

NASAL IMMUNOTHERAPY IS EFFECTIVE IN THE TREATMENT OF RHINITIS DUE TO MITE ALLERGY. A DOUBLE BLIND PLACEBO-CONTROLLED STUDY WITH RHINOLOGICAL EVALUATIONS

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The aim of this paper is to evaluate the efficacy of intranasal hyposensitizing therapy in perennial rhinitis. 36 patients suffering from perennial allergic rhinitis (*Dermatophagoides*-sensitive) underwent a double blind placebo-controlled trial for a period of 8 months. The efficacy of nasal immunotherapy was evaluated by collecting symptoms score and evaluating objective rhinological parameters (nasal resistance, cross areas and volumes, mucociliary clearance times, specific nasal provocation threshold). A significant improvement ($p<0,01$) of symptom score of active against placebo group was observed after treatment. Also objective nasal parameters (total nasal resistances, mucociliary clearance, C-notch area, and provocative threshold) significantly ($p<0,01$) improved after treatment. Adverse local reactions were rare and did not interfere with the protocol. The results underline the efficacy and quickness of local nasal immunotherapy in the treatment of perennial allergic rhinitis documented by the improvement of subjective and objective parameters.

The first experiences on local nasal immunotherapy (LNIT) date back to the first decades of the 20th century by Dunbar (1), but important improvements are recorded from the seventies. Several Authors (2-6) have performed controlled studies on efficacy and tolerability of local intranasal immunotherapy in allergic rhinitis, at first with unrefined extracts, then with modified extracts in aqueous solution and today with lyophilized allergens in powder form at controlled granulometry (7-11).

This therapeutical procedure is non-invasive and well-tolerated and could be considered an effective alternative to the conventional specific subcutaneous immunotherapy in the treatment of allergic rhinitis or as a complementary tool in the treatment of allergic rhinitis associated with asthma.

The possibility of using allergen extract in "macronized" powder form allows clinical efficacy and safety to the treatment thanks to the stability and standardized dosages of the allergen. In fact, the use of powder form avoids all the problems

associated with the preparations of aqueous allergen solution administered into the nostril by means of squeeze bottles: a) poor stability as a result of container absorption and decomposition; b) difficulty in dosing an exact amount of allergen (it is impossible to use metered-dose inhaler because of the chemical incompatibility between the aqueous solution and propellant) (6).

Our study evaluates and documents the efficacy of this intranasal hyposensitizing therapy in perennial rhinitis caused by *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, monitoring over a period of 8 months subjective (symptom score) as well as objective nasal functionality parameters.

MATERIAL AND METHODS

In a double blind trial we evaluated for 8 months thirty-six patients (20 men and 16 women) suffering from perennial allergic rhinitis (*Dermatophagoides*).

They were all caucasian and were randomly divided

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into two groups according to a randomization table. Group 1 (18 subjects) received placebo and group 2 (18 subjects) received active allergen extracts.

In group 1 (11 men and 7 women) the mean age was 25,7 years (range 19-33), in group 2 (9 men and 9 women) the mean age was 22,9 years (range 18-30).

Patients provided written informed consent. Approval was obtained from the Ethic Committee of Medical School of University of Siena.

Inclusion criteria were:

- a) typical history of allergic rhinitis,
- b) 3+ - 4+ positive skin test to *Dermatophagoides*,
- c) Monosensitization to *Dermatophagoides*
- d) RAST positivity to *Dermatophagoides* of at least class 2
- e) positive response to specific nasal provocation test.

Exclusion criteria were:

- a) asthma,
- b) long-term use of nasal topical drugs,
- c) previous specific parenteral immunotherapy,
- d) pregnancy or lactation,
- e) nasal polyposis,
- f) severe septal deviation and nasal stenosis.

All patients received a clinical diary where they had to write their allergic symptoms during the treatment period. Specific symptoms recorded were: nasal obstruction, sneezing, nasal itching and watering. Patients graded each symptom daily for severity (Table I). We evaluated the symptoms all together summing periodically (4th, 12th, 20th, 28th, 32nd week) the score of all symptoms. Daily therapy was also recorded.

