

The Allergic March in Pollinosis: Natural History and Therapeutic Implications

Results of a Long-Term Parallel Controlled Observational Study

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Key Words

Allergic march in pollinosis · Allergic march, specific immunotherapy · Allergic march, observational study

Abstract

Background: That specific immunotherapy (SIT) can slow the march of allergy has been confirmed in controlled clinical trials. However, an assessment of its effects in everyday life, in a large cohort of patients, might provide further useful information. **Methods:** This observational study comprised 3,643 patients allergic to pollens; 1,620 with pure allergic rhinitis or rhinitis and intermittent or mild-persistent bronchial asthma, responding poorly to standard pharmacological therapy (SPT), were treated for 3 years with SPT alone (pure rhinitis, n = 890), or combined with continuous SIT (rhinitis and asthma, n = 730). Symptom/drug scores were recorded, respiratory function and skin tests were done, and methacholine challenge was scheduled at the beginning and end of the study. A series of 2,023 patients with pure rhinitis, responsive to SPT, were asked to 'self-medicate' as needed, serving as a control group to check the incidence of asthma. **Results:** The incidence of rhinitis-asthma comorbidity was highest in the self-medication group (50.8%). Persistent rhinitis was associated with asthma more often than the intermittent form, regardless of the

severity of the symptoms that led to progression to asthma in patients with intermittent rhinitis. Treatment with SIT combined with SPT always slowed the allergic march which, however, was not influenced by drugs alone. **Conclusions:** In routine clinical practice, SIT is effective in preventing the allergic march. Patients with persistent rhinitis, who are at greatest risk of progression to asthma, appear to be the most logical candidates.

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Introduction

Large epidemiological studies have shown that between 15 and 20% of the population suffer from allergic rhinitis, which makes it one of the most common pathologies, in absolute terms [1–3]. The mean prevalence in the general population is around 18%, but among adolescents there are peaks of 25–35%, depending on the geographical area and local factors. Rhinitis is therefore a substantial social and health problem, with a heavy impact on patients' quality of life, causing absence from school, and low productivity at work, and restricting social and leisure activities [4–7].

From the scientific point of view the main feature is probably the close relation between allergic rhinitis and bronchial asthma, since rhinitis, which normally pre-

Table 1. Demographic and clinical data at baseline

	Control group, self-medicated (n = 2,023)		SPT (n = 890)		SPT + SIT (n = 730)	
	M	F	M	F	M	F
Sex	1,164	859	477	413	419	311
Age range	10–46	9–46	7–38	11–44	11–41	10–44
Mean age $\pm$ SD	22.6 $\pm$ 10.71	23.1 $\pm$ 9.38	22.2 $\pm$ 8.94	24.5 $\pm$ 9.08	22.1 $\pm$ 7.52	20.8 $\pm$ 8.47
Group A						
Intermittent pure rhinitis	553	389	211	180	–	–
Group B						
Persistent pure rhinitis	611	470	266	233	–	–
Group C						
Rhinitis and asthma	–	–	–	–	419	311

cedes overt asthma by many years, can be considered an important risk factor. The ARIA report (Allergic Rhinitis and Its Impact on Asthma) [8] indicated that in patients exposed continuously to the allergen, allergic rhinitis is a chronic inflammatory disease, just like asthma. From the pathophysiological angle, therefore, this is an allergic inflammatory process involving the airways as a whole [9].

Clinically speaking, patients with rhinitis must be checked for asthma, and vice versa, since rhinitis may be the sole clinical manifestation of the atopy, even for years. In rhinitic patients with no appreciable clinical signs in the lower airways, an aspecific bronchial provocation test frequently brings to light bronchial hyperresponsivity, which helps identify subjects at risk of developing asthma since this finding – seen in about half the cases – is predictive of the risk of bronchial pathologies [10].

Clinically manifest asthma involves the response to allergens of the immune system in the lower airways. Besides constitutional allergy, an asthmatic syndrome may also be brought on by bronchospastic naso-bronchial reflexes [11], by breathing air that is inadequately filtered in the nose, and – last – by mucus oozing retronasally, and carrying inflammatory mediators, particularly bronchoconstrictive leukotrienes, down into the lower bronchial tree, by gravity [12].

In Italy very few studies have looked into the combination of rhinitis and asthma. In the mid-1980s, therefore, we designed an observational clinico-epidemiological study on a large population of patients with pollinosis (early spring from birch and spring/summer from grami-

naceae and urticaceae), attending a regional reference center for allergy (Respiratory Allergy Outpatient Unit at Cuasso al Monte, Fondazione Macchi Hospital, Varese). Patients were observed between 1987 and 2002. Their baseline demographic and clinical details are summarized in table 1.

