
# Immunoterapia specifica : a che punto siamo?

*Giovanni B Pajno*

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***Università di Messina***

| 1911 | 1960 | 1970 | 1990 | 1998 | 2000 | 2005 | 2007 | 2008 | 2012 |
|---|---|---|---|---|---|---|---|---|---|
| SCIT | First RCT SCIT | SLIT | First RCT SLIT | WHO | ARIA | First META SLIT | First Meta SCIT | Large RCT SLIT | EBM |

Pediatric Allergy and Immunology

REVIEW ARTICLE

# Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement

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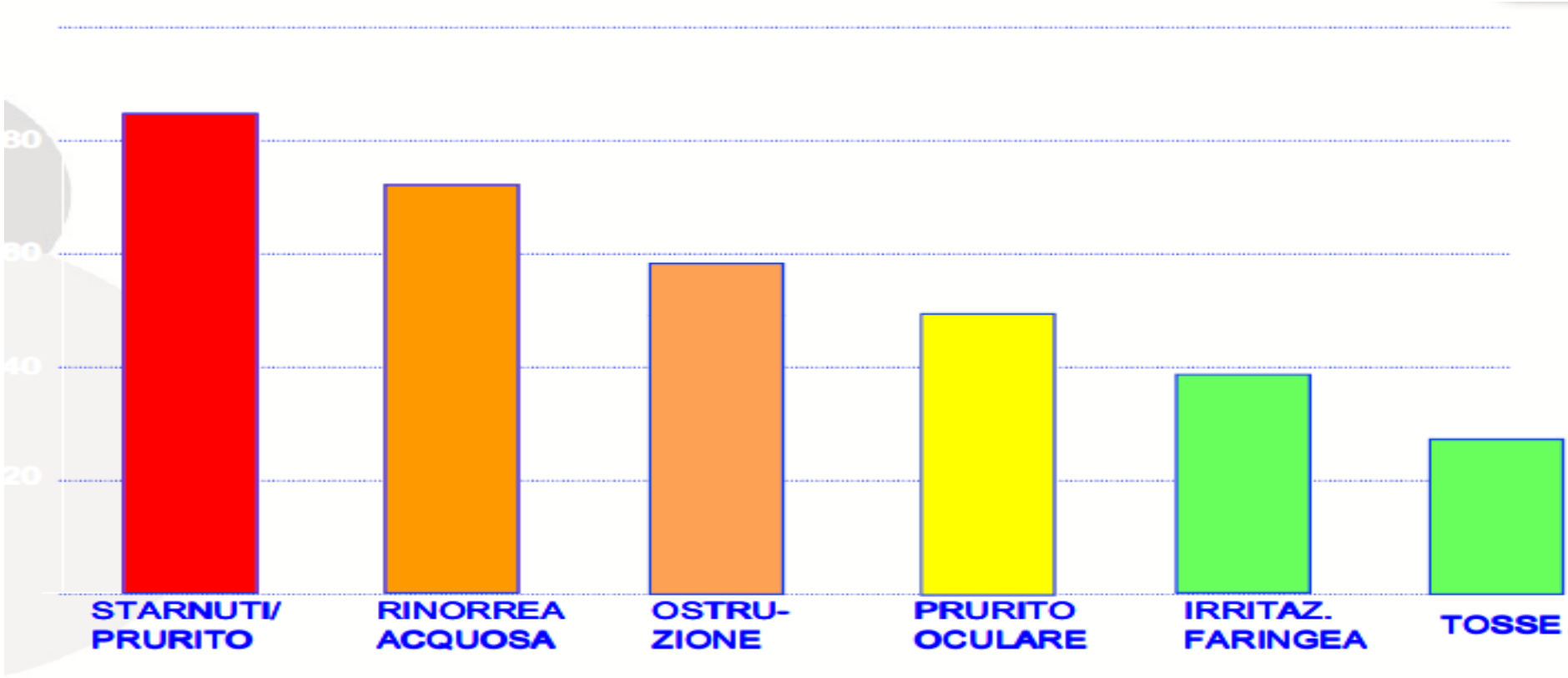
## Metanalisi di RCTs su ITS per la rinite

from Calderon. Immunol Allergy Clin N Am 2011

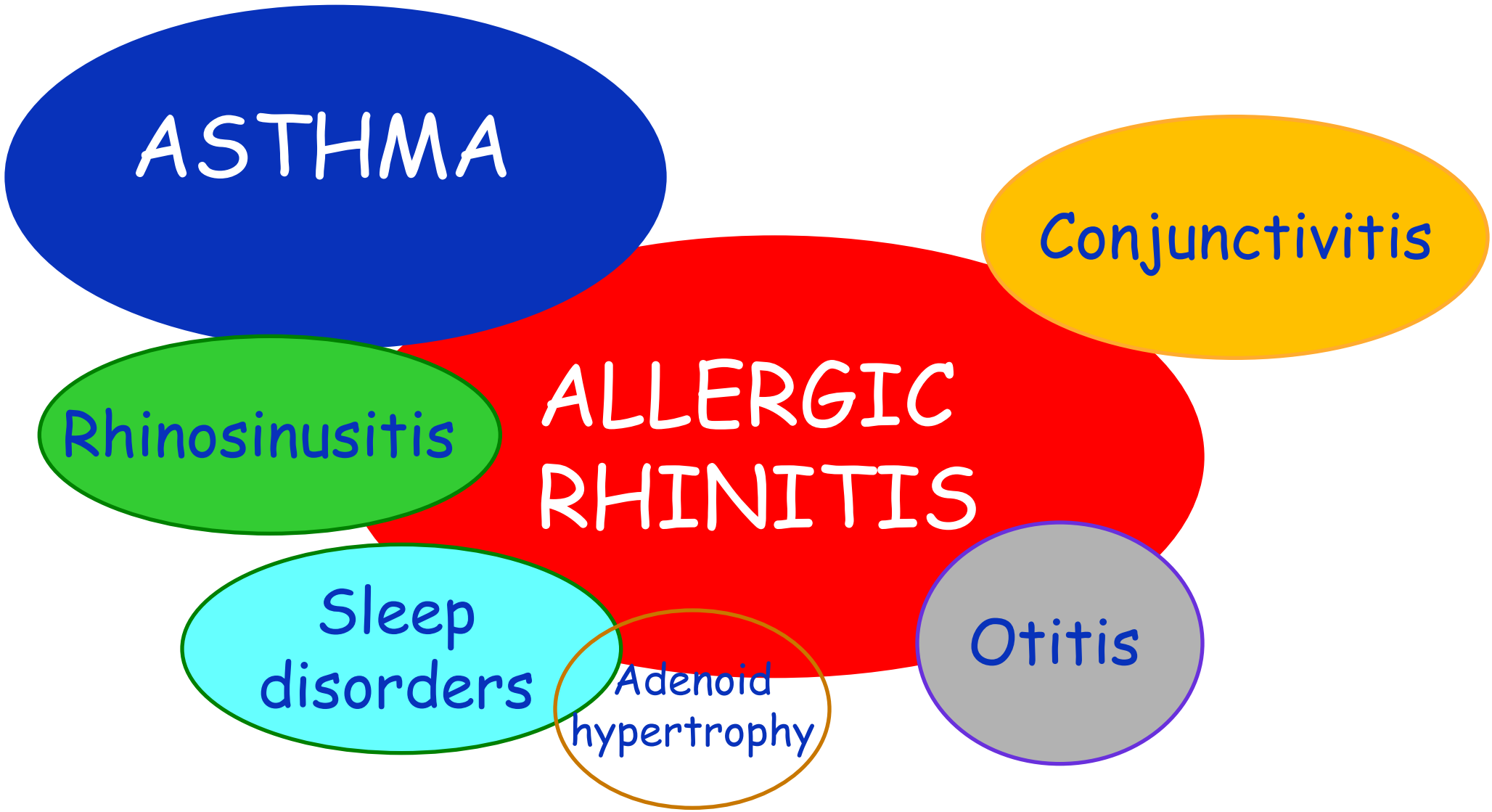
| Studio | pazienti | allergene | Sintomi (SMD) | Farmaci (SMD) | commento |
|---|---|---|---|---|---|
| **Calderon 2007** | 2871 adulti | SCIT stagionale | -0.73 (-0.97,-0.50) | -0.57 (-0.82,-0.33) | Moderata eterogeneità |
| **Radulovic 2010** | 4589 adulti e bambini | SLIT stagionale e perenne | -0.49 (-0,64,-0,34) | -0.32 (-0.43,-0.21) | Notevole eterogeneità |
| **Penagos 2006** | 484 bambini | SLIT stagionale e perenne | -0.56 (-1.01.-0.10) | -0.76 (-1.46, -0.06) | Notevole eterogeneità |
| **Olaguibel 2005** | 232 bambini | SLIT stagionale e perenne | -0.44 (-1.22,0.35) | N.d. | Eterogeneità n.d. |
| **Compalati 2009** | 382 adulti e bambini | SLIT acaro | -0.95 (-1.77,-0.14) | -1.88 (-3.65,-0.12) | Notevole eterogeneità |
| **Di Bona 2010** | 2971 adulti e bambini | SLIT graminacee | -0.32 (-0.44,-0.21) | -0.33 (-0.50, -0.16) | Moderata eterogenetià |