Rhinological examinations.

Before starting specific local immunotherapy, each patient underwent several clinical examinations to assess and monitor the degree of nasal obstruction and the efficacy of the therapeutical protocol. In fact, it is well known that even though nasal obstruction is a frequent symptom, common to different pathologies which affect the nasal cavities, both in acute and chronic form, its subjective evaluation is variable: often the patient finds difficulties in defining his sensation of nasal obstruction. On the contrary, we have some modern, reliable methods such as rhinomanometry, acoustic rhinometry and also the determination of Muco-Ciliary Transport Time for the objective evaluation of nasal conditions.

Our patients underwent:

1. ENT examination with endoscopy of the nasal cavities,
2. Active Anterior Rhinomanometry (AAR) (12)

using Memphis rhinomanometer (normal values of total nasal resistance 0.22-0.28 Pa sec/cc) in basal conditions and after decongestion. This is a dynamic measurement of nasal function that measures nasal resistances.

3. Acoustic Rhinometry (AR) using Stimotron Rhinoklack during basal condition and after decongestion.

Acoustic rhinometry is a rhinological diagnostic method which has attained an even wider diffusion in the last few years. Its success is due to its practical advantages: in a short time it allows to calculate some geometrical parameters of the nasal cavities (cross sectional areas, volumes). However acoustic rhinometry needs some standardization first of all with respect to the execution of the tests and retests. The reliability of the test was improved by using a variable geometry craniostat (13).

4. Mucociliary Clearance Test (MCT) using the colored indicator technique (charcoal powder with 3% saccharine, normal value of charcoal powder 8+/-3 minutes in children and 13+/-2 minutes in adults) (14). MCT time is the only parameter that allows to define a pathology of the mucosa in absence of alterations involving the respiratory function.

5. Skin prick test (Lofarma Allergens - Laboratorio Farmaceutico Lofarma, Milan, Italy),

6. RAST (Sferikit RAST - Lofarma Allergens, Laboratorio Farmaceutico Lofarma, Milan, Italy),

7. Specific Nasal Provocation Test (SNPT) performed according to the following steps (15):

- Basal AAR in order to exclude a respiratory stenosis incompatible with the test;
- Insufflation of lactose into the nasal fossa with the lowest resistance and, after 10 minutes, AAR (these results are considered to be the reference values).

- Administration into the same fossa of the powder containing the liophylized allergen titrated in Allergenic Units (AU) with reference to an international standard (Allerkin - Lofarma Allergens, Laboratorio Farmaceutico Lofarma, Milan, Italy). The stimulation starts with the lowest concentration (2.5 AU) and AAR is repeated after 10-15 minutes. If the resistances do not change we keep going with higher concentrations (5-10-20-40-60-80 AU) until the NPT is considered positive: an increase in unilateral resistance equal to or greater than 100%, in presence of a typical symptomatological crisis (itchness, sneezing, rhinorea, nasal obstruction, tearing, conjunctive hyperemia).

After this preliminary test, the patients were submitted to specific hyposensitizing therapy with the

prevailing identified allergen.

Administration procedure.

Intranasal immunotherapy was carried out by self administration of allergen extract in macronized powder form. This product (Allerkin - Laboratorio Farmaceutico Lofarma, Milan, Italy) consisted of a 50/50 mixture of *Dermatophagoides pteronyssinus* and *D. farinae* in powder form incorporated into an excipient mass (lactose) and dehydrated. For particle-size analysis the powder was suspended in silicone oil, sonicated and analyzed with a laser-light-powered analyzer (model 715 wavelength 632.8, Cilas Alcatel, Marcoussis, France): 75% of the particles were between 15 and 80 μm with partition value (50/50%) around the dimension of 45 μm . This product is titrated in allergenic units (5, 10, 20, 40, 60, 80, 120, 160, 240 AU) and enclosed in hard gelatin capsules characterized in dosages by different colors. The determination of major allergens has been performed according to Luczynska et al (16). The maintenance dose, corresponding to 240 AU, resulted to contain 50 ng of major allergens intended as the sum of *Der p 1* and *Der f 1*. The placebo was lactose with the cover-cap similar to that of the drug. The powder was administered with a manual nasal insufflator (MIAT, Milan, Italy), a manual pneumatic pump which provides the nebulization of the entire content of a capsule, previously perforated, into the nostril by means of a nozzle. In order to avoid diffusion of the allergen into the bronchial tree, patients were asked to vocalize during each administration.