We assessed the initial degree of ‘impairment’ for each patient with rhinitis (classified at the time as either seasonal or perennial) from a practical angle, based on whether the symptoms were continuous or not (sporadic or perennial) and how severe they were (mild, moderate, severe); this approach was very similar to the current ARIA guidelines [8].

To investigate asthma as the main co-morbidity, we employed a mixed clinical/pathophysiological criterion that distinguished clinically manifest asthma (with bronchial obstruction detectable at the baseline spirometry) from bronchial hyperreactivity, in which bronchial obstruction was induced by a provocation test. From the epidemiological viewpoint both these situations fall under the heading of asthma. Clinically speaking, however, we preferred to take their progression separately, since bronchial hyperreactivity is only a risk factor for persistent asthma, so its clinical impact is different from overt chronic obstructive pathology.

Material and Methods

The study was designed with the following aims: (a) to assess the prevalence of asthmatic patients among those with pollen-allergy rhinitis; (b) to assess the incidence of patients whose rhinitis

progressed to asthma; (c) to seek a relation between the initial severity of the rhinitis and the subsequent development of asthma, and (d) to compare the efficacy of specific immunotherapy (SIT) and pharmacological therapy in preventing the allergic march from rhinitis to asthma.

Study Design

Among patients with rhinitis presenting at our allergy outpatient clinic, 19% are sensitive to pollens: graminaceae, betullaceae, or urticaceae. Baseline respiratory function tests showed that 29.76% of these patients had rhinitis and asthma, distributed as follows: (a) graminaceae: 784/2,656 patients, 29.52%, 439 of them hyperreactive and 345 overtly asthmatic; (b) betullaceae: 673/2,169 patients, 31.02%, 271 of them hyperreactive and 402 overtly asthmatic, and (c) urticaceae: 148/567 patients, 26.10%, 80 of them hyperreactive and 68 overtly asthmatic.

After initial examinations, patients were assigned 12 months of preventive/symptomatic drug therapy aimed at controlling symptoms of asthma and/or rhinitis. At the end of this year, patients not responding satisfactorily to the drugs (drug scores + symptom scores >50% from baseline) were divided into three groups: (1) group A: continued for another 36 months with drugs for the basic symptoms (mild or moderate-severe intermittent rhinitis); (2) group B: continued for another 36 months with drugs for the basic symptoms (mild or moderate-severe persistent rhinitis), and (3) group C: continued for another 36 months with drugs for basic symptoms, plus SIT (rhinitis plus intermittent or mild persistent bronchial asthma).

At the end of this treatment, each patient's immuno-allergic and functional profile was established by a skin prick test, spirometry with investigation of bronchial tone, and a clinical score to compare the efficacy of SIT and conventional pharmacotherapy in preventing the progression of rhinitis to asthma. In the group of patients who were initially responsive to conventional pharmacotherapy we assessed the natural progression of the allergic march, from rhinitis to asthma, regardless of the therapeutic strategy employed (conventional or mixed) (tables 2, 3). The subset of patients initially diagnosed as having 'pure' rhinitis, i.e. with no apparent clinico-functional deep lung impairment, were allowed occasional, non-standardized self-medication. They were kept under clinical observation and an overall assessment was made at 36 months to check the incidence of rhinitis/asthma as co-morbidities, and the natural progression in relation to the initial severity of the rhinitis.

Patients

(1) Before enrollment in the study, patients underwent the following diagnostic examinations:

(a) Skin prick test, in accordance with the latest guidelines [13], using standardized, commercially available extracts (Alk Abellö, Lainate, Milan, Italy) of the following allergens: house dust mites, graminaceae, parietaria, cat and dog dander, birch, olive, ragweed, wormwood, *Alternaria* and *Cladosporium*. We ran 1% histamine as positive control, and saline solution as negative control. The results were expressed as the mean of the largest diameters of the wheal, taking reactions >5 mm as positive.

(b) Complete respiratory function tests using computerized spirometry and a plethysmographic cabin (Masterlab, Jaeger, Würzburg, Germany) with an aspecific methacholine (MCh; Methacholine Lofarma SpA, Milan, Italy) bronchial provocation test, in accordance with the latest guidelines [14, 15]. The MCh challenge was

done during the period of maximal exposure to pollen using a constant-pressure dosimeter (Jaeger) activated by inhalation, with fixed delivery times but a variable number of deliveries, so as to plot a cumulative dose-response curve for 30, 60, 120, 240, 390, 690 and 1,290 ms (μg). The test was considered positive (MCh+) when FEV₁ fell 20% at a cumulative dose of 1,290 μg or less.