# Frequenza di presentazione dei sintomi di rinite allergica




*Ryan D. Allergy 2008*

# COMORBIDITIES



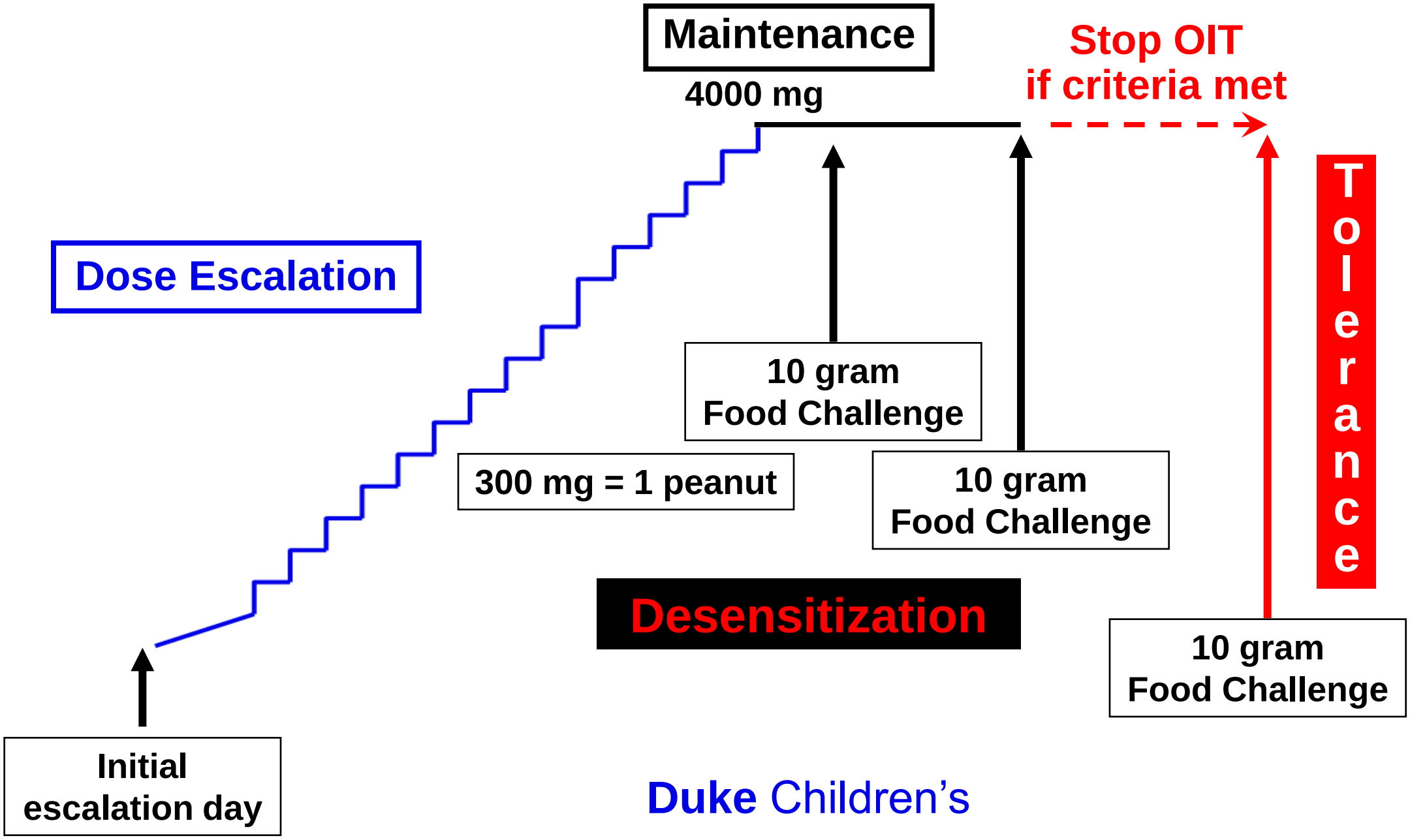
# Trattamento step by step della rinite allergica

## Metanalisi di RCTs su ITS per l'asma

| Studio | pazienti | allergene | Sintomi (SMD) | Farmaci (SMD) | commento |
|---|---|---|---|---|---|
| **Abramson 2010** | 3459 adulti e bambini | SCIT stagionale o perenne | -0.59 (-0.83,-0.35) | -0.53 (-0.80,-0.27) | Notevole eterogeneità, anche open trials |
| **Calamita 2006** | 1706 adulti e bambini | SLIT stagionale e perenne | -0.38 (-0,79,-0.03) | -0.91 (-1.94, 0.12) | Notevole eterogeneità, anche open trials |
| **Penagos 2008** | 441 bambini | SLIT stagionale e perenne | -1.14 (-2.10,-0.18) | -1.63 (-2.83, -0.44) | Notevole eterogeneità |
| **Olaguibel 2005** | 193 bambini | SLIT stagionale e perenne | -1.42 (-2.51,-0.34) | N.d. | Eterogeneità n.d., pochi pazienti |
| **Compalati 2009** | 476 adulti e bambini | SLIT acaro | -0.95 (-1.74,-0.15) | -1.48 (-2.70,-0.26) | Notevole eterogeneità |

| | | |
|---|---|---|
| Immunotherapy | Allergen specific immunotherapy is beneficial in the management of patients with allergic asthma. | B Immunotherapy can be considered in patients with asthma where a clinically significant allergen cannot be avoided. The potential for severe allergic reactions to the therapy must be fully discussed with patients. |

# OIT Study Design – 4000 mg Dose




Duke Children's

# Allergen-specific oral immunotherapy for peanut allergy (Review)

Nurmatov U, Venderbosch I, Devereux G, Simons FER, Sheikh A

THE COCHRANE COLLABORATION®

# Oral immunotherapy for milk allergy (Review)

Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R

THE COCHRANE COLLABORATION®

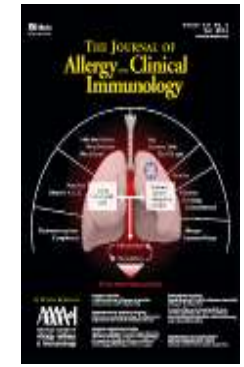
# Efficacy of allergen-specific immunotherapy for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials

**Jung Min Bae, MD,[a,b]* Yoon Young Choi, MD,[c]* Chang Ook Park, MD,[a,b] Kee Yang Chung, MD, PhD,[a,b] and Kwang Hoon Lee, MD, PhD[a,b,d]** *Seoul, South Korea*

**TABLE I.** Characteristics of trials included in the review

| Study, year | Country | Study design | Diagnosis criteria | Participants (age range, y) | Intervention | | | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | | Type | Allergens | Duration (mo) | |
| Kaufman and Roth,[24] 1974 | US | qRCT DB PC | Confirmed by a dermatologist | 52 Children and adults (2-47) uncontrolled AD (+) prick test | SCIT | D, HDM, molds, P | 24 | Treatment success assessed by physician |
| Warner et al,[25] 1978 | England | RCT DB PC | ND | 20 Children (5-14) asthma and AD (+) prick test to DPT | SCIT | HDM | 12 | Treatment success assessed by patient |
| Glover and Atherton,[26] 1992 | England | RCT DB PC | ND | 24 Children (5-16) uncontrolled severe AD (+) prick test to DPT | SCIT | HDM | 8 | Treatment success assessed by patient |
| Leroy et al,[27] 1993 | Belgium | RCT DB PC | Hanifin and Rajka | 23 Children and adults (15-64) severe AD (+) prick test to DPT | SCIT | HDM | 4 | Disease intensity index assessed by physician |
| Galli et al,[28] 1994 | Italy | RCT PC | Hanifin and Rajka | 34 Children (0.5-12) (+) prick test, RAST to DPT | SLIT | HDM | 36 | Treatment success assessed by physician |
| Silny and Czarnecka-Operacz,[29] 2006 | Poland | RCT DB PC | ND | 20 Children and adults (5-40) (+) sensitization to HDM | SCIT | D, HDM, P | 12 | Treatment success assessed by physician |
| Pajno et al,[30] 2007 | Italy | RCT DB PC | ND | 56 Children (5-16) (+) prick test, RAST to HDM | SLIT | HDM | 18 | SCORAD assessed by physician |
| Novak et al,[31] 2012 | Germany | RCT DB PC | Hanifin and Rajka | 168 Adults (18-66) moderate to severe AD subgroup analysis of severe AD (+) prick test, RAST to HDM | SCIT | HDM | 18 | The area under the curve (AUC) values for both SCORAD and the use of basic medication |

*AD*, Atopic dermatitis; *D*, animal dander; *DB*, double-blind; *DPT*, *Dermatophagoides pteronyssinus*; *HDM*, house-dust mite; *ND*, not determined; *P*, pollen; *PC*, placebo-controlled; *RAST*, Radioallergosorbent test; *qRCT*, quasi-randomized controlled trial; *SCORAD*, SCORing Atopic Dermatitis.



