

# RHINITIS AND ASTHMA CO-MORBIDITY IN RESPIRATORY ALLERGY DUE TO HOUSE DUST MITE: RESULTS OF AN OBSERVATIONAL OPEN CONTROLLED PARALLEL GROUP STUDY IN REAL-LIFE SETTING

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## SUMMARY:

**Background:** Some aspects of allergic march still need to be addressed. To prevent the onset of the march is not, at present, a very realistic aim, although therapeutic instruments are available to delay and, if possible, to stop it. We attempted to clarify these points in an observational open controlled three-parallel group study in a real-life setting.

**Methods:** 3838 patients with respiratory allergy due to house dust mite have been enrolled in this observational study. 2200 patients with rhinitis and/or intermittent or mild persistent asthma, poorly responsive to standard pharmacological therapy (SPT) were treated for three years with SPT associated or not with specific immunotherapy (SIT). Symptom medication scores, pulmonary function test (PFT) and methacholine (MCh) challenge were performed at the beginning and at the end of the study. 1638 pure rhinitics, responsive to SPT, enrolled as a control group, used self-medication (SM) on demand to assess the incidence of asthma in non-treated patients with standard therapeutic protocols.

**Results:** 694 patients have been treated with SPT+SIT, 1506 with SPT and 1638 with SM. Co-morbidity rhinitis-asthma incidence was higher in the SM group (an overall 69.27% including asthma and bronchial hyperreactivity). Persistent rhinitis proved more often to be associated with asthma than intermittent rhinitis. Likewise, the moderate-severe forms compared to the mild ones. The addition of SIT to SPT reduced the allergic march in all patients.

**Conclusions:** In everyday clinical practice too, SIT proves its efficacy in the treatment of allergic march. Patients with moderate-severe persistent rhinitis appear as the ideal candidates for this therapy.

**Key-words:** Specific Immunotherapy - Allergic March - Observational Study.

## List of abbreviations:

SIT: Specific Immunotherapy  
SCIT: Subcutaneous Immunotherapy  
LNIT: Intranasal Immunotherapy  
SLIT: Sublingual Immunotherapy  
MCh: Methacholine  
A: Asthma  
R: Rhinitis  
H: Bronchial Hyperreactivity  
PFT: Pulmonary Function Test  
SPT: Standard Pharmacological Treatment  
SM: Self-Medication  
GINA: Global Initiative for Asthma  
Sgaw: specific airway conductance  
Raw: airway resistance

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## INTRODUCTION

The association of asthma with rhinitis has been acknowledged as part of ordinary medical experience. It has been confirmed by a number of epidemiologic studies which, however, owing to their methodologic and classifying limits, have not so far produced uniform data.

Corren (1) in his study indicated that 90% ca. of the overall asthmatic patients had symptoms correlated with allergic rhinitis against 5 to 20% of the general population of patients, whereas 38% of rhinitic patients had also asthmatic symptoms against 3 to 5% of the total number of patients.

In spite of clinical and epidemiologic evidence, only recently were allergic rhinitis and asthma acknowledged as clinical symptoms of only one disease bound together by complex physiologic and pathogenic correlations, so that the World Health Organization worked out a position paper to establish the guidelines for diagnosis and therapy of allergic diseases (2).

The co-existence of allergic rhinitis and asthma not only worsens the quality of life of allergic patients (3)

but it also increases dramatically - up to 46% - the costs of treatment as compared to the lower costs of patients with only asthma.

The prevalence of allergic rhinitis, as assessed by a multicentric study on the general population of patients within the European Community Respiratory Health Survey, amounts to 18.5% in Northern Italy, of which 11.2% is of the perennial type, 29.6% of the seasonal type and 51.5% of the mixed type with proved allergic sensitization in 89% of patients with seasonal rhinitis and in 69% of patients with perennial rhinitis (5). Moreover, as already pointed out, the considerable increase in the association asthma-rhinitis in the last two decades cannot be overlooked (13). The percentages in the young adults - especially in patients with mite sensitization - are far too high and to treat only upper or lower respiratory tract is at present a nonsense from the scientific, methodologic and ethical points of view. Today, the ARIA position paper (2) underlines that the allergic symptoms are the local expression of a systemic pathology in which the respiratory tract (broadening the meaning of the word "respiratory tract" to the mucous membranes exposed to the respiratory allergens not to exclude other allergic diseases that very often coexist such as conjunctivitis, otitis, sinusitis, pharyngitis and, to a lesser degree, laryngitis) is considered as a global problem referred to as "one airway, one disease" (8). Owing to the high risk of developing asthma in patients suffering from allergic rhinitis and other complications and to the increase of both economic and social costs because of the co-existence of the two diseases, a number of international organizations, among which in particular WHO, strive to determine the risk factors and prevent the onset of allergic rhinitis complications. Considering that a few studies on rhinitis-asthma comorbidity existed in Italy, in the mid-eighties we prepared an observational clinical epidemiologic study on a large population of outpatients with house dust mite allergic rhinitis seen at the Allergy Unit, Cuasso al Monte, Macchi Hospital Foundation, Varese. These patients were evaluated in an observation period between 1987 and 2002. According to the data obtained from the analysis of the immunologic and functional clinical profile and of the clinical history, the causes of rhinitis, at the time of diagnosis, were classified as indicated in Tab.2 together with the data on asthma prevalence for each rhinitic etiologic factor.