Patients with no history of asthma and a negative MCh challenge (MCh-) were considered to have pure rhinitis. Patients with no history of asthma but a positive response to MCh (MCh+) were considered hyperreactive. Patients with recurrent episodes of wheezing, cough and tightness in the chest – by day or night – and baseline bronchial obstruction (specific flow resistance >35% and/or specific flow conductance <35% of theoretical), or a positive challenge with MCh (MCh+) were classified as asthmatic.

(2) Patients were instructed on how to keep a detailed monthly clinical diary of symptoms. The clinical efficacy of treatment was analyzed on the basis of this record, using the following items: itchy nose, sneezing, rhinorrhea, blocked nose, cough, wheezing, itching and runny eyes. Each symptom was rated as follows: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. In addition, one point was added for each daily dose of any of the following drugs, allowed by the protocol: oral antihistamines (loratadine or cetirizine 10 mg, 1 tablet/day), topical corticosteroids (nasal/bronchial) (beclomethasone dipropionate 250 μg , 1–2 puffs b.i.d.), systemic corticosteroids (prednisone 1 mg/kg/day for 3–4 days), short-acting β_2 -adren-ergic agents (salbutamol 100 μg , 1–2 puffs as needed).

SIT was prescribed in accordance with the latest position papers [16, 17], using the therapeutic protocols recommended by the manufacturer for the usual subcutaneous route (SCIT) and for the non-injected nasal (LNIT) and sublingual therapy (SLIT) (Lais, Lofarma SpA, Milan, Italy).

Inclusion criteria: Patients had to have intermittent or mild persistent asthma, observed during the first 12-month study period, in accordance with GINA guidelines [18]; these specify that FEV₁ should be within normal limits (i.e. >79% of the theoretical value for each individual).

Exclusion criteria: Age <5 or >60 years, FEV₁ <80% of the theoretical value, multisensitization with allergens likely to cause significant interference with assessment of the endpoints (other pollens in the same observation/evaluation period), long previous corticosteroid therapy, pregnancy, use of β -blockers, cardiopulmonary, autoimmune or neurological diseases, primary and secondary immune deficiencies, anatomo-structural abnormalities of the upper airways, previous SIT.

Statistical Analysis

Comparisons of frequencies were tested with Fisher's exact test or Pearson's χ^2 [19]. The probability level was computed using a complete randomization method (permutation or exact test; p_{exact}) or a Monte Carlo [20] simulation based on 10,000 sampled tables ($p_{\text{Monte Carlo}}$) when computation was not possible. Type I error (α) was set at 0.01. Multiple comparisons of frequencies were taken into account by correcting the α level using the Dunn-Šidák significance level correction method: $\alpha' = 1 - (1 - \alpha)^{1/k}$, where k is the number of comparisons [19]. In our case, comparing the effect of the three different therapies on the progression of the rhinitis, the new significance level was set to $\alpha' = 0.003$.

All statistical analyses were done using the Statistical Package for Social Sciences version 10.05 (SPSS®).

Table 2. Evolution from pure rhinitis to asthma following a 3-year treatment, considering the duration and severity of the initial pathology (rhinitis)

	Evolution to rhinitis severity			
	intermittent rhinitis (n = 832)		persistent rhinitis (n = 968)	
	light	moderate/severe	light	moderate/severe
Rhinitis	317 (70.6%)	198 (51.7%)	170 (39.4%)	199 (37.1%)
Hyperreactivity	80 (17.8%)	100 (26.1%)	132 (30.6%)	147 (27.4%)
Asthma	52 (11.6%)	85 (22.2%)	130 (30.1%)	190 (35.4%)
Overall	449 (100%)	383 (100%)	432 (100%)	536 (100%)

Table 3. Prevention of the evolution to asthma following a 3-year treatment: comparison between SIT and SPT