*Task force report*

# Allergen immunotherapy: A practice parameter third update

***Chief Editors***: Linda Cox, MD, Harold Nelson, MD, and Richard Lockey, MD

***Workgroup Contributors***: Christopher Calabria, MD, Thomas Chacko, MD, Ira Finegold, MD, Michael Nelson, MD, PhD, and Richard Weber, MD

***Task Force Reviewers***: David I. Bernstein, MD, Joann Blessing-Moore, MD, David A. Khan, MD, David M. Lang, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen Tilles, MD, and Dana Wallace, MD

## Measures of efficacy

Summary Statement 15: Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended. A

## SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

### Allergen immunotherapy in children

**Summary Statement 17: Immunotherapy for children is effective and well tolerated. It has been shown to prevent the new onset of allergen sensitivities in monosensitized patients, as well as progression from allergic rhinitis to asthma. Therefore immunotherapy should be considered along with pharmacotherapy and allergen avoidance in the management of children with allergic rhinitis/rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. B**

Immunotherapy can be initiated in young children less than 5 years of age if indicated. Indications should be based on the severity of the disease, risk/benefit ratios, and the ability of the physician to correlate the clinical presentation with appropriate and obtainable allergy testing.

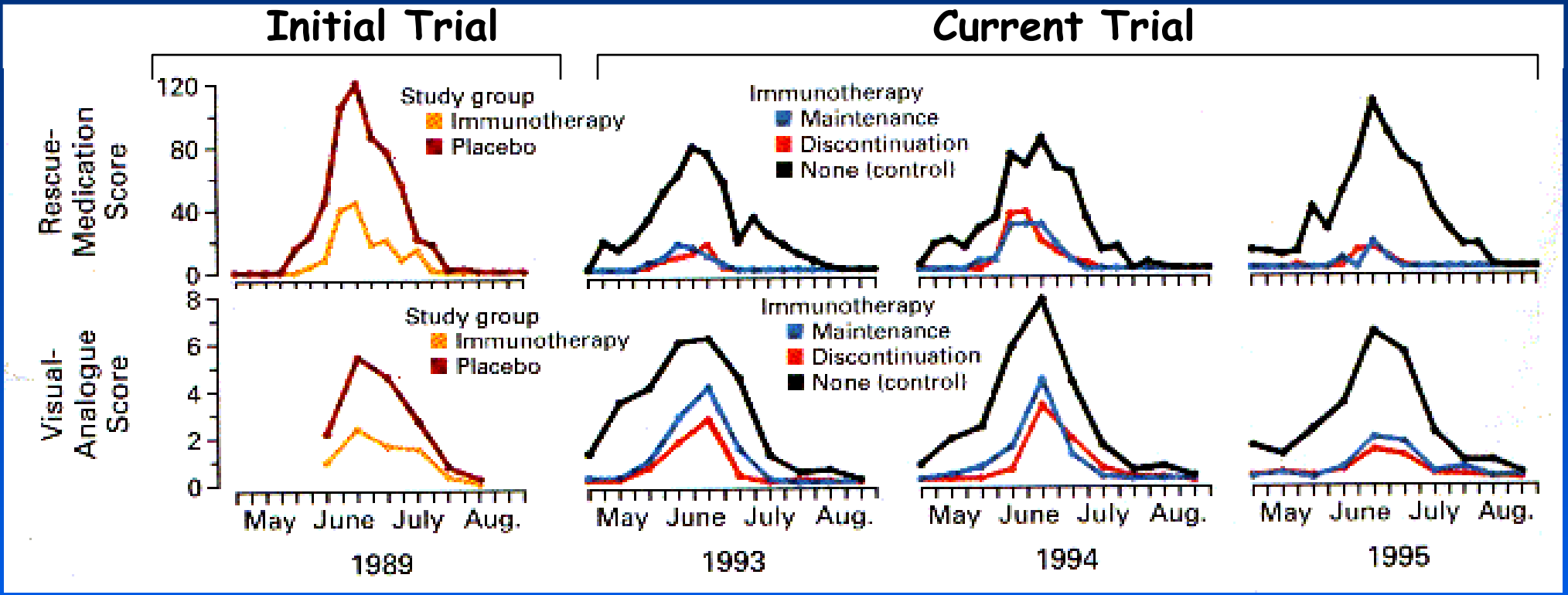
PEDIATRICS®

# Allergen-Specific Immunotherapy for Pediatric Asthma and Rhinoconjunctivitis: A Systematic Review

*Pediatrics* peds.2013-0343

Kim JM et al.

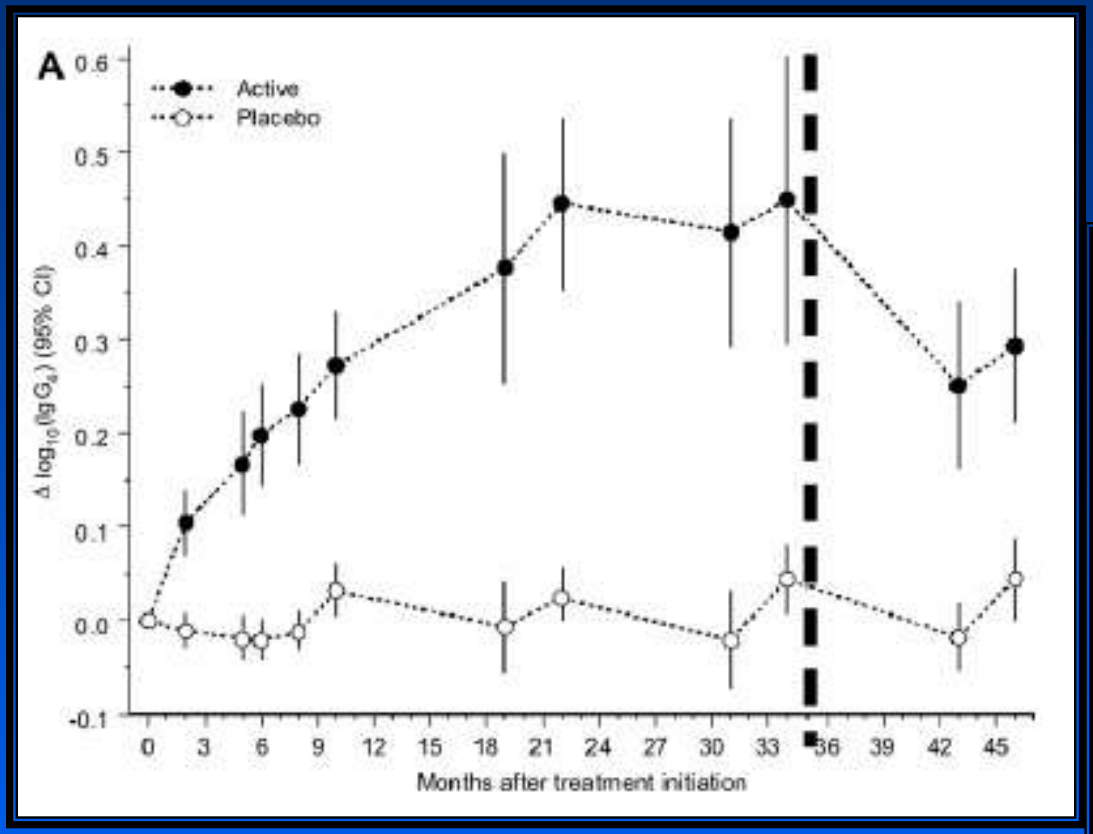
1. L'effetto dell'ITS è duraturo dopo la sospensione?
2. L'ITS è in grado di prevenire le nuove allergie nei bambini monosensibili?
3. L'ITS è in grado di prevenire l'asma nei bambini con rinite?

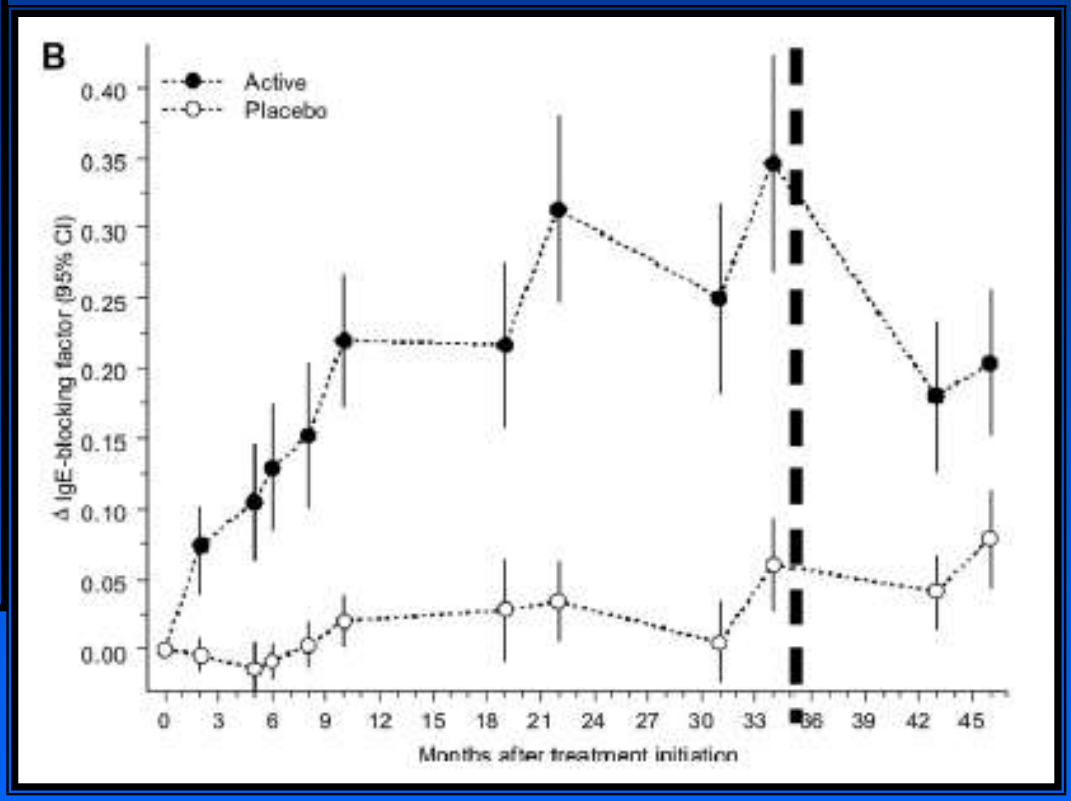



*Durham S.R. et al.*

**Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy.**

**N Eng J Med 1999; 341: 468-475**




Durham SR et Al. J Allergy Clin Immunol 2010;125:131-38.

