

EFFECT OF *DERMATOPHAGOIDES* SPECIFIC IMMUNOTHERAPY ON CUTANEOUS REACTIVITY

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SUMMARY:

■ **Background:** There are several immunological and clinical effects induced by specific immunotherapy (SIT). A reduction of reactivity to allergen is the final propose of this therapy.

The aim of this study was to evaluate the specific cutaneous reactivity, two years after beginning SIT.

■ **Methods:** We included 95 patients with bronchial asthma (BA) and/or allergic rhinitis (AR) to house dust mites (HDM). 74 patients were submitted to subcutaneous SIT with commercial extracts of *Dermatophagoides*. The control group included the 21 patients without SIT. After a two years period, the cutaneous reactivity was reassessed, by skin prick tests (SPT). The effect of SIT in the cutaneous response was evaluated by calculating the difference between the wheal diameter of the SPT before and after treatment. A positive difference indicated a cutaneous reactivity reduction.

■ **Results:** The patients submitted to SIT included 52.7% males and 47.3% females, with a mean age of 18.4 ± 13.9 years old. The cutaneous reactivity to *D. pteronyssinus*, before and two years after the beginning of SIT, were $6.9 \pm 3\text{mm}$ and $5.1 \pm 2.9\text{mm}$, respectively, with 1.87 of difference ($p=0.0001$). The cutaneous reactivity to *D. farinae*, before and two years after the beginning of SIT, were $6.2 \pm 2.4\text{mm}$ and $5.0 \pm 3.7\text{mm}$, respectively, with 0.93 of difference ($p=0.0790$). In the control group, the cutaneous reactivity to *D. pteronyssinus* was $4.4 \pm 2.1\text{mm}$ and two years later it was $8.2 \pm 3.7\text{mm}$. The difference was -1.53 ($p=0.1590$). The cutaneous reactivity to *D. farinae* was $4.6 \pm 2.2\text{mm}$ in the first evaluation and $8.3 \pm 4.7\text{mm}$ two years later. The difference was -2.63 ($p=0.0470$).

■ **Conclusions:** This study showed a significant reduction of specific cutaneous reactivity induced by *Dermatophagoides* SIT. In the control group the cutaneous reactivity to *Dermatophagoides* revealed an increment.

Key-words: Specific immunotherapy - *Dermatophagoides* - Cutaneous reactivity.

INTRODUCTION

Allergen immunotherapy, also referred to as specific immunotherapy (SIT), was introduced by Leonard Noon in 1991 (1). Since then, it has been used for the treatment of allergic disease, namely allergic rhinitis and/or bronchial asthma. The safety and the efficacy of SIT have been well documented, in double-blind, placebo-controlled clinical trials (2-5). SIT is the only treatment capable of modifying the natural course of respiratory allergy by interfering with the underlying immunological mechanisms. However the exact mechanism of SIT is not defined. SIT induces immunological and clinical responses and is related to an allergen reactivity reduction. Several immunological mechanisms have been implicated. The key events are the induction on specific anergy in peripheral T cells by IL-10 and the subsequent activation of distinct cytokine patterns (6, 7). The clinical improvement has been related to the immunological response. A specific cutaneous, bron-

chial and nasal reactivity reduction was documented (8, 9). A decrease of the immediate and late cutaneous specific response has been demonstrated. Indeed, just after Noon described the prophylactic inoculation against hay fever, Colmes and Rackemann (10) reported that 72% of 241 patients with ragweed hay fever had decreased sensitivity to ragweed by titrated scratch tests. The reduction in immediate and late cutaneous specific response has been confirmed (11-12). Several recent studies confirm the cutaneous specific reduction after SIT (13-16).

The aim of this study was to evaluate the specific cutaneous reactivity, two years after beginning SIT.

METHODS

We included 95 patients with bronchial asthma (BA) and/or allergic rhinitis (AR) to house dust mites (HDM), documented by skin prick tests (SPT) - T0. SPT were performed according to international guidelines (17) with commercial standardized extracts (ALKAbelló, Spain) of aeroallergens representative of the region, including HDM, cat and dog dander,

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molds, cockroach and pollens. Tests were carried out on the forearm using positive (histamine 1%) and negative (saline) controls. Lancets with 1 mm (ALKAbelló) were used for prick. All the tests were performed by the same person. The results were expressed as the mean of the major diameter of the wheal reaction plus it's orthogonal. Reactions >3mm were considered positive.

