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*Artículo:*

# Efficacy and safety of standarized pollen immunotherapy in the treatment of allergic rhinitis: A meta-analysis of randomized controlled trials

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# Efficacy and safety of standarized pollen immunotherapy in the treatment of al'lergic rhinitis: A meta-analysis of randomized controlled trials

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*ABSTRACT*

*The efficacy of pollen immunotherapy in patients with allergic rhinitis (AR) has been confirmed in many controlled trials. Recent studies suggest that SIT influence the response of T lymphocytes with a shift away from a TH2 response (IL-4, IL-5) towards a Th1 response (IFN-γ).*
***Objective:*** *To evaluate the efficacy and safety of SIT in the treatment of allergic rhinitis by a meta-analysis of randomized and controlled clinical trials, previously published.*
***Methods:*** *A search was made in the electronic bases. Only controlled and randomized clinical trials were included. The primary outcomes were symptoms severity, adverse effects frequency and rescue medication requirements.*
***Results:*** *Twenty two articles were identified and reviewed. Ten studies (45%) fulfilled the selection criteria. Studies were published from 1997 to 2002. All studies used standarized extracts and were administered by a subcutaneous injection. Six hundred fourteen patients with AR were analyzed. Three hundred sixteen patients received SIT and 288 either placebo or symptomatic treatment. All authors found their studies were effective and safe. AR symptoms were higher in control group compared with SIT group (215 ± 131 vs 100 ± 24, p <0.001). Increase in the associate medication was also demonstrated in control group compared with SIT group (OR = 1.97, 95%CI 1.12 to 3.47, p = 0.02). Adverse effects frequency was higher in SIT group (OR = 2.32, 95%CI 1.05 to 5.1, p = 0.05).*
***Conclusions:*** *The results of this analysis indicate that the specific immunotherapy is effective and safe in patients with allergic rhinitis. The studies in pediatric population must be extended to establish conducts in this population.*

***Key words:*** *Allergic rhinitis, specific immunotherapy, pollen, randomized, clinical trials, evidence based medicine, meta-analysis.*

RESUMEN

La inmunoterapia específica (ITE) en pacientes con rinitis alérgica (RA) ha sido ampliamente utilizada y su eficacia se ha demostrado en diversos ensayos clínicos controlados. Estudios recientes encontraron que la ITE causa un cambio en la respuesta inmune de un perfil tipo TH2 a uno Th1, al favorecer la producción de IFN-γ e inhibir la de IL-4 and 5.
**Objetivo:** Evaluar la eficacia y seguridad de la ITE en el tratamiento de la rinitis alérgica a través de un meta-análisis de los ensayos clínicos controlados y aleatorizados, publicados previamente.
**Métodos:** Se realizó una búsqueda en las bases electrónicas de la Internet. Los desenlaces primarios fueron: la gravedad de los síntomas, la frecuencia de efectos adversos y la necesidad de medicamentos de rescate.

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**Resultados:** Se identificaron y revisaron 22 artículos. Diez (45%) cumplieron los criterios de selección y se publicaron entre 1997 y el 2002. Todos los estudios emplearon extractos estandarizados y se administraron por vía subcutánea. Se analizaron a 614 pacientes con RA. Trescientos dieciséis pacientes recibieron ITE y 288 placebo o tratamiento sintomático. Todos los autores reportaron que la ITE fue eficaz y segura. Los síntomas de RA fueron más altos en el grupo control que en el de ITE (215 ± 131 *vs* 100 ± 24, p < 0.001). Se encontró un incremento en los medicamentos de rescate en el grupo control (OR = 1.97, 95%CI 1.12 to 3.47, p = 0.02). La frecuencia de efectos adversos fue mayor en el grupo de ITE (OR = 2.32, 95%CI 1.05 to 5.1, p = 0.05).
**Conclusiones:** La inmunoterapia específica es efectiva y segura en el tratamiento de la rinitis alérgica en pacientes sensibilizados. Se requiere realizar estudios en niños con el propósito de establecer conductas en esta población.

**Palabras clave:** Rinitis alérgica, inmunoterapia específica, pólenes, ensayos clínicos, aleatorizados, medicina basada en evidencias, meta-análisis.

## BACKGROUND

Specific immunotherapy (SIT) of allergic diseases involves the application of gradually increasing doses of extracts of allergens to which the subject is allergic. Allergen-specific immunotherapy has been widely used for 90 years as a specific treatment for allergic disease. The efficacy of pollen immunotherapy in patients with allergic rhinitis (AR) has been confirmed in many controlled trials. Recent studies suggest that SIT influence the response of T lymphocytes with a shift away from a TH2 response (IL-4, IL-5) towards a TH1 response (IFN-γ). A shift in the cytokine profile can result in inhibition of IL-4 dependent IgE production, reinforced decreased autocrine effect and inhibition of IL-5-dependent eosinophilic inflammation.