Immunotherapy program

During the first therapy period (10 weeks) each patient underwent daily inhalation of the powder allergen (1 cap for each nostril, one day into the right nostril and the next day into the left, and so on) starting from the dosage of 2.5 AU through the higher concentrations until 240 AU or the highest tolerated dosage. In case of allergic symptoms (nasal itching, nasal obstruction, sneezing, watering) the patient could stop the therapy (for 1 day only) and could take topic or systemic antihistamines. The patients were instructed to use these drugs "when needed". The second therapy period (maintenance) lasted until the 32nd week with various dosages (80, 120, 160 or 240 AU) once a week according to the patient's clinical evaluation. In addition, each patient periodically (4th, 8th, 12th, 16th, 20th, 24th, 28th, 32nd week) underwent the functional tests reported previously. *The NPT was performed at the beginning*

and at the end of the therapy.

Statistical analysis was done with non parametric tests. The Wilcoxon W test was used for paired data. Statistical analysis was performed with SPSS program for Windows.

RESULTS

After 32 weeks of treatment a positive result was observed in the mean value of symptoms score which was significantly lower ($P < 0.01$) in the active allergen extract group than in the placebo group. The difference between the two groups was statistically significant starting from the 12th week (Fig. 1). Active anterior rhinomanometry showed a significant decrease of total nasal resistance ($p < 0.01$) in the active patients from the 12th week, whereas no difference was observed in the placebo group (Fig. 2). The nasal mucociliary transport time showed a dramatic improvement only in treated patients (Fig. 3).

Acoustic rhinometry: at the end of treatment the C notch area, which corresponds to the head of the inferior turbinate, was significantly increased ($p < 0.01$) in the active group patients, in comparison with the pre-treatment value ($p < 0.01$) (Fig. 4) The difference between the two groups was statistically

Tab. I. Symptom score card

-	NASAL OBSTRUCTION
0=	breathing through the nose freely and easily
1=	slight difficulty breathing through the nose
2=	moderate difficulty breathing through the nose
3=	breathing through the nose very difficult/impossible
-	SNEEZING
0=	absent
1=	occasionally present (less than 5 episodes per day)
2=	troublesome episodes of sneezing (5-10 episodes/day)
3=	frequent, troublesome episodes of sneezing (>10 episodes/day)
-	NASAL ITCHING AND WATERING
0=	absent
1=	present, mostly unaware of it
2=	present, but not a persistent distraction
3=	present, a persistent distraction