All the patients lived in the same region. The therapeutic approach included avoidance measures of exposure to HDM. 74 patients were submitted to subcutaneous SIT with a mixture of 50% *Dermatophagoides pteronyssinus* and 50% *Dermatophagoides farinae* commercial depot extract (ALKAbelló). The control group included the 21 patients without SIT. After a two years period (T1), the cutaneous reactivity was reassessed, by SPT.

The effect of SIT in the cutaneous response was measured as the difference between the wheal diameter of the first (T0) and the 2nd SPT (T1) to *D. pteronyssinus* and *D. farinae*. A positive difference indicated a cutaneous reactivity reduction.

SPT data have been analysed with the Student's t test for paired samples in each group.

RESULTS

Table 1 represents the demographic and clinical characteristics of both groups. The cutaneous reactivity to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, in both groups, is represented in table 2 and 3, respectively.

In the group of the 74 patients submitted to SIT, 21 presented negative SPT to *D. pteronyssinus* and *D. farinae* two years after beginning treatment. We observed that this subgroup presented lower symptoms duration, as well as lower cutaneous reactivity, compared to the subgroup that did not become negative (table 4).

The cutaneous reactivity to histamine was similar in both groups (table 5). The variation in histamine cutaneous reactivity, in both groups and between T0 and T1, had no statistical significance.

DISCUSSION

SIT is the only treatment capable of modifying the natural course of respiratory allergy by interfering with the underlying immunological mechanisms.

Efficacy of SIT has been well established (2-5). Several *in vivo* and *in vitro* parameters can be used to assess efficacy. *In vivo* subjective parameters includes medication and symptom scores, and *in vivo* objective parameters includes conjunctival, nasal, bronchial and cutaneous reactivity. They are widely used in the monitoring of SIT efficacy. *In vitro* parameters includes evaluation of immunological changes (18). All these variables must be taken into account in assessing the clinical efficacy of a specific desensitization treatment. None of these is considered the best criteria to be used for clinical end points. Indeed, the clinical improvement has been documented with several parameters such as the combined symptom/medication score and the specific and/or inespecific cutaneous, nasal, or

	Group with SIT	Group without SIT
n	74	21
M:F	1.1:1	1.3:1
Mean age $\pm$ SD (years old)	18.4 $\pm$ 13.9	25.1 $\pm$ 14.1
Symptoms evolution $\pm$ SD (years)	6.6 $\pm$ 6.2	9.7 $\pm$ 9.4
Bronchial asthma (%)	28.4	14.3
Allergic rhinitis (%)	22.9	33.3
Bronchial asthma + allergic rhinitis (%)	48.7	52.4

Table 1: Demographics and clinical characteristics.

Wheal diameter (mm)	T0	T1	diff.	95% CI		p
				Lower bound	Upper bound	
Group with SIT	6.9 $\pm$ 3.0	5.1 $\pm$ 2.9	1.87	0.97	2.76	p=0.0001
Group without SIT	4.4 $\pm$ 2.1	8.2 $\pm$ 3.7	-1.53	-3.71	0.66	p=0.1590

Table 2: Cutaneous reactivity to *Dermatophagoides pteronyssinus*.

Wheal diameter (mm)	T0	T1	diff.	95% CI		p
				Lower bound	Upper bound	
Group with SIT	6.2 $\pm$ 2.4	5.0 $\pm$ 3.7	0.93	-0.11	1.96	p=0.0790
Group without SIT	4.6 $\pm$ 2.2	8.3 $\pm$ 4.7	-2.63	-5.21	-0.04	p=0.0470

Table 3: Cutaneous reactivity to *Dermatophagoides farinae*.

	Group with SIT	Group without SIT
n	21	53
M:F	1.3:1	1.1:1
Mean age $\pm$ SD (years old)	19.9 $\pm$ 16.3	17.8 $\pm$ 12.9
Symptoms evolution $\pm$ SD (years)	5.1 $\pm$ 4.9	7.2 $\pm$ 6.6
Bronchial asthma (%)	33.3	28.2
Allergic rhinitis (%)	33.3	50.0
Bronchial asthma + allergic rhinitis (%)	33.3	21.8
SPT before IT (wheal diameter, mm)		
<i>Dermatophagoides pteronyssinus</i>	6.0 $\pm$ 2.8	5.7 $\pm$ 2.1
<i>Dermatophagoides farinae</i>	7.2 $\pm$ 3.0	6.4 $\pm$ 2.5

Table 4: Group submitted to SIT: SPT after two years of beginning SIT.