The initial "impairment" degree of the patients with rhinitis (subdivided into seasonal and perennial) was evaluated on the basis of persistence or abatement of symptoms (sporadic or perennial) and their severity (scored as mild, moderate and severe) according to ARIA guidelines (2).

In the study of asthma a mixed clinical-physiopathologic criterion was followed and clinical asthma (with

bronchial obstruction already elicited from basal spirometry) was distinguished from bronchial hyperreactivity (bronchial obstruction induced after bronchial stimulation): both conditions from the epidemiologic point of view fell into the category of "asthma" whereas, from the clinical point of view, the evolution of the two conditions was considered separately, since bronchial hyperreactivity is only one of the possible risk factors in the onset of persistent asthma, with a consequent different impact on the chronic obstructive lung disease.

## GOALS TO REACH

The study aimed at:

- assessing the prevalence of asthma in patients with house dust mite allergic rhinitis (first end-point);
- assessing the incidence of patients with rhinitis evolving into asthma (second end-point);
- evaluating the existence of a relation between initial severity and duration of rhinitis and subsequent appearance of asthma (third end-point);
- comparing the preventive efficacy of immunologic therapies (SIT: specific immunotherapy) with pharmacotherapies (oral H1 antihistamines, inhaled corticosteroids, beta2-agonist bronchodilators on demand) in the control of allergic march from rhinitis to asthma (fourth end-point).

## STUDY DESIGN (fig. 1)

As shown in table 2, 18% ca. of the rhinitic patients seen in our Allergy Unit presented pathogenic allergic response to perennial inhalants (*Dermatophagoides*). The study of the functional respiratory pattern also showed the combination of rhinitis and bronchial asthma in 30% of these patients (table 2) (first end-point) (1449 out of 4830 patients, of which 956 had hyperreactivity and 493 clinical asthma). After a baseline evaluation patients were controlled in a twelve-month observational period during which they were treated with preventive symptomatic pharmacological therapy to prevent both asthmatic and rhinitic symptoms where necessary or, in case of pure rhinitic patients (without any apparent clinical and functional suffering of the lower airways) simply focus on the upper respiratory tract. At the end of the observational period patients with unsatisfactory clinical response (clinical scores = drug scores + symptom scores >50% compared to baseline) were randomized in three groups:

- **GROUP A:** patients continued treatment for thirty-six months receiving only intermittent pharmacological symptomatic therapy (mild or moderate-severe intermittent rhinitis);

➤ **GROUP B:** patients continued treatment for thirty-six months receiving continuative standard pharmacological symptomatic therapy (mild or moderate-severe persistent rhinitis);

➤ **GROUP C:** patients continued treatment for thirty-six months receiving pharmacological therapy associated with specific immunotherapy (SIT) (Anallergo Srl, Florence, Italy) (rhinitis + intermittent or mild-persistent asthma).

At the end of the 36-month period of treatment the functional profile of each patient was reevaluated (spirometry with bronchial reactivity) to assess the efficacy of SIT as compared to conventional pharmacotherapy in preventing rhinitis from evolving into asthma (table 4) (fourth end-point).

In the group of patients initially responsive to conventional pharmacotherapy the natural evolution of the allergic march, disregarding the therapeutic strategies adopted (both conventional and non-conventional) (table 3), was the object of evaluation. To this end, the subset of patients initially suffering from "pure" rhinitis after a baseline clinical and functional evaluation were studied again during the following thirty-six-month period and were submitted to pulmonary function test and MCh challenge. In this observational period these patients received self-medication mainly to assess:

- the incidence of rhinitis-asthma co-morbidity (second end-point);

- the natural evolution of the allergic march from rhinitis into asthma according to the initial severity and duration of rhinitis (third end-point).