*Allergy 2007: 62: 958–961*



DOI: 10.1111/j.1398-9995.2007.01416.x

**Short communication**

# Prolonged preseasonal treatment phase with Grazax sublingual imm

**"... The length of the treatment period prior to the start of the grass pollen season (the preseasonal treatment period) varied between 4 and 35 weeks. ..."**

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**Metho**
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**Result**
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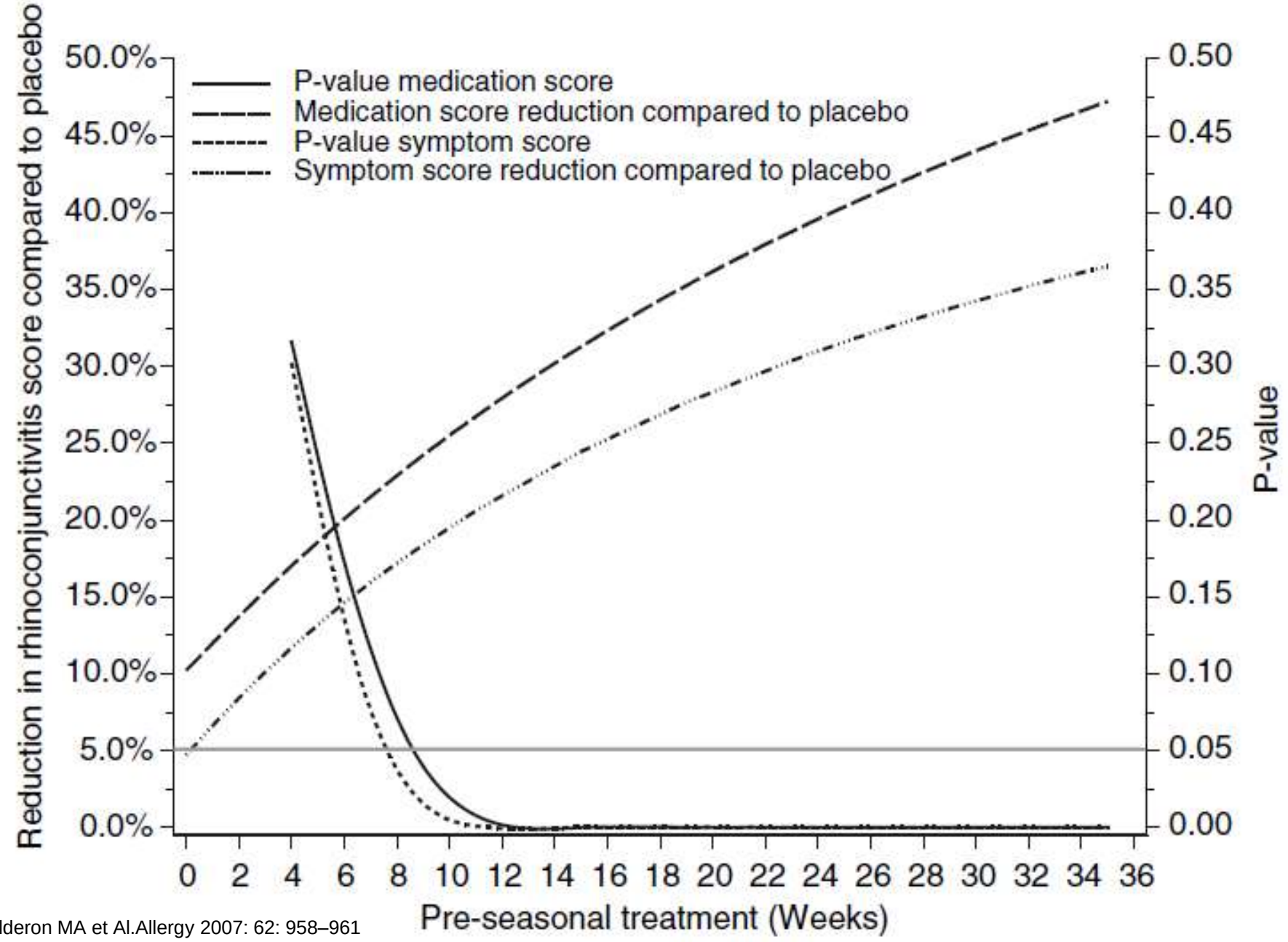
and medication scores increased with longer duration of preseasonal treatment ($P < 0.0001$).
**Conclusions:** Sublingual immunotherapy with Grazax® must be initiated at least 8 weeks prior to the grass pollen season to provide a significant clinical efficacy. A longer preseasonal treatment period (>8 weeks) improves the clinical efficacy (relative to placebo) during the grass pollen season.

Institute,
ark




Calderon MA et Al.Allergy 2007: 62: 958–961

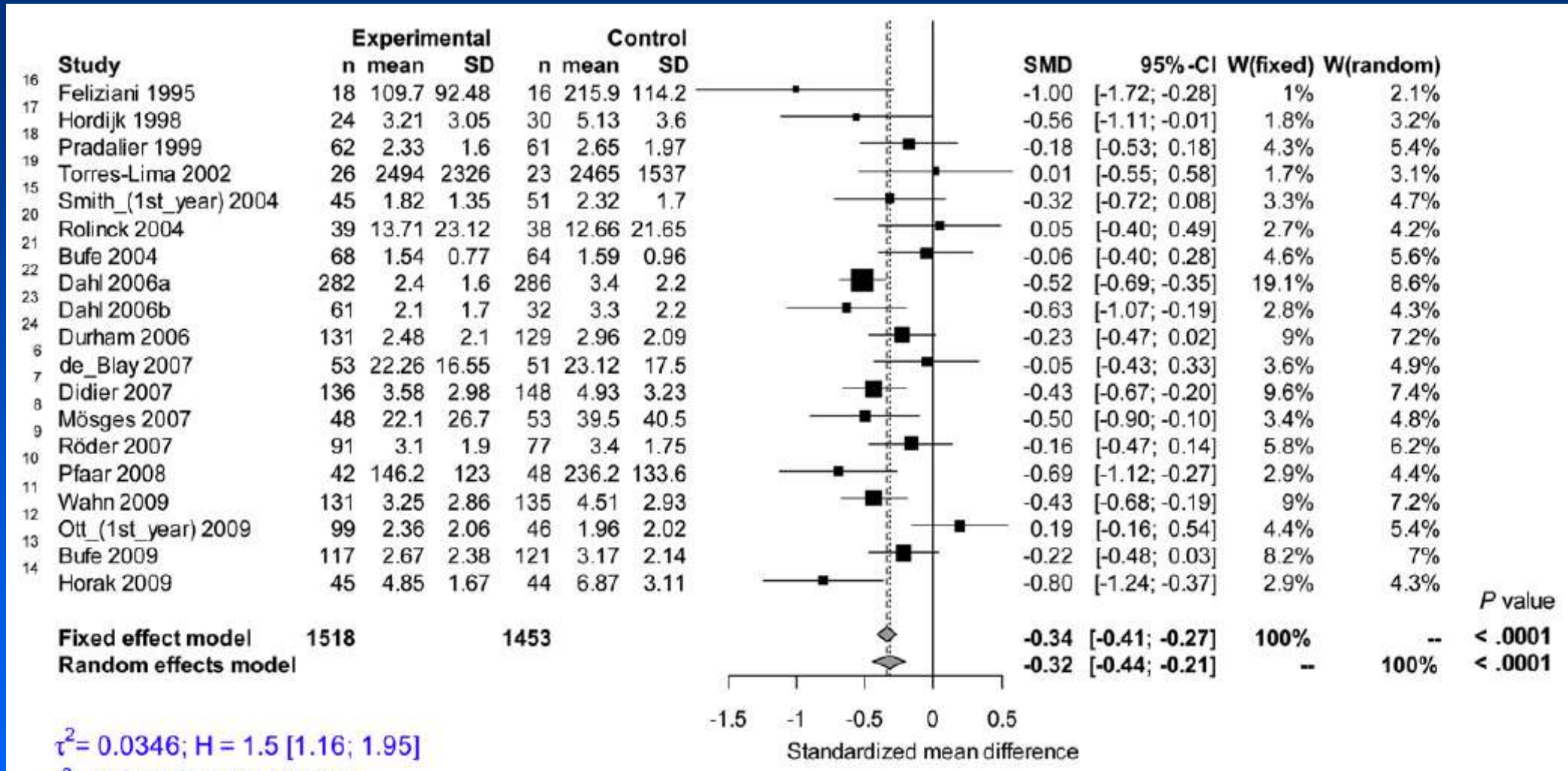
# Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A systematic review and meta-analysis