Wheal diameter (mm)	T0	T1	difference	p
Group with SIT	4.8 $\pm$ 1.0	5.1 $\pm$ 1.1	-0.29	p=0.0760
Group without SIT	5.7 $\pm$ 1.5	4.7 $\pm$ 1.0	0.10	p=0.3850

Table 5: Cutaneous reactivity to *Dermatophagoides farinae*.

bronchial reactivity. Some studies use the combination of these methods to confirm the SIT efficacy. The immediate and late cutaneous reaction to allergen is reduced (10-12). Several recent studies confirm the cutaneous specific reduction after SIT (13-16). SPT have been used to measure the cutaneous reactivity to allergen. It has been used to determine the allergen tolerance (14, 16, 19, 20) or the cutaneous specific reactivity expressed as the mean of the major diameter of the wheal plus its orthogonal (13, 21). We used this method because it reflects much better the real allergen sensitization magnitude. According to Malling H-J *et al.*, it can be a useful marker of SIT efficacy and it should be used every year during SIT (22). Other authors evaluated the variation of cutaneous reactivity during SIT at 6 months (13, 14), 1 year (15, 19, 20), 2 years (19, 20) and more as Palma-Carlos *et al* (16). They analysed the variation of the cutaneous reactivity during SIT during a 5 years follow-up study. In this study, the SPT reactivity was not significantly decreased after 2 years of SIT. Other authors demonstrated that the cutaneous specific reactivity is reduced at 2 years (19), and even earlier (14, 15).

Our study, which compares the cutaneous reactivity before and after 2 years of SIT, showed a specific cutaneous reactivity reduction induced by the treatment. We observed that cutaneous reactivity to *Dermatophagoides pteronyssinus* was significantly reduced ($p=0.0001$). The cutaneous reactivity to *Dermatophagoides farinae* was also reduced but without statistical significance ($p=0.0790$).

We also observed that the SPT became negative, 2 years after the beginning of SIT, in 21 out of the 74 patients submitted to *Dermatophagoides* SIT (21.3%). This fact is not referred in other studies. This subgroup of patients presented lower cutaneous reactivity to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and also lower period of time for evolution of symptoms, comparing to the subgroup that presented reduced cutaneous reactivity but did not become negative on SPT. The other demographic and clinical characteristics were similar. Probably, these clinical differences could explain the different cutaneous reactivity outcome observed.

The control group included 21 patients with similar demographic and clinical characteristics as compared to the group submitted to SIT. We observed that *Dermatophagoides* cutaneous reactivity has increased, 2 years after the first SPT. This increment had statistical significance concerning *Dermatophagoides farinae* ($p=0.0470$). Concerning *Dermatophagoides pteronyssinus* cutaneous reactivity, the increment had no statistical significance ($p=0.1590$).

The inespecific organ reactivity reduction has been well demonstrated, namely conjunctival(13), nasal(19) and bronchial (14) reactivity, after SIT. The inespecific cutaneous reactivity reduction is not well documented. In our study, we observed that the cutaneous reactivity to histamine presented some variations, but without statistical significance.

All these findings corroborate the *Dermatophagoides* cutaneous reactivity reduction induced by SIT. However, there are several studies demonstrating that the cutaneous reactivity is unchanged with SIT. These are not comparable studies, because a different methodology was used, namely evaluation at different periods of time.

Another interesting aspect is the hypothesis that SIT could modify the natural history of allergic disease. The PAT study (23) revealed that SIT prevents the development of asthma in children with seasonal rhinoconjunctivitis. In our study, we observed that *Dermatophagoides* desensitization treatment induced a specific cutaneous reactivity reduction, the *Dermatophagoides* cutaneous reactivity increased in the control group, and the non-specific cutaneous reactivity remained unchanged in both groups. As all the patients live in the same region and they were proposed to the same HDM exposure avoidance measures, we could hypothesize that SIT could modify the natural history of allergic disease, namely preventing the ongoing sensitization in respiratory allergic patients already submitted to avoidance exposure measures and medical treatment.