## PATIENTS

■ Patients whose demographic data at baseline are indicated in table 1 were evaluated through the following tests:

➤ skin prick tests (SPT) were performed according to the latest international guidelines (6) with commercial standardized extracts (Alk Abello, Lainate, Milan, Italy) of the following allergens: house dust mites, grasses, parietaria, cat dander, dog dander, birch, olive, ragweed, mugwort, *Alternaria* and *Cladosporium*. Tests were carried out on the forearm, using positive (histamine 1%) and negative (saline) controls for comparison. The results were expressed as the mean of the major diameter ( $D_1 + D_2/2$ ) of the wheal. Reactions greater than 5 mm. were considered positive.

➤ PFT were performed by a computerized spirometer (Masterlab Yaeger, Wurzburg, Germany) associated to MCh challenge in the control patients in the same period of the year (November to February). A dosimeter (Yaeger, Wurzburg, Germany) activated by the inhalatory effort was used and increasing doses of MCh were administered: 30-60-120-240-390-690-1290 micrograms ( $\mu$ g). The test was considered positive

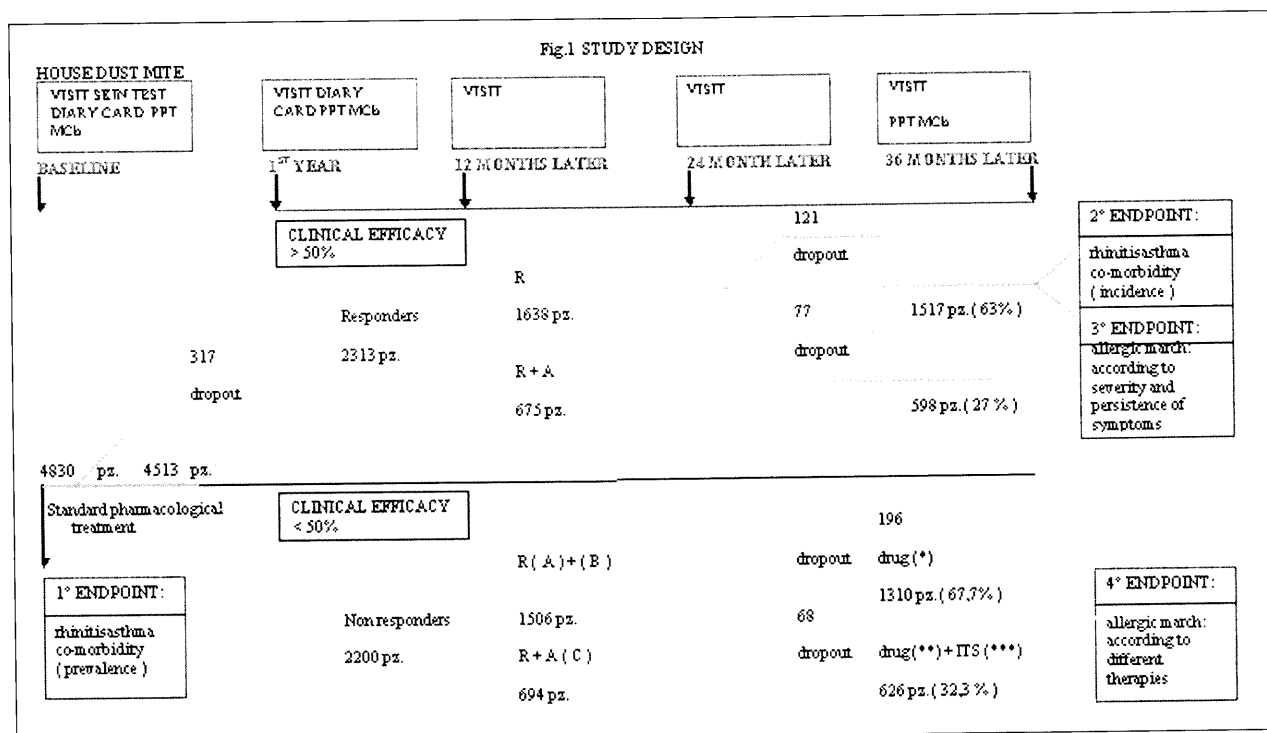


**Figure 1:** Study design. (A): intermittent rhinitis group; (B): persistent rhinitis group; (C): rhinitis with intermittent/mild persistent asthma group; Drug (\*): oral anti-histamines + topic nasal steroids; Drug (\*\*): oral anti-histamines + topic nasal and bronchial steroids + 2 short-acting on demand; SIT (\*\*\*): LNIT = 98 pz.; SLIT = 464 pz.; SCIT = 64 pz.