Danilo Di Bona, MD, PhD,[a,e] Antonella Plaia, PhD,[b] Valeria Scafidi, PhD,[a,c] Maria Stefania Leto-Barone, MD,[d] and Gabriele Di Lorenzo, MD[d] *Palermo, Italy*

**Background:** The benefit of sublingual immunotherapy (SLIT) with grass allergens for seasonal allergic rhinitis has been extensively studied, but data on efficacy are still equivocal.
**Objective:** To assess the effectiveness of SLIT with grass allergens in the reduction of symptoms and medication in patients with seasonal allergic rhinitis to grass pollen.
**Methods:** Computerized bibliographic searches of MEDLINE (1995-2010) were supplemented by hand searches of reference lists. Studies were included if they were double-blind randomized controlled trials (RCTs) comparing SLIT to placebo and if they included patients with history of allergy to grass pollen treated with natural grass pollen extracts. Nineteen RCTs with 2971 patients were analyzed. The outcomes assessed were symptom and medication scores.
**Results:** Using a random-effects model, SLIT with grass allergens significantly reduces both symptoms (standardized mean difference, –0.32; 95% CI, –0.44 to –0.21) and medication use (standardized mean difference, –0.33; 95% CI, –0.50 to –0.16) compared with placebo. The treatment is more efficacious in adults than in children. Prolonging duration of preseasonal treatment for more than 12 weeks improves the treatment efficacy.
**Conclusion:** This meta-analysis found that SLIT with grass allergens is effective in patients with seasonal allergic rhinitis compared with placebo. The benefit is clinically modest, and criteria are needed to identify patients most likely to benefit from SLIT. (J Allergy Clin Immunol 2010;126:558-66.)

***Key words:*** *Sublingual immunotherapy, rhinitis, grass, meta-analysis*

*Abbreviations used*
AE: Adverse event
AR: Allergic rhinitis
RCT: Randomized double-blind controlled trial
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SMD: Standardized mean difference




$\tau^2$= 0.0346; H = 1.5 [1.16; 1.95]

$I^2$= 55.8% [26.1%; 73.6%]

Test of heterogeneity

Q = 40.74, *df* = 18, *P* value = .0017

**Di Bona D. et Al. J Allergy Clin Immunol 2010;126:558-66.**

**TABLE I.** Patient and study characteristics of the randomized controlled trials in the meta-analysis

| Study | N | Male (%) | Mean or mean ± SD age (range) | Adults or child (%) | Asthma (%) | Type of treatment | Allergens | Monthly dose | Length of preseasonal treatment (wk) | Duration (mo) |
|---|---|---|---|---|---|---|---|---|---|---|
| [16]Feliziani 1995 | T 18 -> 18<br>P 16 -> 16 | NR | NR<br>(14-48) | NR | NR | Drops | 5* | 120 μg of 5 grass pollen | <4 | 3 |
| [17]Hordijk 1998 | T 27 -> 24<br>P 30 -> 30 | 47 | 27.5<br>(18-45) | Adults | NR | Drops | 5† | 168 μg of Lol p 5 | 12 | 10 |
| [18]Pradalier 1999 | T 63 -> 62<br>P 63 -> 61 | 52 | 29 ± 11<br>(7-58) | Adults<br>(86.5) | 34 | (Drops)<br>Tablet | 5‡ | 255 μg of Phl p 5 | 8 | 5 |
| [19]Torres-Lima 2002 | T 28 -> 26<br>P 28 -> 23 | 57 | 34<br>(21-55) | Adults | NR | Drops | 1§ | 900 μg of Phl p 5 | 8-30 | 12-18 |
| [15]Smith 2004 | T 62 -> 45<br>P 62 -> 51 | 48 | 38.5‖<br>(18-58) | Adults | NR | (Drops)<br>Tablet | 5‡ | 867 μg Lol p 1<br>504 μg Dac g 5 | 12 | 24 |
| [20]Rolinck-Werninghaus 2004 | T 49 -> 39<br>P 48 -> 38 | 67 | NR<br>(3-14) | Children | 40 | Drops | 5‡ | 6 μg major allergen group 5 | 4 | 32 |
| [21]Bufe 2004 | T 82 -> 68<br>P 79 -> 64 | NR | 9.3 ± 3<br>(NR) | Children | 42 | Drops | 1§ | 273 μg of Phl p 5 | 20 | 36 |
| [22]Dahl 2006a | T 316 -> 282<br>P 318 -> 286 | 59 | 34.2 ± 9.8<br>(18-65) | Adults | NR | Tablets | 1§ | 450 μg of Phl p 5 | 16 | 6 |
| [23]Dahl 2006b | T 74 -> 61<br>P 40 -> 32 | 67.5 | 35.7 ± 10.2<br>(18-64) | Adults | 100% | Tablets | 1§ | 450 μg of Phl p 5 | 10-14 | 5 |
| [24]Durham 2006 | T 153 -> 131<br>P 150 -> 129 | 61.5 | 36.5<br>(18-65) | Adults | NR | Tablets | 1§ | 450 μg of Phl p 5 | 8 | 6 |
| [6]de Blay 2007 | T 61 -> 53<br>P 57 -> 51 | 66.3 | 25 ± 7.5<br>(12-41) | Adults<br>(89.4) | 27.9 | Drops | 3¶ | 275 μg major allergen group 5 | 32 | 10 |
| [7]Didier 2007 | T 155 -> 136<br>P 156 -> 148 | 56.9 | 29.4 ± 7.3<br>(18-45) | Adults | 10 | Tablets | 5‡ | 750 μg major allergen group 5 | 20 | 6 |
| [8]Mösges 2007 | T 48 -> 48<br>P 53 -> 53 | NR | NR<br>(18-50) | Adults | NR | Drops | 5‡ | 600 μg of Phl p 5 | 16 | 9 |
| [9]Röder 2007 | T 108 -> 91<br>P 96 -> 77 | 56.5 | 12.7 ± 2.7<br>(6-17) | Children | 58.3 | Drops | 5‖ | 168 μg of Lol p 5 | 24 | 24 |
| [10]Pfaar 2008 | T 94 -> 42<br>P 91 -> 48 | 62.5 | 33.1<br>(17-59) | Adults | 29.2 | Drops | 6# | 1200 μg of Phl p 5 | 16 | 24 |
| [11]Wahn 2009 | T 139 -> 131<br>P 139 -> 135 | 64.3 | 10.9 ± 3.22<br>(5-17) | Children | 21.4 | Tablets | 5‡ | 600 μg of Phl p 5 | 16 | 8 |
| [12]Ott 2009 | T 123 -> 99<br>P 60 -> 46 | 59 | 33.3 ± 10.4<br>(7.9-64.7) | NR | 13.1 | Drops | 5‡ | 600 μg of Phl p 5 | NR | 3 × 3 |
| [13]Bufe 2009 | T 126 -> 117<br>P 127 -> 121 | 66 | 10.1<br>(5-16) | Children | 42 | Tablets | 1§ | 450 μg of Phl p 5 | 8 | 6 |
| [14]Horak 2009 | T 45 -> 45<br>P 44 -> 44 | NR | NR<br>(18-50) | Adults | NR | Tablets | 5‡ | 600 μg of Phl p 5 | NR | 4 |

*NR*, Not reported; *P*, placebo; *SD*, Standard Deviation; *T*, SLIT.

**Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, *Phleum pratense*, and *Poa pratensis*.

†*Anthoxanthum odoratum*, *Cynodon dactylon*, *Dactylis glomerata*, *Holcus lanatus*, and *Phleum pratense*.

‡*Dactylis glomerata*, *Poa pratensis*, *Lolium perenne*, *Anthoxanthum odoratum*, and *Phleum pratense*.

§*Phleum pratense*.

¶*Dactylis glomerata*, *Phleum pratense*, and *Lolium perenne*.

‖*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*, and *Holcus lanatus*.

#*Lolium perenne*, *Phleum pratense*, *Dactylis glomerata*, *Holcus lanatus*, *Poa pratensis*, and *Festuca elatior*.

