ORIGINAL ARTICLE

# Predicting Patients at High-Risk of Systemic Reactions to Cluster Allergen Immunotherapy: A Pilot Prospective Observational Study

JL Justicia,* MJ Barasona, P Serrano, C Moreno, F Guerra

Allergy Service, Reina Sofía University Hospital, Córdoba, Spain

## Abstract

*Objective:* The purpose of this study was to identify factors associated with increased risk of adverse systemic reactions to cluster allergen immunotherapy and to create a preliminary predictive clinical model.
*Methods:* In a prospective observational study, the tolerance of 611 patients with seasonal respiratory diseases who were receiving cluster immunotherapy was monitored and all systemic reactions were recorded. Associations between potential prognostic factors (sex, age, respiratory disease, severity, duration of disease, previous immunotherapy, nonseasonal symptoms, skin prick test, total immunoglobulin (Ig) E, specific IgE, treatment schedule, allergenic composition, batch, date of treatment, habitat, place of residence) and systemic reactions were estimated. Multivariate stepwise logistic regression analysis was used to build a predictive clinical model and estimate the probability of systemic reactions to cluster immunotherapy.
*Results:* Sixty-five patients (10.6%) suffered systemic reactions. Only 7 independent risk factors were retained in the final model: age over14 years (odds ratio [OR], 2.6), previous immunotherapy (OR, 0.3), skin prick test positive to *Chenopodium album* (white goosefoot) (OR, 3.0), elevated specific IgE to grass pollen (OR, 2.3), elevated specific IgE to olive pollen (OR, 4.1), olive pollen 100% composition (OR, 2.6) and treatment schedule (OR, 1, 1.6 or 7.1, depending on the cluster immunotherapy schedule).
*Conclusions:* This predictive model, derived from simple clinical variables, has excellent ability to assess individual risk of suffering systemic reactions to cluster allergen immunotherapy. Detecting high-risk patients can help clinicians to prevent and eliminate many severe adverse reactions to cluster immunotherapy.

**Key words:** Allergen-immunotherapy. Adverse reactions. Rhinitis. Asthma. Pollen. Predictive clinical model.

## Resumen

*Objetivos:* El propósito de este estudio fue identificar factores asociados con un mayor riesgo de reacciones adversas sistémicas por inmunoterapia agrupada y crear un modelo clínico predictivo preliminar.
*Métodos:* Mediante un estudio observacional y prospectivo, se monitorizó la tolerancia de 611 pacientes con enfermedades alérgicas respiratorias que recibieron inmunoterapia agrupada, y se registraron todas las reacciones sistémicas. Se estimó la asociación entre reacción sistémica y posibles factores pronósticos (sexo, edad, enfermedad respiratoria, gravedad, duración de la enfermedad, administración previa de inmunoterapia, síntomas no estacionales, pruebas cutáneas, inmunoglobulina (Ig) E total, IgE específica, esquema terapéutico, composición de la vacuna, lote, fecha de tratamiento, hábitat y lugar de residencia). Mediante regresión logística multivariante, se construyó un modelo clínico predictivo y se estimó la probabilidad de reacción sistémica por inmunoterapia agrupada.
*Resultados:* Sesenta y cinco pacientes (10.6%) sufrieron reacciones sistémicas. En el modelo final sólo permanecieron siete factores de riesgo: edad mayor de 14 años (odds ratio [OR]; 2.6), inmunoterapia previa (OR: 0.3), prueba cutánea positiva a Chenopodium album (OR: 3.0), IgE específica frente a gramíneas elevada (OR: 2.3), IgE específica frente a olivo elevada (OR: 4.1), vacuna compuesta de Olivo 100% (OR; 2.6) y pauta de administración (OR: 1 ó 1.6 ó 7.1 según la pauta utilizada).
*Conclusiones:* Este modelo predictivo, construido a partir de variables clínicas fácil de obtener, tiene una excelente capacidad para valorar el riesgo individual de sufrir reacciones sistémicas por inmunoterapia con alérgenos administrada mediante pautas agrupadas. La detección de pacientes de alto riesgo puede ayudar a los clínicos a prevenir y eliminar muchas reacciones adversas graves por inmunoterapia agrupada.