Treatment ameliorates the severity of the allergic disease and leads to cessation of allergic symptoms. Recently, many double-blind, placebo-controlled studies have proved the clinical efficacy of specific immunotherapy with standardized extracts of inhaled allergens, such as grass pollen, ragweed, mite, latex and cat dander. However, we have not a large and homogeneous study about efficacy of pollen immunotherapy in sensitized patients.

The objective of this study was to evaluate the efficacy and safety of specific immunotherapy in the treatment of allergic rhinitis by a meta-analysis of randomized and controlled clinical trials, previously published.

## MATERIAL AND METHODS

A search was made in the electronic bases MEDLINE, Mdconsult, OVID and science@direct. We looked for studies from 1966 to 2003 with the following key words: *allergic rhinitis, pollen, standarized immunotherapy, randomized, clinical trials, objective outcome and allergen*. Only controlled and randomized clinical trials were included (Strength of recommendation A). Studies whose main purpose was to evaluate the efficacy and safety of immunotherapy were included. All the articles in full text format were reviewed by the authors (JHL & MPP), who extracted and analyzed the data.

Authors registered the following variables: Study design, control drug, informed consent request, clinical diagnosis, allergen type, adjuvant used, administration route, age, sample size, symptoms severity, adverse effects, rescue medication requirements, outcome units and author's study conclusion.

Articles were rated by category of evidence and used to establish the strength of recommendation *(Table I)*.

**Table I. Classification of evidence and recommendations.**

| Category of evidence | | Strength of recommendation | |
|---|---|---|---|
| Ia | Meta-analysis of randomized controlled trials | A | Directly based on category I evidence |
| Ib | At least 1 randomized controlled trial | B | Based on category II or extrapolated from I |
| IIa | At least 1 controlled study without randomization | C | Based on category III or extrapolated from IV |
| IIb | At least 1 other type of quasi-experimental study | D | Based on category IV or extrapolated from I, II or III category |
| III | Non experimental descriptive studies, such as comparative studies, correlation studies and case-control studies | E | Directly based on Laboratory based evidence |
| IV | Expert committee reports or opinions or clinical experience of respected authorities | | |

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**Table II. Clinical trial characteristics.**

| Study | Study design | Control drug | Informed consent | Reference | Evidence level | Evidence Strength | Study conclusion |
|---|---|---|---|---|---|---|---|
| Zenner[55] | RCT, DB | Placebo | Obtained | J Allergy Clin Immunol 1997 | Ib | A | Effective |
| Durham[15] | RCT, DB | Placebo | Obtained | N Engl J Med 1999 | Ib | A | Effective |
| Klimek[28] | RCT, SB | Symptomatic | Obtained | J Allergy Clin Immunol 1999 | Ib | A | Effective |
| Klimek[29] | RCT, Open | Symptomatic | Obtained | Clin Exp Allergy 1999 | Ib | A | Effective |
| Walker[52] | RCT, DB | Placebo | Obtained | J Allergy Clin Immunol 2001 | Ib | A | Effective |
| Leynadier[32] | RCT, DB | Placebo | Obtained | Clin Exp Allergy 2001 | Ib | A | Effective |
| Rak[45] | RCT, DB | Budesonide | Obtained | J Allergy Clin Immunol 2001 | Ib | A | Equivalent |
| Arvidsson[4] | RCT, DB | Placebo | Obtained | J Allergy Clin Immunol 2002 | Ib | A | Effective |
| Möller[36] | RCT, SB | Symptomatic | Obtained | J Allergy Clin Immunol 2002 | Ib | A | Effective |
| Bødtger[5] | RCT, DB | Placebo | Obtained | Allergy 2002 | Ib | A | Effective |

RCT: Randomized clinical trial, DB: Double blind, SB: Single blind.

We select as primary outcomes symptoms severity, adverse effects frequency and rescue medication requirements. Statistical analysis included Kolmogorov-Smirnov test, Odds ratio (OR), 95% confidence intervals (95%IC) and Fisher's test exact calculation. Mann-Whitney U test was used to compare quantitative variables. All outcome measures were captured into a database. Because outcomes varied considerably from one study to another, it was not possible to reduce the entire data to a single format. A p value less than 0.05 was considered significant. We use both SPSS v10 (SPSS, Chicago Ill, USA) and Meta-Analysis Program, Version 5 (Freie Universität Berlin, Germany).

## RESULTS

### Study selection

Twenty two articles were identified and reviewed. Ten studies (45%) fulfilled the selection criteria. All of them were RCT, controlled either placebo or symptomatic treatment. Seven were double blind, two single blind and one study was open. All authors obtained an informed consent from patient. Studies were published from 1997 to 2002. All of them had a category of evidence Ib and a strength of recommendation A *(Table II)*.