(MCh+) if the dose causing a fall of 20% of FEV1 was equal or less than 1290 mg. Patients without clinical evidence of asthma and negative MCh challenge (MCh-) were considered pure rhinitics; patients with negative clinical evidence of asthma and positive MCh challenge (MCh+) were considered affected by bronchial hyperreactivity; patients with recurrent episodes of wheezing, cough or chest tightness (diurnal or nocturnal) and with baseline bronchial obstruction (Raw >

35% and/or Sgaw < 35% of theoretic value) or positive MCh challenge (MCh+) were considered asthmatics.

➤ At the baseline and after the run-in period (twelve months later) all the patients were instructed to fill a diary card during the period of significant exposure to their causal allergens in Northern Italy (from November to February for Dermatophagoides). The following symptoms were considered: nasal itching, sneezing, rhinorrhea, nasal obstruction, cough, whee-

|                  | 1628 PATIENTS      |                | 567 PATIENTS     |                | 939 PATIENTS     |                | 694 PATIENTS   |                |
|------------------|--------------------|----------------|------------------|----------------|------------------|----------------|----------------|----------------|
|                  | CONTROL GROUP (SM) |                | SPT INTERMITTENT |                | SPT CONTINUATIVE |                | SPT + SIT      |                |
| SEX              | M                  | F              | M                | F              | M                | F              | M              | F              |
| SEX              | 870                | 768            | 298              | 269            | 571              | 368            | 360            | 334            |
| AGE RANGE        | 13-41              | 14-42          | 10-36            | 13-35          | 9-45             | 8-38           | 11-37          | 7-35           |
| MEAN AGE<br>+ SD | 23,7<br>+ 8,49     | 23,4<br>+ 8,31 | 22,2<br>+ 8,42   | 22,0<br>+ 7,65 | 20,3<br>+ 7,34   | 22,0<br>+ 7,39 | 20,9<br>+ 7,29 | 20,4<br>+ 8,00 |

**Table 1:** Demographic data at baseline.

|                                                                 |                                               | %  | CO-MORBILITY<br>WITH ASTHMA(%) |
|-----------------------------------------------------------------|-----------------------------------------------|----|--------------------------------|
| 1) INFECTIVE<br>RHINITIS(28%)                                   | VIRAL                                         | 15 | 26                             |
|                                                                 | BACTERIAL                                     | 12 | 18                             |
|                                                                 | OTHER INFECTIVE AGENTS                        | 1  | 4                              |
| 2) ALLERGIC<br>RHINITIS (38%)                                   | INTERMITTENT                                  | 9  | 30                             |
|                                                                 | OR                                            | 7  | 31                             |
|                                                                 | PERSISTENT                                    | 3  | 26                             |
|                                                                 | HOUSE DUST                                    |    |                                |
|                                                                 | MITES                                         | 18 | 30                             |
|                                                                 | OTHER ALLERGENS                               | 1  | 21                             |
| 3)ALLERGIC AND<br>NON ALLERGIC<br>OCCUPATIONAL<br>RHINITIS (6%) | INTERMITTENT                                  | 2  | 10                             |
|                                                                 | PERSISTENT                                    | 4  | 16                             |
| 4) DRUG RELATED<br>RHINITIS (3%)                                | ASPIRIN SENSITIVITY                           | 2  | 27                             |
|                                                                 | OTHER DRUGS                                   | 1  | 15                             |
| 5)HORMONAL<br>RHINITIS(1%)                                      |                                               | 1  | 3                              |
| 6) OTHER<br>RHINITIS (14%)                                      | CHEMICAL AND PHYSICAL                         |    |                                |
|                                                                 | INFLAMMATORY AGENTS                           | 5  | 2                              |
|                                                                 | FOODS                                         | 1  | 1                              |
|                                                                 | NARES( NON ALLERGIC<br>EOSINOPHILIC RHINITIS) | 6  | 19                             |
|                                                                 | EMOTIONAL                                     | 1  | 12                             |
|                                                                 | ATROPHIC                                      | 1  | 2                              |
| 7) IDIOPATHIC<br>RHINITIS (10%)                                 |                                               | 10 | 5                              |

**Table 2:** Rhinitis and asthma co-morbidity: observational evaluation.

zing and conjunctival itching/redness. The following medications were allowed: oral antihistamines (Loratadine or Cetirizine 10 ug, 1 tablet/day) topic nasal and/or bronchial corticosteroid ( beclometasone dipropionate 250 mgr 1-2 puffs b.i.d.), inhaled albuterol (100 ugr 1-2 puffs on demand).