**Palabras clave:** Inmunoterapia específica. Reacciones adversas. Rinitis. Asma. Polen. Modelo clínico predictivo.

* Currently, JL Justicia works as Medical Director at Stallergenes Ibérica, SA, in Spain.

## Introduction

Allergen-specific immunotherapy is a treatment that modifies the immunological response to allergens and induces a state of clinical tolerance [1]. It involves 2 phases: a build-up phase (up-dosing or induction phase) and a maintenance phase. The duration of the build-up phase depends on the frequency of the injections but generally ranges from 3 to 4 months. Although specific immunotherapy is highly effective in carefully selected patients with immunoglobulin (Ig) E mediated diseases [2-4], inconvenience, primarily due to the time involved, is usually the reason for not choosing this treatment and it is one of the most frequent reasons for discontinuing it [5].

Cluster subcutaneous immunotherapy is a build-up schedule wherein several allergen injections are given sequentially in a single day of treatment on nonconsecutive days. It offers the advantage of fewer office visits, saving patients' time, and it may allow patients to experience the benefits of immunotherapy more rapidly because the maintenance dose is reached in a shorter period than with a conventional schedule.

Despite the fact that cluster immunotherapy schedules have been successfully tried [6], their use is limited, probably due to the perception that they are associated with a greater risk of serious adverse reactions [7]. A predictive tool that estimates the likelihood of a patient suffering systemic reactions might be very useful in patient selection for cluster immunotherapy and in adopting preventive measures in high-risk patients.

The purpose of this study was to identify factors associated with increased risk of adverse systemic reactions to cluster allergen-specific immunotherapy and to develop a simple clinical model capable of predicting these reactions.

## Patients and Methods

From January 1996 to December 2002, we selected 1984 patients with allergic respiratory diseases to receive subcutaneous specific immunotherapy according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines [8]. Thus, all injections during the induction phase (until the maximum dose recommended by the manufacturer or tolerated by the patient had been reached) were administered at an immunotherapy unit by staff properly trained in this treatment. Prospectively, immunotherapy safety was evaluated by recording post-injection adverse effects. Demographic and clinical data (sex, age, respiratory disease, severity and duration, allergic sentization, seasonal and nonseasonal symptoms, previous immunotherapy, skin prick tests, total IgE, specific IgE, treatment schedule, allergenic composition of extracts, manufacturer, batch, date of treatment, habitat, place of residence), and peak expiratory flow before and after injection were recorded by the investigators on a standardized form.

### *Immunotherapy Treatment*

To avoid heterogeneity, only biologically standardized aluminum-adsorbed allergen extracts (ALK, Madrid, Spain) from olive and grass pollens (the most important allergens from our region) were selected for this trial.

A clustered induction schedule was employed, with 2 to 4 injections a day at 30-minute intervals until the maintenance dose was reached (2, 3, or 4 visits) (Table 1). Allergen vaccines were administered subcutaneously according to EAACI guidelines [8] after the patients had given their informed consent.

Table 1. Clustered Induction Schedules

| | 4 Visits | | | | 3 Visits | | | | 2 Visits | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Schedule 1 (n=87) | | Schedule 2 (n=65) | | Schedule 3 (n=153) | | Schedule 4 (n=243) | | Schedule 5 (n=63) | |
| Day | Vial | Volume, mL | Vial | Volume, mL | Vial | Volume, mL | Vial | Volume, mL | Vial | Volume, mL |
| 0 | 1 | 0.20<br>0.40<br>0.80 | 2 | 0.10<br>0.20 | 2 | 0.20<br>0.40 | 2 | 0.30<br>0.50 | 2<br>2<br>3 | 0.40<br>0.80<br>0.15 |
| 7 | 2 | 0.20<br>0.40<br>0.80 | 2 | 0.40<br>0.40 | 3 | 0.10<br>0.20 | 3 | 0.10<br>0.15 | 3 | 0.40<br>0.40 |
| 14 | 3 | 0.10<br>0.20 | 3 | 0.10<br>0.20 | 3 | 0.40<br>0.40 | 3 | 0.30<br>0.50 | | |
| 21 | 3 | 0.40<br>0.40 | 3 | 0.40<br>0.40 | | | | | | |