### Allergens

All studies used standarized extracts and were administered by a subcutaneous injection. Most of them (9/10), used aluminum as adjuvant *(Table III)*.

### Patients

Six hundred fourteen patients from the 10 studies were considered for the analysis. Three hundred sixteen patients received SIT and 288 either placebo or symptomatic treatment. All patients had a clinical diagnosis of allergic rhinitis. Median age was 30 years old (IQR 28 – 32) *(Table III)*.

**Table III. Study Characteristics.**

| Study | Clinical diagnosis | Allergen | Type | Adjuvant | Route | Median age | n | SIT group | Control group |
|---|---|---|---|---|---|---|---|---|---|
| Zenner[55] | AR | 6 grasses | Standarized | Aluminum | SC | 27 | 86 | 45 | 41 |
| Durham[15] | AR | Grass | Standarized | Aluminum | SC | 38 | 47 | 32 | 15 |
| Klimek[28] | AR, A | 6 grasses | Standarized | Aluminum | SC | 30 | 48 | 24 | 24 |
| Klimek[29] | AR | *Betula alba* | Standarized | Aluminum | SC | 28 | 37 | 19 | 18 |
| Walker[52] | AR | *Phleum pratense* | Standarized | Aluminum | SC | 32 | 44 | 22 | 22 |
| Leynadier[32] | ARC | 5 grasses | Standarized | Calcium-phosphate | SC | 29 | 39 | 16 | 13 |
| Rak[45] | ARC, A | *Betula verrucosa* | Standarized | Aluminum | SC | 29 | 41 | 21 | 20 |
| Arvidsson[4] | ARC, A | *Betula verrucosa* | Standarized | Aluminum | SC | 33 | 46 | 22 | 24 |
| Möller[36] | AR | *Phleum pratense* | Standarized | Aluminum | SC | 10 | 191 | 97 | 94 |
| Bødtger[5] | ARC | *Betula verrucosa* | Standarized | Aluminum | SC | 31 | 35 | 18 | 17 |

ARC: Allergic rhinoconjunctivitis, AR: Allergic rhinitis, A: Asthma, SC: Subcutaneous, SIT: Specific immunotherapy.

### Primary outcomes

Several outcomes were considered in the studies. That included clinical scores, rescue medication use, cytokine and antibodies levels, T-cell proliferation and cytokine production assays, eosinophil cationic protein, eosinophil chemotactic activity, challenge test responses, skin biopsies, methacholine bronchial provocation tests, peak flow measurement, asthma development and statistical results. However, although authors published most of outcomes, units were not consistent between studies. Some of them were quantitative, others were qualitative and some data was not available. All studies included symptoms scores, rescue medication use and adverse events frequency. We used this measurements to perform the meta-analysis.

### Efficacy and safety

All authors found their studies effective and safe. Overall, allergic rhinitis symptoms were higher in control group compared with SIT group (215 ± 131 *vs* 100 ± 24, $p < 0.001$) (Mean score ± SD). Increase in the associate medication was also demonstrated in control group compared with SIT group (OR = 1.97, 95%CI 1.12 to 3.47, $p = 0.02$). Adverse effects frequency was higher in SIT group (OR = 2.32, 95%CI 1.05 to 5.1, $p = 0.05$), most of them were mild, although was not reported in all the studies *(Table IV)*.

## DISCUSSION

A link between AR and asthma is evident, and more than 70% of asthma patients report nasal symptoms. Approximately 20% of all hay fever patients develop asthma later in life. It has been found that 11% to 73% of hay fever patients show bronchial hyperresponsiveness (BHR) outside the pollen season and that up to approximately 50% of such patients show BHR during the season. Rhinitis frequently precedes the onset of asthma and patients with allergic rhinitis who also have BHR are more likely to develop asthma.

T-cell-derived cytokines play a key part in allergic inflammation. Pollen-specific T cells from patients with atopy produce greater quantities of cytokines such as interleukin-4, interleukin-13 and interleukin-5 (Th2) than do cells from control subjects without atopy, which favor the production of interferon-γ (Th1 cells). Allergen-specific Th2 lymphocytes play a predominant role in allergic diseases, since cytokines produced by this T cell subset (IL-4, IL-13) are potent IgE-switching factors, whereas interleukin-5 has specific pro-eosinophilic properties. IgE-dependent activation of mast cells results in an immediate response to allergen and may contribute to the development of the late response.