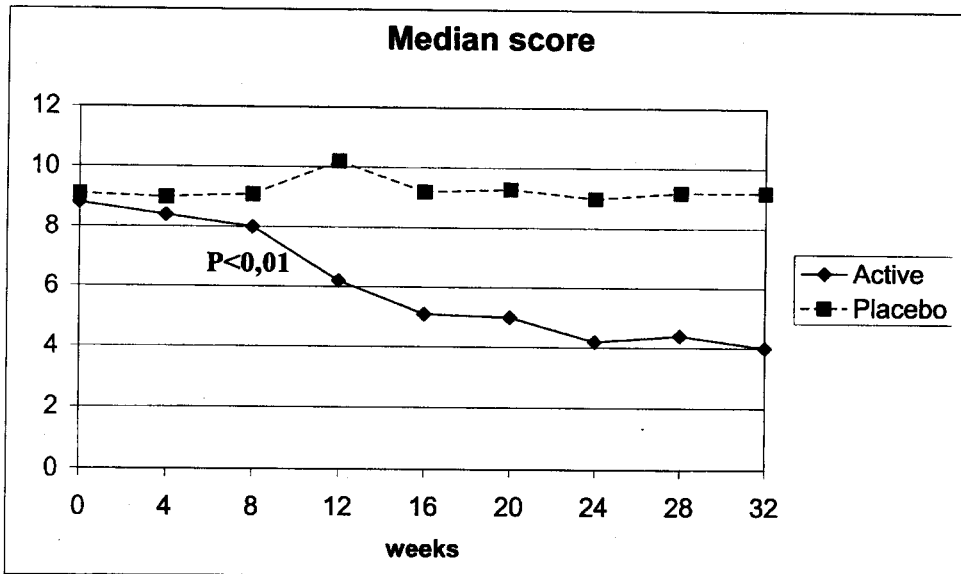


Fig. 1. Median monthly score of all symptoms during local intranasal immunotherapy (LNIT) in active and placebo group.

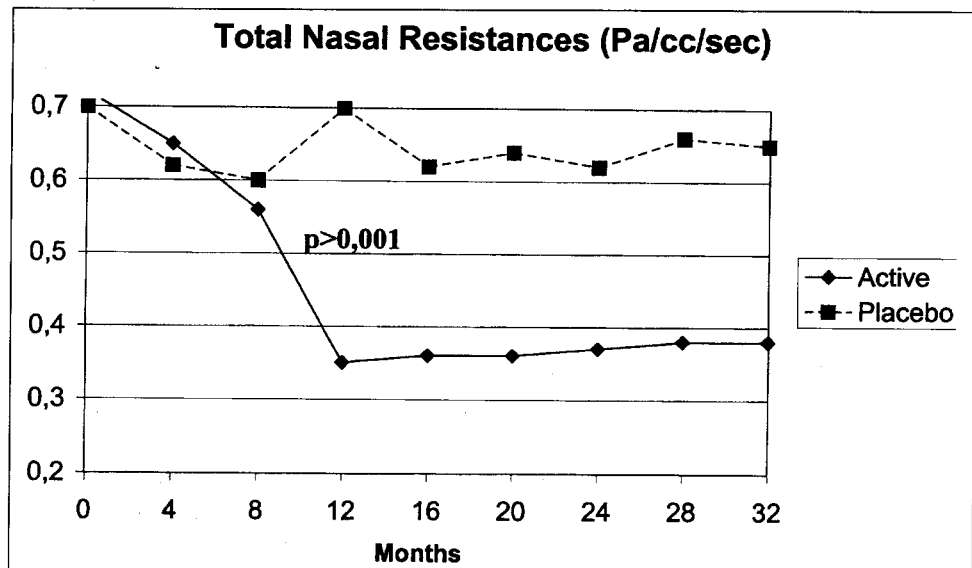


Fig. 2. Median total nasal resistance measured by AAR in active and placebo group during the follow-up.

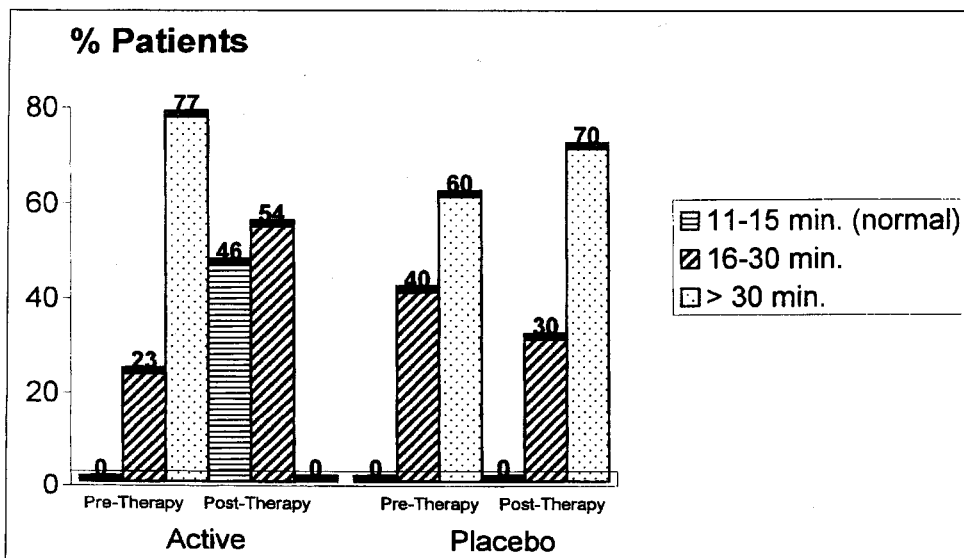


Fig. 3. Nasal mucociliary transport times before and 8 months after LNIT in active and placebo group.