## Adverse Reactions to Immunotherapy

The investigators assessed the adverse reactions to immunotherapy according the EAACI classification [9], and systemic reaction was chosen as the main outcome measure. In order to neutralize any possible nocebo effect, grade 0 reactions (nonspecific symptoms) were excluded. Local reactions were not considered.

## Data Analysis

Candidate variables (Table 2) were selected from clinical variables based on results from other published studies [10,11] and on clinical expert opinion. A logistic regression model was used to examine the individual relationship between each variable and systemic reaction to cluster immunotherapy. Variables that reached a significance level of $\alpha$ less than 0.30 were eligible to enter a multivariable stepwise logistic regression (backward elimination) analysis. Only those variables associated with an $\alpha$ level of 0.05 or less were retained in the final model. Interactions using the significant prognostic variables were explored, and the variable date (year of treatment) was introduced into the final regression model to check its association with the main outcome measure, systemic reaction.

The goodness-of-fit of the final regression model was evaluated using the Hosmer–Lemeshow test. The model's

Table 2. Candidate Variables for a Multivariable Logistic Regression Model*

| |
|---|
| Patient and Clinical Characteristics |
| Gender |
| Age |
| Disease |
| GINA classification |
| Disease duration |
| Previous immunotherapy |
| Nonseasonal symptoms |
| Prick test olive-pollen |
| Prick test grass-pollen |
| Sensitization to other allergens (HDM, animals, pollens, molds) |
| Total IgE |
| Specific IgE to olive pollen |
| Specific IgE to grass pollen |
| Ratio, total IgE/Specific IgE |
| Treatment Schedule |
| Cluster schedule |
| Allergenic Extract |
| Composition |
| Batch |
| Other |
| Year of SIT |
| Date (trimester) |
| Region |
| Habitat |

* SIT indicates specific immunotherapy; GINA, Global Initiative for Asthma; HDM, house dust mite; Ig, immunoglobulin.

Table 3. Patients' Demographic and Clinical Characteristics

| | No. of Patients (%) | Median (IQR) |
|---|---|---|
| Gender | | |
| Women | 287 (47.0) | |
| Men | 324 (53.0) | |
| Age, y | | 18 (12.5-26) |
| Disease | | |
| Rhinitis | 611 (100) | |
| Asthma | 529 (86.6) | |
| GINA Classification | | |
| NA (patients with rhinitis only) | 82 (13.4) | |
| Intermittent | 106 (17.3) | |
| Mild Persistent | 126 (20.6) | |
| Moderate Persistent | 154 (25.2) | |
| Severe Persistent | 18 (3.0) | |
| Data missing | 125 (20.5) | |
| Duration, y | | 6 (4-11) |
| Previous immunotherapy | | |
| No | 411 (67.3) | |
| Yes | 200 (32.7) | |
| Non seasonal symptoms | | |
| No | 502 (82.2) | |
| Yes | 109 (17.8) | |
| Habitat | | |
| Rural (<5000 inhabitants) | 104 (17.0) | |
| Semirural (5000-20 000 inhabitants) | 156 (25.5) | |
| Urban (>20 000 inhabitants) | 351 (57.5) | |
| Total IgE (kU/L) | | 276 (129-587) |
| Total IgE adjusted by age | | |
| Normal | 268 (46.4) | |
| Elevated | 309 (53.6) | |
| Specific IgE (kU/L) | | |
| Olive pollen | | 29.5 (9.3-83.4) |
| Grass pollen | | 34.8 (11.4-82.1) |

GINA indicates Global Initiative for Asthma; NA, not applicable; IgE, immunoglobulin E.