**Di Bona D. et Al.**
**J Allergy Clin Immunol 2010;126:558-66.**

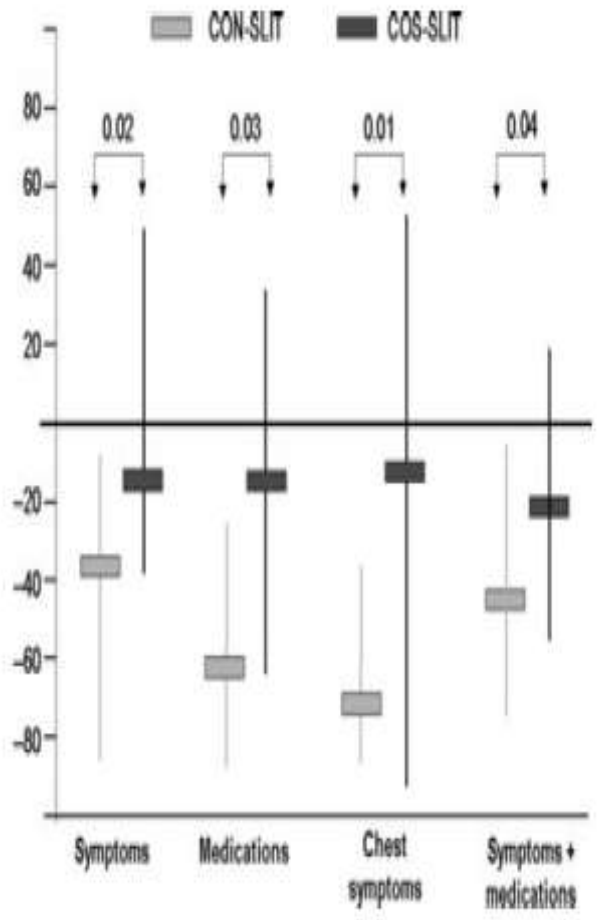



**Figure 2** Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms at the 1st year of treatment.

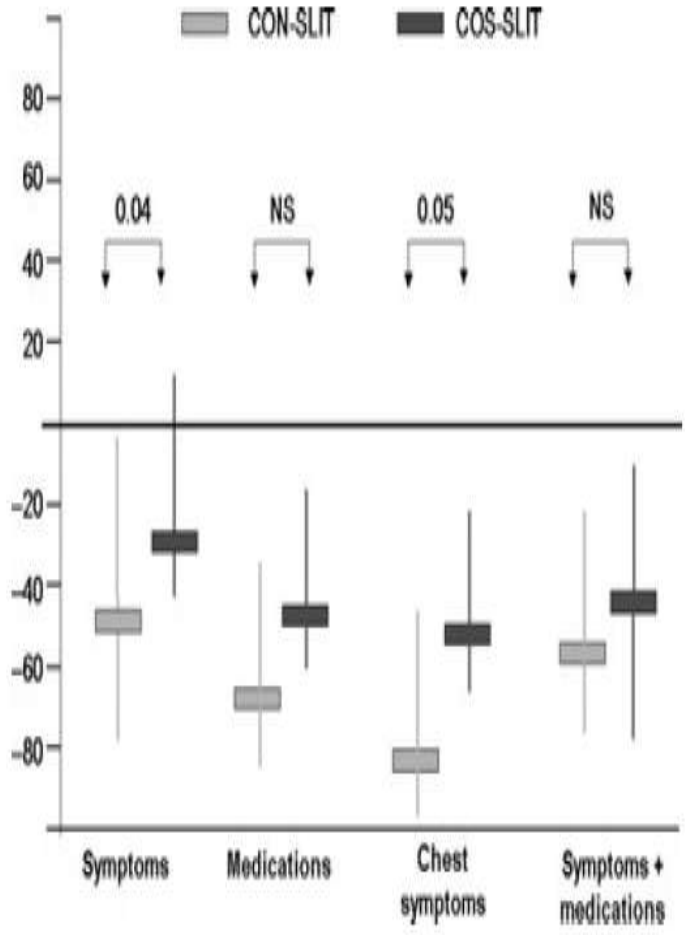



**Figure 3** Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms at the 2nd year of treatment.

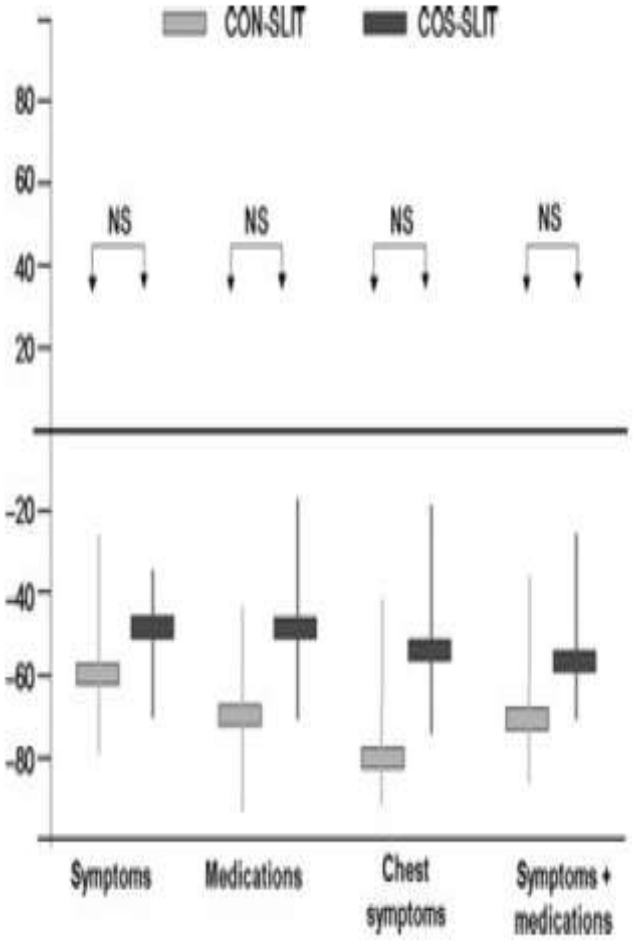



**Figure 4** Percentage reduction (median and interquartile range) vs. baseline for symptoms plus medication score (SMS), symptoms score, medication score, and chest symptoms score at the 3rd year of treatment.

# Table I. Development of new sensitivities

| | | New sensitivities | | | | |
|---|---|---|---|---|---|---|
| Initial sensitivity | No. of patients | None | Cat | Dog | Alt | Grass |
| SIT group | 22 | 10 | 6 | 4 | 2 | 1 |
| Control group | 22 | 0 | 12 | 8 | 6 | 6 |

*Alt, Alternaria* species.

Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. J Allergy Clin Immunol. 1997 Apr;99(4):450-3.