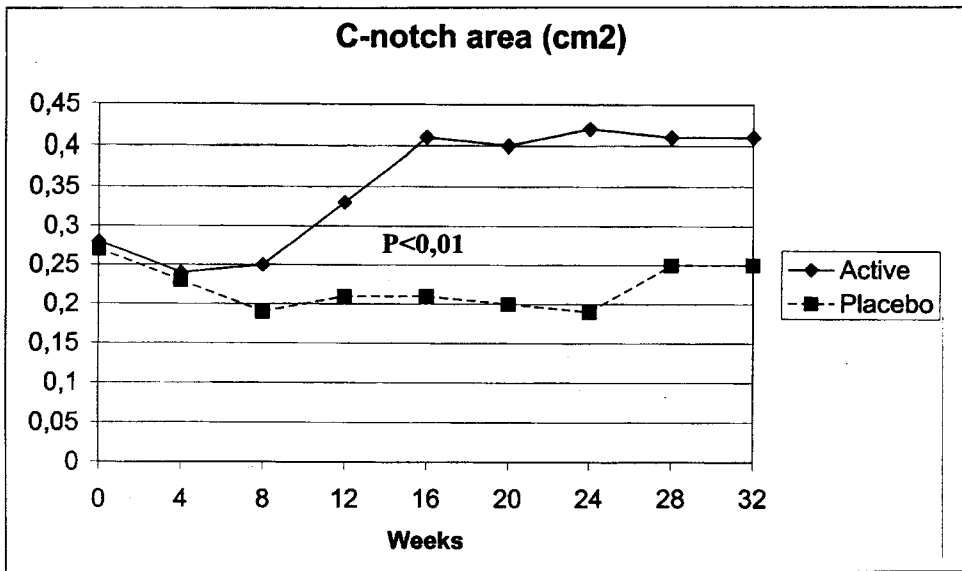


Fig. 4. Median cross areas measured at the level of inferior turbinate by means of acoustic rhinometry in active and placebo group during the follow-up.

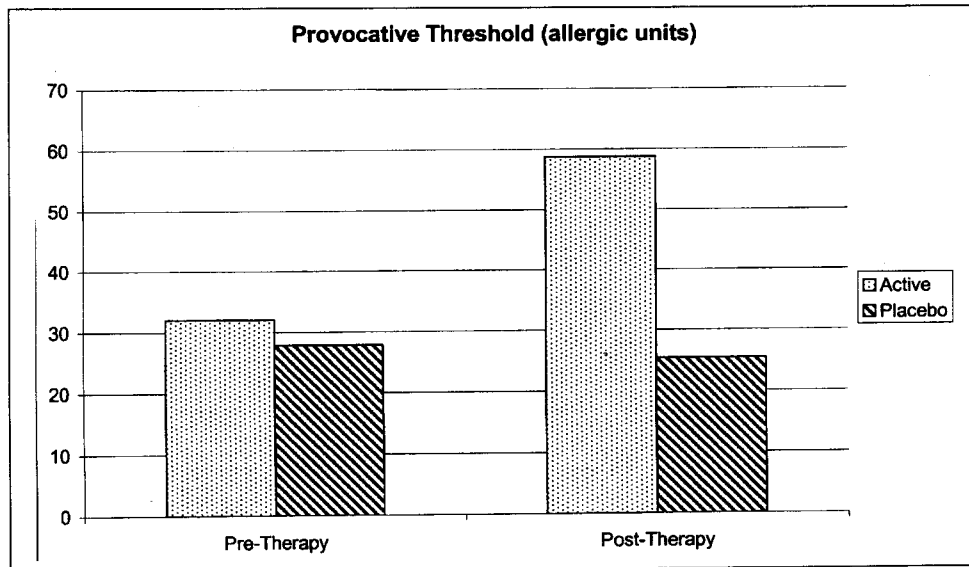


Fig. 5. Allergen sensitivity evaluated by nasal provocation test in active and placebo group before and 8 months after LNT.