Table 4. Final multivariable logistic regression model*

| | No. of Patients | Systemic Reaction,% | *P* | OR (95% CI) |
|---|---|---|---|---|
| Age | | | | |
| 0 to 14 y | 205 | 5.4 | | |
| >14 y | 406 | 13.3 | .016 | 2.6 (1.2-5.6) |
| Previous immunotherapy | | | | |
| No | 411 | 12.4 | | |
| Yes | 200 | 7.0 | .010 | 0.3 (0.2-0.8) |
| Prick test *Chenopodium* species | | | | |
| Negative | 447 | 8.3 | | |
| Positive | 164 | 17.1 | .001 | 3.0 (1.6-5.6) |
| IgE to olive pollen | | | | |
| ≤20% total IgE | 402 | 7.7 | | |
| >20% total IgE | 138 | 21.0 | <.001 | 4.1 (2.1-7.9) |
| IgE to grass pollen | | | | |
| ≤20% total IgE | 439 | 6.5 | | |
| >20% total IgE | 95 | 14.1 | .042 | 2.3 (1.0-5.4) |
| Composition | | | | |
| Mixture olive + grasses | 358 | 8.1 | | |
| Olive only | 253 | 14.2 | .021 | 2.6 (1.1-5.9) |
| Cluster schedule | | | | |
| 4 visits | 152 | 5.9 | .001 | |
| 3 visits | 396 | 10.6 | .299 | 1.6 (0.7-3.6) |
| 2 visits | 63 | 22.2 | <.001 | 7.1 (2.5-20.0) |

* OR indicates odds ratio; CI, confidence intereval; IgE, immunoglobulin E.

discriminative power was assessed by a receiver operating characteristic (ROC) curve, which plotted the sensitivity of systemic reaction detection against the false positive (1-specificity) across a spectrum of threshold probabilities. Accuracy of calibration was evaluated by rank-ordering patients according to their predicted probability of a systemic reaction, dividing them into 10 risk groups (deciles) from highest to lowest probability, and then graphically comparing the mean predicted probability for each decile group with the group's corresponding prevalence of systemic reaction.

## Results

Data were obtained from 611 patients. Their demographic characteristics and clinical features are shown in Table 3.

Only 86 of 611 patients (14.1%) showed a skin prick test positive to a single allergen (olive pollen), whereas 133 individuals (21.8%) had double sensitization (grass and olive pollens), and 392 (64.1%) were sensitized to grass, olive and other multiple allergens, especially *Chenopodium album* (white goosefoot), *Plantago lanceolata* (plantain) and *Helianthus annus* (sunflower).

Three hundred and fifty-eight patients (58.6%) received allergen immunotherapy with a mixture of grass pollen (50%) and olive pollen (50%). The other 253 patients (41.4%) received immunotherapy with olive-only pollen extracts. The maintenance dose was reached in 2 visits by 63 patients, in 3 by 396, and in 4 by 152.

### *Incidence of Systemic Adverse Reactions*

A total of 4446 doses were injected and 71 patients suffered 88 systemic reactions during the 7-year study period. None had life threatening reactions. After 9 grade 0 reactions (nonspecific symptoms) in 6 individuals had been excluded, the incidence of systemic reactions to cluster allergen immunotherapy was 10.6% and 17.8 per 1000 doses.