CONCLUSION

Our study shows the *Dermatophagoides* cutaneous reactivity reduction induced by SIT, as revealed by the specific cutaneous reactivity reduction in the group submitted to SIT, as well as compared to the group without SIT. Some of the patients submitted to SIT presented a negative SPT, two years after beginning the desensitization treatment. All these findings could be assumed as *Dermatophagoides* desensitization treatment efficacy is assessed. It also supports that the SPT has not only a diagnosis importance. Indeed SPT is a useful marker in the monitorization of SIT efficacy.

References

1. Noon L. - Prophylatic inoculation against hay fever. *Lancet* 1911;1572-1573
2. Bousquet J., Lockey R.-F., Malling H.-J. - World Health Organization position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53 (Suppl 44):1-42.

- 3; Abramson M.-J., Puy R.-M., Weiner J.-M. - Immunotherapy in asthma: an updated systematic review. *Allergy* 1999; 54(10):1022-1041.
4. Bousquet and the ARIA workshop group. - Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-S276.
5. Global Initiative for Asthma. - NHLBI/WHO Workshop report. 2002.
6. Akdis C.-A., Blaser K. - Mechanisms of allergen-specific immunotherapy. *Allergy* 2000;55:522-530.
7. Schmidt-Weber C.-B., Blaser K. - New insights into the mechanisms of allergen-specific immunotherapy. *Current Opinión Allergy Clin Immunol* 2005;5:525-530.
8. Nelson H.-S. - Immunotherapy for inhalants allergens. In: *Allergy Principles & Practice*, Middleton E, Reed C *et al.* Eds. St Louis, CV Mosby, 5th edition, 1998:1050-1062.
9. Passalacqua G., Canonica G.-W. - Allergen specific sublingual immunotherapy for respiratory allergy. *BioDrugs* 2001;15:509-519.
10. Colmes A., Rackemann F.-M. - Further observations on the changes in skin tests following specific pollen therapy. *J Allergy* 1932-3;4:473-480.
11. Bousquet J., Calvayrac P., Guerin B. *et al.* - Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. *In vivo* and *in vitro* parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734-744.
12. Nish W.-A., Charlesworth E.-N., Davis T.-L. *et al.* - The effect of immunotherapy on the cutaneous late phase response to antigen. *J Allergy Clin Immunol* 1994;93:484-493.
13. Muro M.-D., Tabar A.-I., Lizaso M.-T., Quirce S., Polo F., Garcia B.-E. - Cluster versus conventional immunotherapy in patients allergic to *Dermatophagoides pteronyssinus*: a controlled study of *in vivo* and *in vitro* parameters. *J Investig Allergol Clin Immunol* 1999;9(3):146-154.
14. Ferrer A., Garcia-Sellés J. - Significant improvement in symptoms, skin test and specific bronchial reactivity. *J Invest Allergol Clin Immunol* 2003;13(4):244-251.
15. Varney V.-A., Tabbah K., Mavroleon G., Frew A.-J. - Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003;33:1076-1082.
16. Palma-Carlos M.-L., Palma-Carlos A.-G. - Effect of specific immunotherapy on *skin prick tests: a 5 years follow-up*. *Allergy Clin Immunol Int: J World Allergy Org* 2005; Supplement 1:537-538.
17. Dreborg S., Frew A. - Position paper: allergen standardization and skin tests. *Allergy* 1993;48(Suppl 14):49-82.
18. Durham S.-R., Till S.-J. - Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157-164.
19. Tonnel A.-B., Scherpereel A., Douay B., Mellin B., Leprince D., Goldstein N., Delecluse P., Andre C. - Allergic rhinitis to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59(5):491-497.
20. Guez S., Vatrinet C., Fadel R., André C. - House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55(4):369-375.
21. Marogna M., Spadolini I., Massolo A., Canonica G.-W., Passalacqua G. - Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. *Allergy* 2004;59(11):1205-1210.
22. Malling H.-J., Weeke B. - Immunotherapy Position Paper. *Allergy* 1993;48(Suppl 14) 9-35.
23. Moller C., Dreborg S., Ferdousi H.-A., Halken S., Host A., Jacobsen L., Koivikko A., Koller D.-Y., Niggeman B., Norberg L.-A., Urbanek R., Valorvita E., Wahn U. - Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002 Feb;109(2):251-6.