significant starting from the 16th week. Also the basal value of the nasal volumes were increased (+20%), according to the rhinomanometric values, in the active group at the end of the treatment. Nasal sensitivity to *Dermatophagoides* allergens significantly decreased after treatment ($p < 0.01$) in the active allergen extract patients, whereas no difference was observed in the control group (Fig. 5).

At the end of the study there were no systemic reactions. During the treatment we found only some local side effects that did not interfere with the dose schedule.

Concerning the use of topic or systemic antihistamines, 3 patients of the active group and 2 of the placebo group used them but only occasionally and in any case starting the treatment (mean value 5 times in the first two weeks of treatment).

DISCUSSION

This study investigated local nasal immunotherapy with allergen extracts (powder form) in patients suffering from perennial allergic rhinitis caused by *Dermatophagoides* species.

In the past years the use of unmodified aqueous extracts showed good results, but important local side effects, not tolerated by the patients, were observed (4). On the contrary, low doses were well tolerated but did not show any clinical efficacy (17). The use of chemically modified allergen showed a good clinical efficacy with small local side effects (18-20). The more recent allergen extracts in powder form are characterized by a good clinical efficacy associated to high tolerability also in children linked to the absence of systemic side effects and scarce local side effects.

Our program of immunotherapy is different from other previous studies (4). In fact, instead of the administration of allergen every second day in alteranate nostrils, we had daily administration in alternate nostrils. This permitted a reduction of the length of treatment in the first therapy period and the limitation of allergen administration to once a week during the second maintenance period. Total length of treatment was thus shorter: only 32 weeks.

It is well known that specific immunotherapy is conducted, according to international guidelines for a period of 2-3 years or more, until a substantial relief in symptomatology has been achieved. As regards the intranasal immunotherapy administration schedule, it has been designed some years ago on "alternate days" basis. This choice was due to the expectation of late reactions to the allergen administration, and the desire to avoid an overlapping between a possible immediate reaction to the allergen and the late reaction to the previous administration (9).

The wide clinical experience with this product acquired in the last years demonstrated that late reaction were absent, and induced us to design a shorter and more practical administration schedule. In fact, in the conventional schedule the increasing dose phase lasts 14 weeks, while in the schedule followed by us in present study it lasted 10 weeks.

On this basis we decided to shorten the total treatment period for the present experimental study. At the end of the treatment we reported a significant improvement of symptoms score and of the results of objective rhinological parameters (nasal resistance, cross areas and volumes, muco-ciliary clearance time). Concerning the subjective symptomatology, we obtained a dramatic decrease of the mean score of all symptoms in treated

patients. Total nasal resistances significantly decreased after therapy in the treated group even if normal values were not obtained. The result of therapy was also indicated by the minor swelling of the head of the inferior turbinate as measured by AR. We registered an improvement of nasal mucociliary transport time in the active group where 46% of the patients showed a normal time range after therapy, while in the placebo group no patients showed a normal time range.

Finally, in treated patients the provocative threshold of NPT significantly increased after therapy demonstrating a decrease of nasal sensitivity to *Dermatophagoides*. Although our data are preliminary, we suggest that nasal specific hyposensitizing therapy could be considered a good alternative to systemic immunotherapy or symptomatic therapy in the treatment of patients affected by allergic rhinitis without asthma, because it produces a prompt and effective clinical response with no side effects. Besides, the quickness of the improvement of symptoms achieved in the present study (during the 3rd month of treatment the difference between active and placebo treated groups was evident) must be underlined. The sporadic use in few patients for short periods of antihistamines "when needed" could not interfere with the efficacy of the treatment; on the contrary could be considered as a demonstration of the good tolerability of LNIT.

Furthermore, in this self-administered treatment, the patient avoids injections and needs only a few clinical check-ups.

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