### *Clinical Prediction Model*

Only 7 independent risk factors (age >14 years, previous immunotherapy, skin prick test positive to *C album*, elevated level of specific IgE to grass pollen, elevated level of specific

 

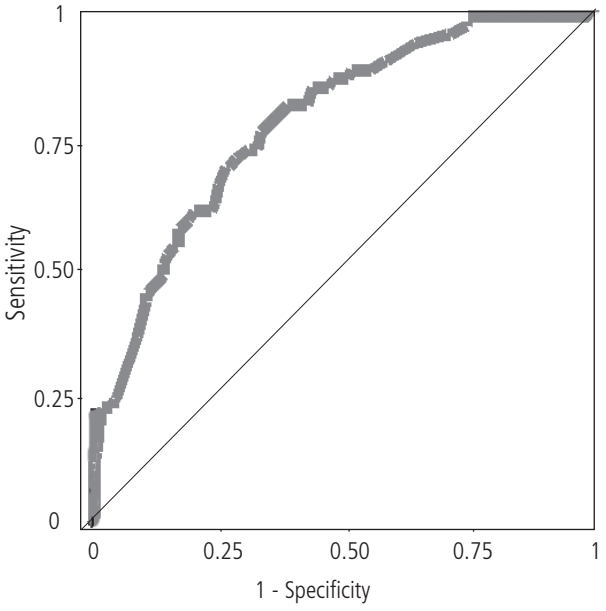


Figure 1. Discriminative power of the final predictive model assessed by the receiver operating characteristic curve

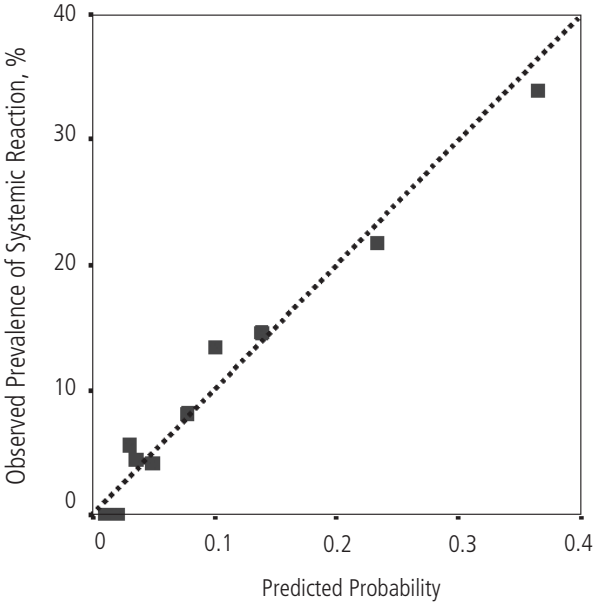


Figure 2. Correlation of systemic reactions to the immunotherapy predictive model. The diagonal line indicates perfect correlation. Pearson correlation coefficient, 0.987 ($R^2 = 0.973$, $P < .001$), estimated by least squares regression analysis

IgE to olive pollen, vaccine composition, and treatment schedule) were retained in the final regression model (Table 4). There were no interaction terms that significantly contributed to the model's overall predictive performance.

There was adequate goodness-of-fit of the final predictive model (Hosmer–Lemeshow $\chi^2 = 2.91$; $P = .94$).

The ROC curve demonstrating the trade-off between sensitivity and specificity for systemic reactions that results from various probability thresholds is shown in Figure 1. The area under the curve was 0.794 ($P < .001$) and the maximum discrimination point was a cutoff probability of 0.085. This cut point produced the following values indicating diagnostic utility: sensitivity, 0.82 (95% confidence interval [CI], 0.71-0.90); specificity, 0.62 (95% CI, 0.57-0.66); positive predictive value, 0.20 (95% CI, 0.16-0.26); negative predictive value, 0.97 (95% CI, 0.94-0.98); positive likelihood ratio, 2.15 (95% CI, 1.82-2.53); and negative likelihood ratio, 0.28 (95% CI, 0.16-0.50).

As expected, the predictive model's overall calibration was excellent (Figure 2). There was a close relationship between the predicted probability of systemic reactions and the prevalence of such reactions observed within each decile risk group.