Each symptom was scored as 0= absent, 1= mild, 2 = moderate, 3 = severe. In addition, each dose of each rescue drug was scored as 1. For each patient the monthly sum of drugs + symptoms was obtained, the mean sum of the months in each period of observation ( four months) was used for statistical analysis.

➤ SIT was also administered continuatively for not less than three years according to the latest international guidelines (10-11) and to therapeutic protocols suggested by the producer (Anallergo srl - Florence, Italy) both for subcutaneous immunotherapy (SCIT) and for local nasal immunotherapy (LNIT) and sublingual immunotherapy (SLIT).

➤ Patients who had received previous courses of immunotherapy, sensitized to others perennial allergens, with anatomical abnormalities of the upper respiratory tract, suffering from malignancies or systemic immunological disorders, with pregnancy, who used beta-blockers or corticosteroids for long-lasting periods, with lung and/or heart and/or neurologic diseases were excluded from this study. Moreover, only the patients with intermittent or mild persistent asthma were enrolled in this study according to GINA guidelines (12) (with FEV1 in the range of normality, i.e. > 79% of individual theoric value).

## STATISTICAL ANALYSIS

Comparison between frequencies have been tested by Fisher Exact test or Pearson Chi-square test (14). The probability level has been computed using a complete randomisation method ( permutation or

|                                                     |                         | Light                   |        | Moderate/Severe |                            |
|-----------------------------------------------------|-------------------------|-------------------------|--------|-----------------|----------------------------|
|                                                     |                         | N                       | %      | N               | %                          |
| Intermittent                                        | Rhinitis                | 94                      | 14.2   | 63              | 7.4                        |
|                                                     | Hyper-reactivity        | 37                      | 5.6    | 101             | 11.8                       |
|                                                     | Asthma                  | 33                      | 5.0    | 81              | 9.5                        |
|                                                     | TOTAL                   | 164                     |        | 245             |                            |
|                                                     | X <sup>2</sup> = 41.603 | df = 2                  |        |                 | P <sub>exact</sub> < 0.001 |
| Persistent                                          | Rhinitis                | 195                     | 29.5   | 114             | 13.3                       |
|                                                     | Hyper-reactivity        | 176                     | 26.6   | 219             | 25.6                       |
|                                                     | Asthma                  | 127                     | 19.2   | 277             | 32.4                       |
|                                                     | TOTAL                   | 498                     |        | 610             |                            |
|                                                     | X <sup>2</sup> = 71.011 | df = 2                  |        |                 | P <sub>exact</sub> < 0.001 |
| Intermittent vs Persistent light rhinitis           |                         | X <sup>2</sup> = 23.254 | df = 2 |                 | P <sub>exact</sub> < 0.001 |
| Intermittent vs Persistent moderate/severe rhinitis |                         | X <sup>2</sup> = 16.632 | df = 2 |                 | P <sub>exact</sub> < 0.001 |

**Table 3:** Evolution from rhinitis to asthma of mite-positive rhinitis patients following a three year treatment, considering both the duration and severity of the initial pathology (rhinitis).

| THERAPY                              | EVOLUTION |                  |        | Total | X <sup>2</sup> | df      | P <sub>MonteCarlo</sub> |         |
|--------------------------------------|-----------|------------------|--------|-------|----------------|---------|-------------------------|---------|
|                                      | RHINITIS  | HYPER-REACTIVITY | ASTHMA |       |                |         |                         |         |
| INTERMITTENT SPT                     | N         | 155              | 209    | 122   | 486            | 23.815  | 2                       | < 0.001 |
|                                      | %         | 31,9             | 43,0   | 25,1  | 100            |         |                         |         |
| CONTINUATIVE SPT                     | N         | 327              | 286    | 211   | 824            | 25.197  | 2                       | < 0.001 |
|                                      | %         | 39,7             | 34,7   | 25,6  | 100            |         |                         |         |
| CONTINUATIVE SIT                     | N         | 495              | 81     | 51    | 627            | 589.206 | 2                       | < 0.001 |
|                                      | %         | 78,9             | 12,9   | 8,1   | 100            |         |                         |         |
| Overall                              | N         | 977              | 576    | 384   | 1937           | 312.275 | 4                       | < 0.001 |
|                                      | %         | 50,4             | 29,7   | 19,8  | 100            |         |                         |         |
| INTERMITTENT SPT vs CONTINUATIVE SPT |           |                  |        |       | 17.118         | 2       | < 0.001                 |         |
| CONTINUATIVE SIT vs INTERMITTENT SPT |           |                  |        |       | 639.172        | 2       | < 0.001                 |         |
| CONTINUATIVE SIT vs CONTINUATIVE SPT |           |                  |        |       | 404.090        | 2       | < 0.001                 |         |