Previous studies found decreases in serum IgE concentrations, increases in IgG, and inhibition of recruitment or activation of effector cells such as mast cells and eosinophils in the target organ in response to immunotherapy. Since each of these processes is thought to be largely T-cell–dependent, one possibility is that immunotherapy exerts a prolonged effect by altering the T-cell response to subsequent allergen exposure. Further studies of cutaneous-biopsy specimens obtained at 24 hours suggested that this Th1 response may have been driven by interleukin-12. Taken together, these studies suggest that pollen immunotherapy may act either by inducing immune deviation of Th2 and Th0 T-cell re-

**Table IV. Main study outcomes.**

| Study | Symptoms (SIT *vs* Placebo) | p | Outcome units | Rescue medications (SIT *vs* Placebo) | p | Outcome units | Adverse events (SIT) | Adverse events (CG) |
|---|---|---|---|---|---|---|---|---|
| Zenner[55] | 82.2 ± 10.1 *vs* 116 ± 13 | 0.02 | MS | 11% *vs* 20% | 0.06 | % Use | 9% | 2% |
| Durham[15] | 921 (0-2,299) *vs* 2,863 (774-12,033) | < 0.05 | Mean AUC | 672 (0-1,827) *vs* 4729 (1,197-8,505) | < 0.05 | Mean AUC | 2% | NAD |
| Klimek[28] | 134 (65-366) *vs* 386 (185-563) | 0.02 | MS | 37% *vs* 70% | 0.02 | % Use | 2.9% | NAD |
| Klimek[29] | NAD | < 0.001 | Mean AUC | NAD | < 0.001 | Mean AUC | 12% | 8% |
| Walker[52] | 2,576 (1,630-3,515) *vs* 1,962 (1,124-3,002) | 0.01 | Median AUC | 357 (49-2,236) *vs* 1851 (476 *vs* 3,947 | 0.007 | Median AUC | 13% | 0% |
| Leynadier[32] | 49.5 *vs* 56.0 | > 0.05 | Mean AUC | 11.1 *vs* 40.8 | 0.005 | % Use | 43% | 15% |
| Rak[45] | 20 ± 5 *vs* 10 ± 2.5 | 0.03 | Symp score | 10 ± 6 *vs* 5 ± 5 | 0.06 | Med Score | NAD | NAD |
| Arvidsson[4] | 2.6 (0.0-6.5) *vs* 4.3 (2.4-9.1) | 0.005 | AVS | 8 *vs* 16 | 0.004 | MS | 27% | 19% |
| Möller[36] | Improvement with SIT, exact data NA | < 0.01 | AVS | 20% *vs* 20% | > 0.05 | % Use | NAD | NAD |
| Bødtger[5] | Improvement with SIT, exact data NA | < 0.05 | MS | Improvement with SIT, exact data NA | < 0.01 | Med score | NAD | NAD |

AUC: Area under curve, NAD: No available data, CG: Control group, AVS: Analogue visual scale, MS: Mean score, Symp score: Symptom score, Med Score: Medication score.

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sponses in favor of Th1 profile or by diminishing Th2 and Th0 T-cell responses.

Specific immunotherapy (SIT) proved to be an efficient treatment for patients suffering from type I allergy to airborne allergens. Its usefulness is highlighted in a recent World Health Organization report, which advocates its use in selected patients with specific IgE antibodies to clinically relevant allergens. The vaccine routinely used for SIT consists of standardized total allergen extracts adsorbed to aluminum hydroxide. However, aluminum hydroxide has been shown to induce Th2-type rather than Th1-type immune responses. In case of atopic allergy, the use of vaccine adjuvants fostering Th1-like immune responses could certainly augment the efficacy of the treatment.

In this systematic review, all authors reported efficacy and safety in their primary outcomes. Only Rak's study found a negative effect of SIT on clinical scores. However, control group received a nasal steroid (budesonide). In this study, SIT prevented seasonal increase in bronchial hyperresponsiveness, eosinophil number, eosinophil cationic protein, and eosinophil chemotactic activity only in asthmatic patients.

Few studies are a limitation of the present analysis. However, inclusion criteria were rigid and strength of recommendation of all articles was high. There is not enough available studies carried out in children; therefore, this findings must be applied only to adult population.

Currently, several strategies are been proved in order to enhance the deviation of Th immune response. Bacterial DNA (BCG, *Mycobacterium vaccae*) and synthetic oligodeoxynucleotides containing CpG-motifs (CpG-ODN) have attracted attention because they acted as Th1-promoting adjuvants. However, results are preliminary yet.

This study indicates that SIT is safe and effective and raise the question of whether allergen-injection immunotherapy should be considered earlier in the course of allergic disease to prevent disease progression or the development of multiple allergies. This Fact was proved in PAT-study that demonstrated a 3-year course of SIT in children with allergic rhinoconjunctivitis significantly reduces the risk of developing clinical asthma and improves BHR.

## CONCLUSIONS

The results of this meta-analysis indicate that specific immunotherapy is effective and safe in patients with allergic rhinitis. Pediatric studies must be extended to establish conducts in this population.

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