## Discussion

Previous studies have documented several risk factors for systemic reactions to immunotherapy [10,11], but multiple sources of risk information cannot be integrated without support from a multivariable model. The predictive multivariable model derived from this study could help clinicians estimate the individual risk of patients who receive cluster allergen immunotherapy. Risk stratification is important for optimal triage and management: identifying low-risk patients on whom cluster immunotherapy can be used without adverse consequences (eg, a predicted risk <10% has a negative predictive value >95%), identifying patients whose risk of systemic reaction is greater than the benefits of cluster immunotherapy, correcting potentially modifiable risk factors (eg, treatment schedule), and establishing prophylactic treatment (eg, antihistamines) in order to reduce the risk of systemic reactions.

Some reports have shown a higher frequency of adverse effects in children than in adults [12,13]. However, in our study, there were more systemic reactions in patients over 14 years of age. It is likely that longer disease duration induces a more "consolidated" immunological shift to the type 2 helper T cell pattern (favoring the allergic process), and provokes irreversible tissue lesions. Both factors ("consolidated" immunological deviation and irreversible lesions) might well reduce tolerance and produce greater reactivity to allergens.

Several studies have documented that patients with asthma are at higher risk of severe systemic reactions [14,15]. This multivariable model did not show asthma to be a risk factor, probably due to careful selection of patients and the exclusion of uncontrolled asthmatic patients. The higher frequency of adverse reactions in patients with asthma is probably related to allergen source. All the patients in this study were sensitized to grass and olive pollens, and the risk of systemic adverse effects in seasonal allergen-induced asthma might be lower than in perennial allergen-induced asthma.

Allergen immunotherapy induces a state of clinical and immunological tolerance [1]. In addition, its effects persist for several years after it has been discontinued [16,17]. Either

fact might explain why patients who received immunotherapy before starting the study suffered fewer reactions when they were vaccinated afterwards.

A surprising finding was that patients sensitized to *C album* (white goosefoot) pollen, were at 3 times greater risk than nonsensitized patients. Simultaneous sensitization to several allergen sources may be due to immunological cross-reactivity to similar molecules [18], which may be present in many unrelated plant pollens and foods and which are usually considered as minor allergens. Currently, specific immunotherapy is performed using crude allergen extracts whose content of minor allergens is unpredictable. Exposure to high levels of minor allergens in sensitized patients may give rise to unwanted effects during immunotherapy

The validity of any scientific work that is carried out over a long time may obviously be limited by factors associated with changes that take place over time. This study recruited patients over a period of 7 years. In the course of this period, the criteria applied to allergy patients for their treatment with immunotherapy may have changed, the manufacturing processes of the extracts used in treatment might have changed, or the experience accumulated by the health caregivers involved might have changed the way in which they behaved in the process of administering the therapy. In order to be certain that the dependent variable (systemic reaction to immunotherapy) was not affected by factors associated with the year of treatment, we introduced this last as a variable in the final regression model, but found no significant effect.

It is possible that some of the systemic reactions could have been caused by errors made in administering the treatment rather than by the influence of the factors detected in this study. However, given that the treatment was administered by highly experienced nursing personnel in an immunotherapy unit under the supervision of a clinical specialist, and pulmonary function and clinical condition were checked before and after every injection, this possibility remains highly unlikely.

To achieve the highest level of evidence, after creating a clinical decision rule (or predictive clinical model), we must prospectively validate it in a different population and demonstrate change in clinician behavior with beneficial consequences [19]. We have performed a rigorous process in building the predictive model (all important predictors were included, they were present in a significant proportion of the study population, all the outcome events and predictors were clearly defined, those assessing the outcome event were blinded to the presence of the predictors and those assessing the presence of predictors were blinded to the outcome event, the sample size was adequate, and the predictive model makes clinical sense); nonetheless, we have only carried out an internal validation. We cannot therefore recommend the immediate clinical application of the model until a rigorous external validation process has been carried out.