**Table 4:** Prevention of the evolution to asthma of mite-positive rhinitis patients following a three year treatment: comparison between intermittent SPT, continuative SPT, and continuative SIT. Chi-square test results are reported.

exact test;  $P_{\text{exact}}$ ) or by a Monte Carlo (15) simulation based on a 10,000 sampled tables ( $P_{\text{Monte Carlo}}$ ) when computation was not possible. The type I error ( $\alpha$ ) has been set at the 0.01 level. Multiple comparisons of frequencies were taken into account by correcting the  $\alpha$  level using the Dunn-Sidak significance level correction method:  $\alpha' = 1 - (1 - \alpha)^{1/k}$ , where  $k$  is the number of comparisons (14); in our case, comparing the effect of the 3 different therapies on the evolution of the rhinitis, the new significance level was set to  $\alpha' = 0.003$ .

## RESULTS

In the study design 4830 patients were evaluated in the period 1 January 1987-1 December 2002. 4051 patients concluded the follow-up (779 drop-outs):

- 1936 patients with *Dermatophagoides* allergic rhinitis (R) with possible association of asthma (R+A), poorly responsive to conventional drug therapy after a twelve-month observational period (clinical efficacy  $<50\%$  compared to baseline) were subdivided as follows: 486 patients were suffering from intermittent rhinitis (Group A) and 824 from persistent rhinitis without co-existing asthma were treated for the following thirty-six months only with traditional drug therapy, whereas 626 patients (Group C) (32.3%) with persistent rhinitis and bronchial hyperreactivity and/or intermittent or mild-persistent asthma received pharmacotherapy plus specific immunotherapy (SIT).

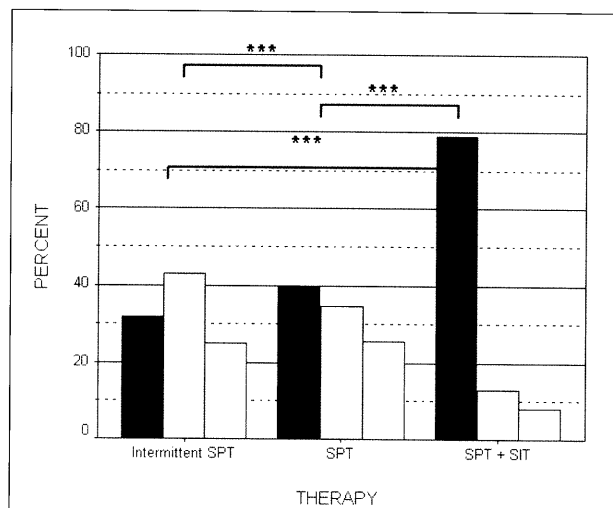


**Figure 2:** Clinical evolution of rhinitis patients positive to mite, submitted to occasional intermittent Standard Pharmacological Therapy, continuous Standard Pharmacological Therapy, and to continuous Standard Pharmacological Therapy + SIT. Black stripe = rhinitis; grey stripes = hyper-reactive; white stripes = asthma. In figure are also reported the results of the Pearson chi-square test to compare evolution of rhinitis following the different therapies. Chi square test results are reported: \* =  $P_{\text{Monte Carlo}} < 0.05$ ; \*\* =  $P_{\text{Monte Carlo}} < 0.01$ ; \*\*\* =  $P_{\text{Monte Carlo}} < 0.001$ ; ns = not significant.