Disease/therapy		Evolution to			χ^2	d.f.	$P_{\text{Monte Carlo}}$
		pure rhinitis	hyperreactivity	asthma			
Group A							
Intermittent pure rhinitis/SPT	From	367	0	0	53.139	2	<0.001
n = 367	To	180 (49.0%)	121 (33.0%)	66 (18.0%)			
Group B							
Persistent pure rhinitis/SPT	From	476	0	0	75.508	2	<0.001
n = 476	To	244 (51.3%)	93 (19.5%)	139 (29.2%)			
Group C							
Rhinitis and asthma/SPT + SIT	From	0	379	275	593.844	2	<0.001
n = 654	To	511 (78.1%)	90 (13.8%)	53 (8.1%)			
Overall, 1,497		935 (62.5%)	304 (20.3%)	258 (17.2%)	160.083	4	<0.001
Overall χ^2							

Results

Between January 1, 1987 and December 31, 2002, we examined 5,392 patients: 1,274 patients dropped out during the study and 821 were excluded from the analysis because they were asthmatics and responders to drugs. The remaining 3,297 completed the follow-up, as follows:

(a) 1,497 patients with allergic rhinitis due to pollens, combined in some cases with bronchial asthma, responding poorly to conventional pharmacotherapy (clinical efficacy <50% from baseline). After the first 12 months' observation, 367 of these had intermittent rhinitis (group A) and 476 persistent rhinitis (group B), without asthma, so they were assigned 36 months of standard pharmacological therapy (SPT). Then there were 654 patients

(group C, 45.6%) with persistent rhinitis plus bronchial hyperreactivity and/or intermittent or mild persistent asthma, who were assigned SIT with SPT.

(b) 1,800 patients with pure allergic rhinitis due to pollens, good responders to drugs. These patients were allowed uncontrolled self-medication, and were kept under observation for 36 months, to follow the natural course of the allergic march, independently of the therapeutic strategy adopted.

In relation to the study aims, the results can be summarized as follows. At the time of enrollment in the study the prevalence of bronchial asthma or aspecific bronchial hyperreactivity was 29.76% (1,605 out of 5,392). Three years later the incidence of bronchial asthma, as a co-morbidity in the 1,800 patients with pure rhinitis – regardless of the therapeutic strategy used and the severity of the

initial rhinitis – was 25.38% (457 patients); the incidence of bronchial hyperreactivity was 25.50% (459 patients) (table 2).

The clinical course of the pathology seems to be related to the severity only in cases with intermittent rhinitis ($\chi^2 = 32.638$; d.f. = 2; $p_{\text{exact}} < 0.001$); in patients with persistent rhinitis, the progression followed a similar pattern for light or moderate/severe disease ($\chi^2 = 3.199$; d.f. = 2; $p_{\text{exact}} > 0.05$). The progression did differ significantly, however, between intermittent and persistent rhinitis, either light or moderate/severe (table 2) ($p_{\text{exact}} < 0.001$).

Even though the overall frequency of progression to asthma was expected to be lower with all the treatments – and this was actually observed (table 3) – the three therapies were not equally efficient in preventing asthma.

There was significantly less progression to asthma (18%) in intermittent rhinitics who received SPT than in patients with persistent rhinitis who took SPT (29.2%; $\chi^2 = 50.058$; d.f. = 2; $p_{\text{Monte Carlo}} < 0.001$); this confirms the importance of the initial level of rhinitis in relation to the likely progression.

SIT was efficacious, as regards the frequency of progression to asthma, also in rhinitic patients with asthma non responder to drugs: reduction of evolution to asthma was in fact observed in 91.9% of patients ($p_{\text{Monte Carlo}} < 0.001$).

Discussion

The allergic march, which progresses from atopic dermatitis to rhinitis and asthma, is the clinical reflection of the natural course of the constitutionally atopic background of an allergic subject [21]. The prevalence of atopic diseases is steadily rising and now involves 10–20% of the world's population, with high social costs. This explains the unflagging interest in strategies to prevent or slow down the march.

In theory it would be possible to stop the march even getting under way, but this is not easy on a large scale. Action could be taken prenatally [22] or – more feasible – in newborns, limiting exposure to environmental and food allergens [23, 24] although reports on this topic are conflicting [25]. In children at risk because of a family history of atopy, it might be useful to recommend that their mothers breast-feed them, avoiding exposure to cigarette smoke, and taking all measures to reduce environmental allergen loads [26], although here again not all opinions agree [27].

Probably secondary and tertiary prevention offers the best prospects, meaning the use of therapeutic tools to slow or, if possible, stop the allergic march. In addition to the control of environmental and food allergens, this involves the use of drugs, and SIT.