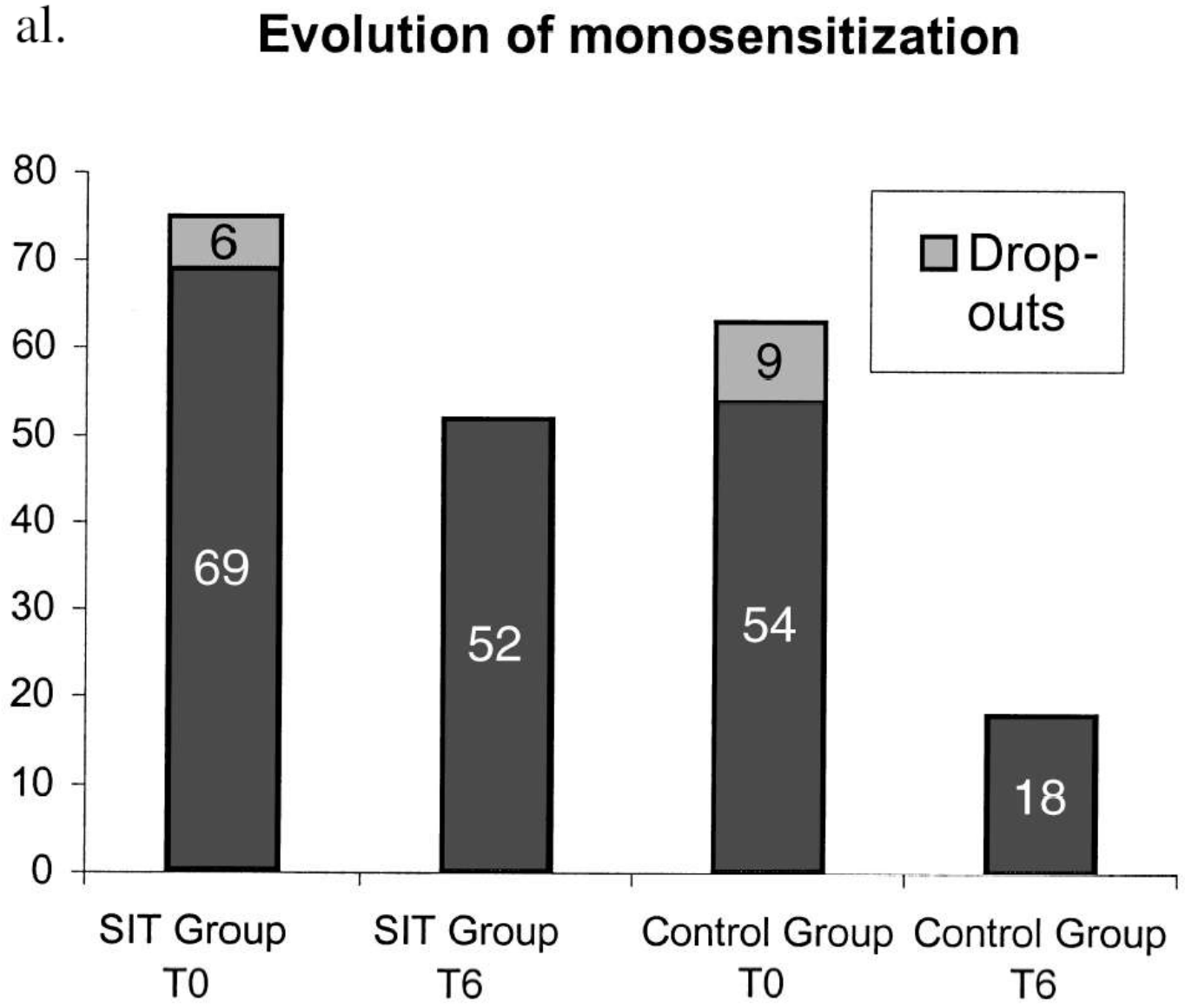
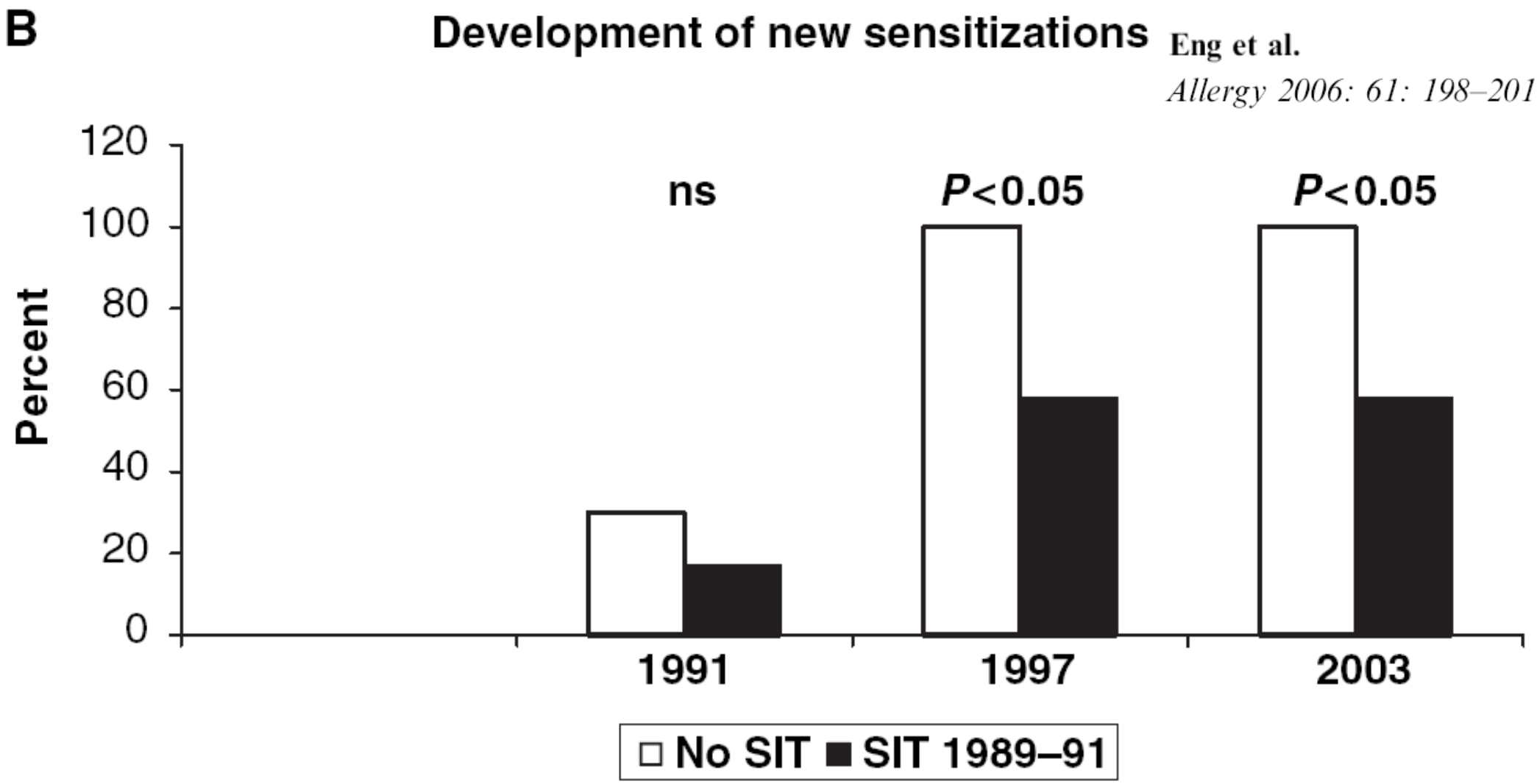



**Fig. 1.** Absolute number of monosensitized subjects in the SIT Group and in the Control Group at the beginning of the trial (T0) and six years after (T6).

*Clinical and Experimental Allergy*, 2001, Volume 31, pages 1392–1397


B
Development of new sensitizations
Eng et al.
Allergy 2006: 61: 198–201
Percent
120
100
80
60
40
20
0
ns
P<0.05
P<0.05
1991
1997
2003
No SIT
SIT 1989–91

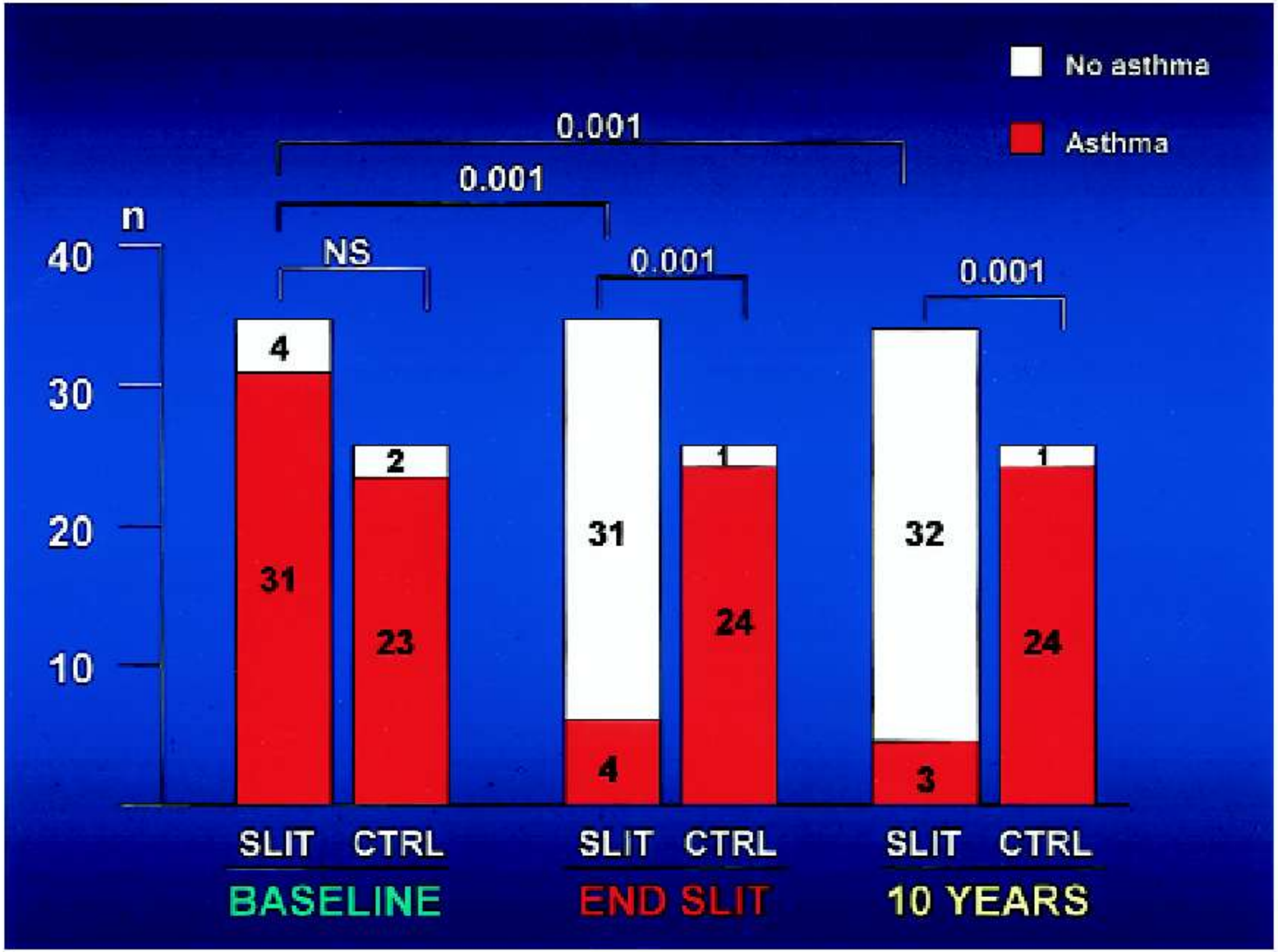



**FIG 4.** Number of patients with and without asthma, at baseline, at the end of the 5-year SLIT course, and 5 years after SLIT discontinuation. Significant intragroup and intergroup *P* values are indicated on the *bars* (from reference 133). **(Di Rienzo V et al. *Clin Exp Allergy 2003;33:206-210)***