- 2115 patients with house dust mite rhinitis of which 1517 had pure rhinitis (R), whereas 598 of them (27%) were also affected by asthma (R+A). In the following thirty-six-month period the group of pure rhinitis was evaluated to assess the natural development of allergic march independently of possible therapies (sporadic non-controlled self-medication). Referring to the clinical end-points the following remarks can be made:

- At baseline, the prevalence of asthma, also in the form of only aspecific hyperreactivity (H) was equal to 30% (1449 patients out of 4830) of the patients that had been evaluated at the time of enrolling.
- After thirty-six months the incidence of asthma as rhinitis co-morbidity in 1517 patients with initial pure rhinitis was of 34.14% (518 patients out of 1517); the incidence of aspecific bronchial hyperreactivity was of 35.13% (533 out of 1517 patients) (table 3) irrespective of the therapies received. (Self-medication).
- The entity of rhinitis seemed to influence the evolution of the pathology both in case of persistent and intermittent rhinitis (table 3).
- As far as the efficacy of therapies is concerned, the continuative SIT showed a significant higher reduction in evolution of hyperreactivity and asthma than intermittent or continuative SPT (table 4) (fig. 2).
- The further comparisons of evolution of rhinitis in self-medicated patients and in patients submitted to SPT (fig. 3), showed significant differences of evolution both for intermittent rhinitis ( $X^2 = 14.818$ ;  $df = 2$ ;  $P_{\text{Monte Carlo}} < 0.001$ ) and continuative ones ( $X^2 = 90.123$ ;  $df = 2$ ;  $P_{\text{Monte Carlo}} < 0.001$ ); these differences in the first group, seem to depend entirely on a clear decrement in the frequency of evolution to hyperreactivity as far as the intermittent rhinitis are concerned, while

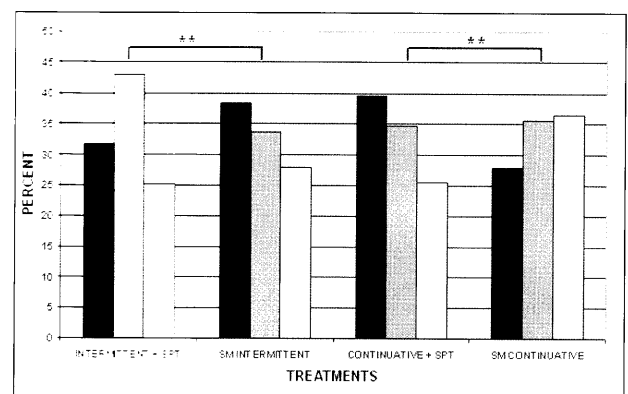


**Figure 3:** Comparison between Standard Pharmacological Therapy (SPT) and self-medication (SM) intermittent/continuative rhinitis in a long term (3 years) observational study. In figure are also reported the results of the Pearson chi-square test to compare evolution of rhinitis following the different therapies. Chi square test results are reported: \* =  $P_{\text{Monte Carlo}} < 0.05$ ; \*\* =  $P_{\text{Monte Carlo}} < 0.01$ ; \*\*\* =  $P_{\text{Monte Carlo}} < 0.001$ ; ns = not significant. Black stripe = rhinitis; grey stripes = hyper-reactive; white stripes = asthma.

st for persistent rhinitis it seems to be ascribable to the lower evolution into asthma in treated patients. Actually, no significant evolution into asthma is notable, neither in intermittent rhinitis, nor in the continuative ones.

These data on the other hand stress the importance of a continuative pharmacotherapy especially when the causal allergen is perennial, since the clinical symptoms of this systemic immunologic disorder can be better evaluated through an accurate control of allergic immunoflogosis; on the other hand it was clear that bronchial hyperreactivity evolved independently of asthma, notably, in intermittent rhinitis it paradoxically improves in the self-medicated control group as compared to those patients who received standard protocol. Persistent rhinitic patients do not show any improvement with massive therapy as compared to the self-medicated controlled ones.

## DISCUSSION

The allergic march that appears in the early childhood as a skin disease (atopic dermatitis) and then develops into respiratory tract disease with rhinitic and asthmatic symptoms (16) represents the natural evolution of atopic disease.

At present the prevention of the onset of the march is not a very realistic aim, however therapies are available to hinder and, possibly, to stop it.

ETAC study (17) proved that in subgroups of children with house dust mite and grass allergy who were administered cetirizine they were much less likely to develop asthma (but not in the total group) than children who received a placebo-therapy.

At present specific immunotherapy (SIT) is considered as the more suitable therapy to modify the natural history of allergic disease (18) at variance with drugs.

