunol 2009	Timothy grass, Timothy grass extract plus 9 additional pollens	54	No significant differences in medication or rhinoconjunctivitis symptom scores
SCIT vs SLIT				No available data to compare the efficacy of multi-allergen SCIT versus SLIT in asthma

III. Safety of SCIT and SLIT



Adverse Effects: SCIT

- **Local reactions**
 - redness, swelling, pruritus, or induration at the injection site
 - usually mild and were more common than systemic reactions
- **Systemic reactions**
 - anaphylaxis, asthma, rhinitis, or urticaria
 - The most common systemic reactions were **respiratory reactions**
 - The risk is greater in subjects with **asthma** and with accelerated dosing schedules.
 - Pretreatment with oral H₁-antihistamines during the induction phase reduces the frequency and severity of systemic side effects.
- Thirteen anaphylactic reactions were reported in four trials.

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.



Adverse Effects: SLIT

- SLIT has a better safety profile than SCIT → Home administration
- Local reactions
 - Itching, swelling, or pain in the lips and floor of the mouth
 - These symptoms appear within minutes or hours after taking SLIT and are usually of short duration (less than 14 days).
 - They do not require medical treatment or dose adjustment
 - typically observed in 60% to 85% of patients
- Systemic reactions
 - ocular, rhinitis/nasal, respiratory/asthma, cutaneous, gastrointestinal, and cardiovascular adverse effects
 - No clear risk factors for SRs
- 11 cases of anaphylaxis to SLIT have been published.

Jutel M, et al. Current Treat Opt Allergy 2014;1:213-9

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.

Calderon MA, et al. J Allergy Clin Immunol 2011;127:30-8

Cochrane Meta-analysis of SCIT for Asthma

- Local reactions
 - reported by 16 studies.
 - The pooled relative risk was 1.4 (95% CI 0.97 to 2.02)
 - If 16 patients were treated with IT, one would be expected to develop a local reaction.
- Systemic reactions
 - reported by 32 studies.
 - The pooled relative risk was 2.45 (95% CI 1.91 to 3.13)
 - If 9 patients (95% CI 6 to 14) were treated with IT, one would be expected to develop a systemic reaction

	Local Reaction	Systemic Reaction	Non-fatal Reaction	Fatal Reaction
Per patient	26% to 82%	5% to 7%		
Per injection	0.7% to 4%	0.06% to 1.01%	1 per million	1 per 2.5 million

Bernstein DI, et al. JACI 2004/ Amin HS et al. JACI 2006

SCIT Safety (AAAAI/ACAAI Surveillance)

- Before 2002
 - there were an estimated 3.4 fatal reactions per year to SCIT
- From 2008 to 2011
 - No fatal reactions
 - 7.1 grade 1, 2.6 grade 2, and 0.4 grade 3 SRs per 10,000 injection visits.
 - Screening for worsening asthma symptoms was highly prevalent (86% always screened).
- From 2008 to 2012; 23.3 million injection visits
 - Overall SR rates remained stable at 0.1%.
 - Very severe (WAO grade 4) SRs: 1 in 1 million injections
- SR rates have remained stable and fatalities appear to be declining.

Epstein TG, et al. J Allergy Immunol Pract 2014;2:161-7

SLIT Safety

	Total No. of Patients	No. of Patients ^a	Range of Patients, % ^a	Adverse Events	
				Description	Severity
					% of Total Reported Events
Local reactions by allergen^b: grass mix,^{11,12,17,19,30,31,33,43,49,50,60,69} dust mite,^{9,15,25,29,35,51,62,66} trees,^{39,41,53-55,61,68,73} multiple allergens,^{13,14,21,24,34,63} <i>Parietaria</i>,^{30,48} <i>Alternaria</i>,⁴⁵ ragweed,¹⁰ cat⁵⁹					
Sublingual immunotherapy groups (n = 39 studies)	2520	681	0.2-97	Unspecified Mild Moderate	45 54 1
Placebo groups (n = 24 studies)	933	191	3-38.5	Unspecified Mild	26 74
Local reactions to Timothy grass^{56,C}					
Sublingual immunotherapy group	28	380 reactions	4.75 events per patient	Mild	100
Control group	28				
Upper respiratory reactions by allergen^d: grass mix,^{11,12,17,32,43,49,50} dust mite,^{9,29,36} trees,^{41,55,73} <i>Parietaria</i>,³⁰ multiple allergens^{8,21,24}					
Sublingual immunotherapy groups (n = 19 studies)	1201	347	3-92	Unspecified Mild Severe	73 25 2
Control groups (n = 12 studies)	572	228	1.6-93	Unspecified Mild Moderate	94 5 1
Lower respiratory reactions by allergen^e: grass mix,^{17,32,43,49,50} dust mite,^{9,29,36} trees,^{41,55,73} <i>Parietaria</i>,³⁰ multiple allergens^{8,21,24}					
Sublingual immunotherapy groups (n = 16 studies)	1033	197	0.3-63	Unspecified Mild Moderate Severe	93 4 1 1
Control groups (n = 10 studies)	522	145	3-67	Unspecified Mild Moderate Severe	94 4 1 1
Cutaneous reactions by allergen^f: grass mix,^{17,31,43,50} dust mite,^{29,36,66} trees,^{53,55} multiple allergens^{13,14,24,34}					
Sublingual immunotherapy groups (n = 15 studies)	1336	151	0.7-57	Unspecified Mild	93 7
Control groups (n = 6 studies)	535	105	0.6-65	Unspecified Mild	90 10

Systemic reactions were **rarely** reported, but were more common in the SLIT groups than in comparator groups.

No life-threatening reactions, or death were reported.

Comparison of Safety between SCIT and SLIT

Author	Journal	SCIT	SLIT
Keles S, et al.	J Allergy Clin Immunol 2011	2/11 Systemic reactions (SRs) -dyspnea and wheezing	0/13 SRs
Eifan AO, et al.	Clin Exp Allergy 2010	2/16 SRs	0/16 SRs
Khinchi MS, et al.	Allergy 2004 (Birch pollen, rhinoconjunctivitis)	15/15 Grade 2 SRs 5/15 Grade 3 1/15 Grade 4	14/14 Grade 2 SRs 0/14 Grade 3 or 4 SR (Placebo group: 1/11 Grade 3)



Adverse Effects: SCIT vs SLIT

- The sample sizes of studies comparing SCIT and SLIT are **small**, making it more **difficult to make direct comparison** of safety parameters.
- The recording and reporting of the adverse events was **neither uniform nor comparable** across studies.
- There were **no reported deaths** in the included studies.
- Although severe reactions are rare with SLIT, local side effects are experienced in most subjects.
 - The first dose of SLIT should be taken under medical supervision.

Lin SY, et al. AHRQ Comparative Effectiveness Review No. 111.
Bauer CS, et al. J Allergy Clin Immunol 2014;134:765

Take Home Message

- SCIT and SLIT are **effective** in reducing symptoms and medication need.
- **Little or no statistical difference** between SCIT and SLIT in symptom scores and medication scores.
- **SCIT may improve asthma symptoms** more effectively than SLIT (low strength of evidence).
- SCIT and SLIT are **usually safe**, although local reactions are commonly reported regardless of the mode of delivery.
- It is **difficult** to make **direct comparison** of safety parameters between SCIT and SLIT.



Thank You for Your Attention



행복한 설날 되세요