The ETAC study (Early Treatment of the Atopic Child) assessed the utility of the antihistaminic drug cetirizine in preventing asthma in a large cohort of children with atopic dermatitis [28]. This study gave only partially encouraging results: there was a significantly lower probability of developing asthma only in the subgroups of children sensitized to dust mites and graminaceae, and the overall prevalence was the same for active treatment and placebo. The limit of this study lies in the fact that antiallergic drugs do not prevent sensitization to allergens, and only the loss or reduction of this sensitivity can change the natural course of the allergic march.

Only SIT actually modifies the biological response to the allergen [17]. This is clear from the fact that it prevents the progression from rhinitis to asthma [29, 30] and also prevents new sensitizations to inhalant allergens [31–35]. This ability to prevent new sensitizations plays a key role in the therapeutic possibilities of this approach. The curative potential of SIT is greatly reduced in patients sensitive to too many allergens [36]. It now appears that SIT's effects persist for long periods after the treatment has ended [37–39].

The clinical efficacy of SIT is clear from many controlled trials using placebo, from recent meta-analyses, and from the main guidelines. However, many of these trials have intrinsic limitations that make them less suitable for investigating the real impact of SIT on large populations in routine clinical practice. The selection of patients is usually very strict, and tends to exclude any with multiple sensitivities, making the study immediately less representative of everyday clinical reality. In addition, these trials mostly only use a short period of treatment – rarely 2 years, and never any more. This means they cannot answer some of the questions about SIT, such as its optimal duration. Currently it is usually continued for 3–5 years, though sometimes longer. We have therefore to conclude that as a whole these controlled trials, comparing active treatments with placebo, inevitably leave unanswered many questions arising in the routine use of SIT. It is therefore important to flank these fundamental trials with observational studies conducted in real-life conditions, on large patient populations, so as to obtain a realistic assessment of the efficacy of treatment, of patients' compliance, of its safety and other considerations.

The present findings do confirm various old and new beliefs on the best approach to treating respiratory allergies. These can be summed up as follows:

(1) Patients with persistent rhinitis are at the highest risk of progressing to asthma, regardless of how severe their symptoms are (tables 2, 3). These patients should have regular outpatient follow-up with fairly frequent clinical examinations, and should be considered for the best available therapeutic protocols, for example those that exploit the synergy between standard pharmacotherapy and SIT.

(2) SIT is the only treatment strategy that actually influences the natural course of the allergic march. This is clear not only from the comparison with patients treated using the SPT protocol, but even more from the comparison of these patients and the self-medication group. The progression to asthma was seen in a similar proportion of patients in both the latter groups.

As regards the routes of administration, in many European countries, including Italy, non-injective immunotherapy is now more widely used than the traditional subcutaneous route. The present findings confirm the efficacy of SIT by an alternative route in preventing the allergic march. As a matter of fact, according to therapeutic decisional tree adopted in our allergy unit [40], a total of 460 patients in this study used SIT, taking the monomeric allergoid in the sublingual form (70.3%), and 103 (15.7%) used the intranasal route; this gave a cumulative prevalence of non-injected SIT of 86% compared to 14% by the subcutaneous route.

A feature of the present study is the absence of immunological evaluations (specific and total IgE, IgG, etc.) and of a placebo-treated group. This was an open obser-

vational study on a large number of outpatients (3,643 in total) attending our allergy unit, who were diagnosed (skin-prick test, spirometry and methacholine bronchial provocation test) and assigned therapy in strict observance of the standard flow chart, then followed for 3 years. This study might therefore be criticized because it only took into consideration functional parameters, and no immunological or other factors (sex, age, clinical score). However, spirometric functional findings are still the only objective means of quantifying the progression of rhinitis to asthma.

Another potential limitation is the open study design. We set out to observe a large group of pollen-allergic patients and follow their functional profile during pharmacological therapy and SIT, but we considered it unrealistic to try and keep track of more than 3,000 patients in a 3-year double-blind trial.

It would be justifiable to note that in patients receiving immunotherapy in addition to SPT the 'placebo effect' on the clinical outcomes (symptom scores, etc.) may reach 30% [41]. It was to avoid this sort of interference that we used spirometry and methacholine challenge as functional parameters, as they are quantitative findings that can only be influenced to a limited extent by individual subjectivity.

To conclude, this observational study found that it is possible to exert an effect on the allergic march by careful selection of the patients most at risk (i.e. those with persistent allergic rhinitis), as candidates for the most appropriate therapeutic approach.

Today this is SIT, which is the only strategy offering the capacity for prevention, and – as appropriate – ally-ing it with symptomatic pharmacotherapy.

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