Specific immunotherapy: beyond the clinical scores
Passalacqua G
Annals of Allergy 2011;107:401-406

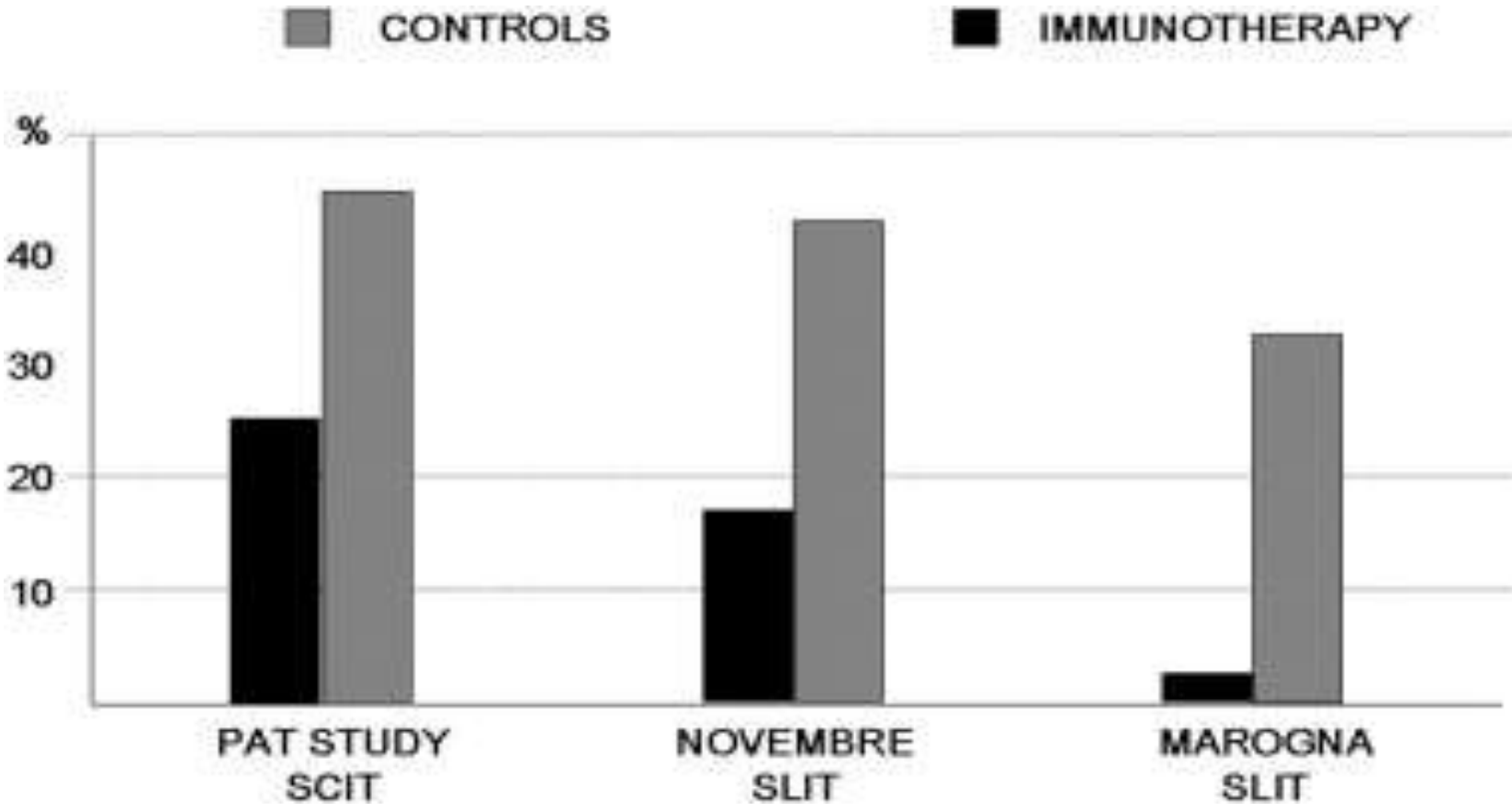




Figure 1. **Percentage of children in the immunotherapy and control groups who developed asthma after 3 years, in the 3 available trials. In the study by Marogna et al,37 the development of persistent asthma was assessed**

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REVIEW ARTICLE

# Untangling asthma phenotypes and endotypes

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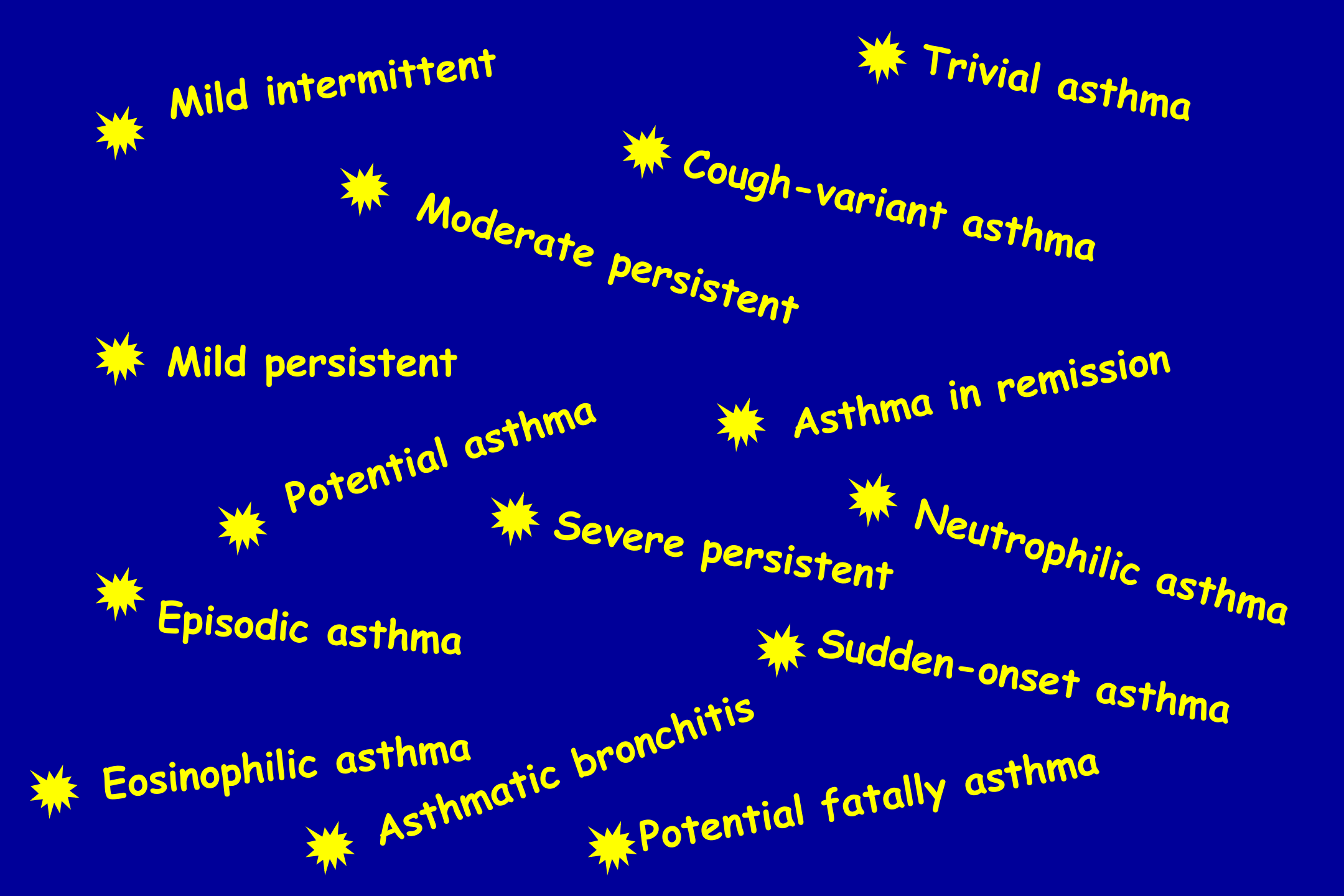
Mild intermittent
Trivial asthma
Cough-variant asthma
Moderate persistent
Mild persistent
Asthma in remission
Potential asthma
Neutrophilic asthma
Severe persistent
Episodic asthma
Sudden-onset asthma
Eosinophilic asthma
Asthmatic bronchitis
Potential fatally asthma

# CONCLUSIONI

- L'efficacia dell'ITS è duratura dopo la sospensione, tuttavia studi a lungo termine sono necessari per precisare l'effettiva durata dell'effetto terapeutico.
- L'ITS somministrata per via sottocutanea è in grado di prevenire la comparsa di nuove sensibilizzazioni nei pazienti monosensibili allergici agli acari della polvere.
- A causa della variabilità della clinica dell'asma bronchiale, della complessità dei fenotipi e degli endotipi, ulteriori studi sono necessari per verificare la possibilità di prevenire con l'ITS l'asma nei pazienti affetti da rinite allergica.