It is important to emphasize that the primary objective of this study was to develop a preliminary predictive model which could be improved and validated by subsequent studies. In order to avoid sample heterogeneity, we included only patients who had been vaccinated with extracts of olive pollen or with a mixture of olive pollen and Graminea species, adsorbed on aluminum hydroxide and manufactured by a single laboratory. This limits the possibility of extrapolating our results to other patients treated with different vaccines, given that other authors have indicated the influence of the composition [20], adjuvant [21], and manufacturer [22] on the incidence of systemic reactions to immunotherapy. Nor can we assume that our results would be repeated under dose regimes that differed from those used by us; nor can the usefulness of the model for the administration of immunotherapy during the maintenance phase, or by sublingual administration, be guaranteed.

In conclusion, this study has developed a clinical prediction model with easily obtainable indicators that allows patients who receive cluster allergen immunotherapy to be classified according to their individual risk of systemic reactions, and preventive measures to be adopted in those patients that are at highest risk.

## References


1. Frew AJ, Norman PS, Golden DB, Adelman D. Inmunoterapia. In: Holgate ST, Church MK, Lichtenstein LM, editors. Alergia. 2nd ed. Madrid: Ediciones Harcourt; 2002. p. 175-85.
2. Malling HJ. Immunotherapy as an effective tool in allergy treatment. Allergy. 1998;53:461-72.
3. Calderón MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database of Systematic Reviews 2007, Issue 1. Art No.: CD001936. DOI: 10.1002/14651858.CD001936.pub2.
4. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001186. DOI: 10.1002/14651858.CD001186.
5. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. Ann Allergy Asthma Immunol. 2002;88:391-4.
6. Parmiani S, Fernández-Távora L, Moreno C, Guardia P, Rico P. Clustered schedules in allergen-specific immunotherapy. Allergol Immunopathol (Madr). 2002;30:283-91.
7. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol. 2006;97:126-38.
8. Malling HJ, Weeke B. Immunotherapy. Position Paper of the EAACI. Allergy. 1993;48 (suppl 14):9-35.
9. Álvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standars for practical allergen-specific immunotherapy. Allergy. 2006;61(Suppl. 82):1-20.
10. Cook PR, Farias C. The safety of allergen immunotherapy: a literature review. Ear Nose Throat J. 1998;378-88.
11. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. Drug Saf. 2000;23:32.
12. Tabar AI, Lizaso MT, Garcia BE, Echechipia S, Olaguibel JM, Rodriguez A. Tolerance of immunotherapy with a standardized extract of Alternaria tenuis in patients with rhinitis and bronchial asthma. J Investig Allergol Clin Immunol. 2000;10:327-33.


 

13. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Specific immunotherapy with a standardized Dermatophagoides pteronyssinus extract: IV. Systemic reactions according to the immunotherapy schedule. J Allergy Clin Immunol. 1990;85:473-9.
14. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol. 2004;113:1129-36.
15. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006;117:169-75.
16. Golden DB, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: outcome after five years. J Allergy Clin Immunol. 1996;97:579-87.
17. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. N Eng J Med. 1999;341:468-75.
18. Pauli G. Evolution in the understanding of cross-reactivities of respiratory allergens: the role of recombinant allergens. Int Arch Allergy Immunol. 2000;123:183-95.
19. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature. XXII: How to use articles about clinical decision rules. JAMA. 2000;284:79-84.
20. Mellerup MT, Hahn GW, Poulsen LK, Malling H. Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. Clin Exp Allergy. 2000;30:1423-9.
21. Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM, Scordamaglia A, Canonica GW. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol. 1997;7:151-4.
22. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Muñoz D. Systemic reactions to immunotherapy: influence of composition and manufacturer. Clin Exp Allergy. 2003;33:470-4.

*Manuscript received May 8, 2007; accepted for publication July 10, 2007*

**Pilar Serrano**

Allergy Service, Reina Sofía University Hospital
Av. Menéndez Pidal, s/n
14004 Córdoba, Spain
Córdoba, Spain
E-mail: pilar_serrano@ozu.es