In a clinical pediatric study on 210 children observed until they were 16 years old and published as early as 1968 Johnston and Dutton proved that the incidence of asthma at the end of the observation period was of 28% in patients treated with SIT but it increased to 78% in placebo control group (19). Most of the double blind placebo controlled studies refer to subcutaneous immunotherapy (SCIT) (20,21,22). Of the two alternative immunotherapy routes (i.e. local intranasal immunotherapy (INIT) and sublingual immunotherapy (SLIT)) the most successful is SLIT. A recent revision (Cochrane Library 2003) (23) definitely demonstrated SLIT efficacy in reducing clinical symptoms and drug uptake in rhinitic patients. It also improved citomorphological and biological molecular aspects of nasal immunoflogosis: SIT is the only treatment capable, as a biological response modifier, to stop the allergic march (20, 21, 22) whilst pharmacotherapy is not able

to prevent the onset of new allergen sensitization. Its preventive efficacy towards new sensitizations plays a key-role in the allergic march control (24, 25, 26, 27, 28). Furthermore, SIT maintains its clinical efficacy even many years (3 to 5) after its discontinuation, as confirmed by several recent studies (29, 30, 31).

Therefore, if SIT clinical efficacy is proved by several double-blind placebo controlled studies, it must be admitted that this type of studies shows limits when SIT real impact is studied on large populations of patients in real-life setting. In such studies patients are treated for a short period (rarely for 1 to 2 years and never for longer periods). Moreover, patients are carefully selected and have homogeneous sensitization (only monosensitized patients are generally enrolled). Due to the said factors these studies do not correspond to everyday clinical practice. The problems still existing about SIT cannot be solved by these studies (for example its ideal duration, since at present it is normally delayed for 3 to 5 years and more). It is therefore necessary to randomize placebo-controlled trials in addition to observational studies in real life on large populations of patients to get more realistic information on clinical efficacy, adherence and safety of the treatment.

The results of this study show that patients with a markedly severe initial rhinitis are more likely to develop asthma: prognosis is worst in persistent rhinitis than in intermittent ones and in severe-moderate cases than in mild ones (Tab.3). Patients at risk will be accordingly followed-up in Allergy Units more frequently and the best therapeutic resources will be used (i.e. specific immunotherapy associated, if needed, to standard pharmacotherapy).

SIT must be considered as the only treatment capable of modifying the natural history of allergic march, as is not the case with drugs administered with standard protocol (table 4, fig. 2) and drugs used by patients on demand (fig. 3).

In several European countries (Italy included) non-injective immunotherapy is more used than traditional subcutaneous route. This study implicitly proves the efficacy of non-injective SIT; as a matter of fact, according to therapeutic decisional tree adopted in our Allergic Unit (32), 464 patients studied received sublingual immunotherapy (74.1%) whereas 98 patients (15.7%) were treated with intranasal immunotherapy for a total of 89.8% of patients who received non-injective SIT against subcutaneous route (10.2%):

As seen above, bronchial hyperreactivity evolves independently of asthma. It must be consequently considered a risk factor in the onset of asthma and not its predominant cause. What is more, the evolution from pure rhinitis into bronchial hyperreactivity is independent of the mode of using drugs (intermittent, sporadic and persistent administration) and this is a further confirmation that drugs cannot control the allergic march.

A feature of the present study is the absence of immunological evaluations (specific and total IgE, IgG, etc.) and of placebo-treated group. In fact, this is an open observational study on a large number of outpatients who came to our allergological service and submitted to diagnosis (based on skin-prick test, spirometry and methacholine bronchial provocation test) and therapeutic regimens in strict accordance to standard flow chart and monitored for a 3-year period.

Finally, a placebo-effect of 30% ca. (33) can be expected from the clinical outcomes (symptom scores, quality of life schedules, etc.) in patients receiving SIT in addition to drugs. The choice of the pulmonary function test as the main parameter of judgement in this study aimed at avoiding all possible interference of placebo-effect.

The results of this open observational study on parallel groups of patients treated with immunologic therapy (SIT) and/or non immunologic therapy (standard pharmacotherapy) indicated that in everyday clinical practice SIT acts as a biological response modifier stopping allergic march, whilst drug proved its inefficacy in this respect.

The follow-up of a control group that received non-controlled self-medication also shows that rhinitis is a predisposing factor of asthma directly proportional to its initial severity.

In conclusion, the rhinitic patients must be submitted as early as possible to specific immunotherapy associated to standard pharmacological treatment.

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