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CLINICAL PRACTICE IMPROVEMENT PROGRAM FOR IMMUNOTHERAPY OF RESPIRATORY ALLERGIC DISEASES

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The aim of this study was to develop a clinical practice improvement (CPI) program for the allergen immunotherapy of allergic respiratory diseases. The study was conducted between 1994 and 1999, using an observational methodology in line with normal clinical practice, in a Hospital allergy center. The program comprised four basic steps: setting up a decisional tree, standardizing the main diagnostic-therapeutic aspects, recording of the data and statistical evaluation of the main clinical endpoints in a long period (36 months).

A total of 256 patients were admitted, all with dust mite allergy; if pharmacological therapy failed after 12 months, they were assigned to immunotherapy (95 patients), either by subcutaneous injection or by the intranasal or sublingual route, depending on the main clinical-prognostic features taken into consideration. For each group of patients a control group was set up, given proper pharmacological therapy (40 patients). Allergen-specific immunotherapy was effective and well tolerated. Bronchial hyper-reactivity (BHR) tests indicated that subcutaneous or sublingual immunotherapy seemed to give some protection against asthma or BHR worsening. In the group only given pharmacological therapy, an increasing percentage of patients gradually became non-responders, hence potential candidates for allergen immunotherapy.

The present findings, even though obtained by a non-randomized approach, are based on a large, selected case list and show that setting up a CPI program can render possible a better overall efficacy of immunotherapy, through appropriate selection and continuous follow-up of patients.

IgE-mediated diseases have become increasingly frequent in recent decades in the industrialized countries with western style of life. Clinical allergology has tried to tackle this rise in prevalence in a coherent way, developing a range of tools and methods for following patients throughout diagnosis and therapy. Setting up a clinical practice improvement (CPI) (1-3) program is a novel approach in this field, but fulfils the following basic needs:

- standardization of the methods for selecting and treating patients;
- uniformity of methods for data collection and analysis of key clinical endpoints;
- observational studies on large caselists with correction - as necessary - of diagnostic and therapeutic methods.

CPI programs are already working in other therapeutic areas and have permitted everyday application of disease management programs and of diagnostic/therapeutic guidelines (4-6). The need to work on an observational basis arises from the fact that randomized controlled clinical trials often do not adapt well to real life, since experimental schemes are not easily transferred into clinical practice (7,8). This is illustrated by the complexity of checking compliance with treatment in everyday clinical practice (9).

Key words: Respiratory allergy, house dust mite, local immunotherapy, subcutaneous immunotherapy, clinical practice improvement program

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There are also some peculiarities of allergological practice that may be misunderstood or underestimated, the following being just a few examples:

- the multidisciplinary approach required in allergology;
- the need for a personalized approach, focused on each individual patient in order to optimize complex therapeutic measures. Examples include the necessary avoidance measures (mites control) or optimization of pharmacologic treatment;
- the inadequacy of standardized, objective tools for assessing patients;
- the need for long-term clinical trials - often lasting two or three years.

Establishing a CPI program based on an observational study may provide an answer to some of these practical needs, while at the same time permitting an assessment of the efficacy and safety of therapies used. In this study a CPI program was set up using an observational method borrowed from controlled clinical trials. Our aim was to overcome some of the barriers of traditional clinical research and select a large case list of patients with respiratory allergies (oculo-rhinitis, asthma) due to house dust mites, and follow them up for at least three years. This study was designed to develop tools for establishing a CPI program and to assess whether these tools were useful in assessing the efficacy and safety of allergen-specific immunotherapy (SIT) in outpatients attending the allergy center, for respiratory allergies such as rhinitis or asthma, due to house dust mites.

MATERIAL AND METHODS

The study was run between 1994 and 1999, using an observational method. This choice appeared justified on the following counts:

- closeness to clinical reality;
- assessment of the main diagnostic/therapeutic endpoints on an ample, homogeneous case list;
- feasibility of studying a large population for at least 36 months.

We set up the study in several steps, as follows:

1.drawing up a decisional tree for selecting patients to receive SIT;

2.choice and definition of the main clinical endpoints;

3.development of criteria for standardizing the diagnosis, allocation of therapy and assessment of main clinical endpoints;

4.statistical analysis of the results and implementation of any corrective measures to the diagnostic/therapeutic routine.

Patients

Four groups of outpatients were followed throughout the study; all had respiratory allergies due to house dust mites.

Group A was given SIT by subcutaneous (sc) injection (allergen extracts coprecipitated in aluminium hydroxide - Lofarma SpA, Milan, Italy). Group B received intranasal SIT (cod. Allerkin® nasal powder - Lofarma SpA, Milan, Italy). Group C was given sublingual allergoid SIT (cod. Lais® - Lofarma SpA, Milan, Italy). For each group treated with SIT there was a control group that was given only proper pharmacological treatment (see below).

The nasal immunotherapy (Allerkin) consisted in allergens incorporated into a macronized (median particles size 45 mm) lactose powder, titrated in Allergenic Units (AU) and to be administrated by a nasal insufflator. The sublingual immunotherapy (Lais) consisted in allergens submitted to chemical modification by alkaline cyanate (carbamylation of amino groups) in order to obtain monomeric allergoids, titrated in Allergenic Units (AU) and incorporated into orosoluble tablets. Allergenic Unit is a biological unit defined as 1/40 of the mean provocative dose by specific nasal challenge in a large number of allergic volunteers.

The subcutaneous immunotherapy has been performed with depot extracts co-precipitated in aluminum hydroxide. These extracts are titrated in therapeutic units (U), established for injection immunotherapy and not comparable with the biological Allergenic Units used for intranasal and sublingual treatment. The dosage can be adjusted for each patient according to sensitization, clinical course et., mainly during the build-up phase. During the maintenance phase the planned therapeutic dosage per year is around the following: Allerkin 25.000 AU, LAIS 100.000 AU, aluminum hydroxide depot 84.000 U.

Patients were assigned to one of the four groups on the basis of the decisional tree shown in Fig. 1, in which certain details are worth highlighting:

- to ensure homogeneity throughout the case list only patients with house dust mite allergy were followed;
- patients were only assigned to SIT after at least one year of pharmacological therapy, in cases where the

response was clinically unsatisfactory (less than 50%);

- patients were allocated to one of the SIT groups (sc, intranasal or sublingual) on the basis of multivariate analysis taking account of the prevalent pathology (rhinitis/conjunctivitis, asthma severity), the patient's clinical history, and some functional parameters (FEV_1 and BHR);

- the control group given only pharmacological therapy was matched with the patients receiving SIT but stated they preferred to carry on taking drugs.

The main clinical variables were followed in all patients for a "window" of four months between November and February, which is the season when patients are most exposed to house dust mites according to a previous published trial (10).

Before entering the study patients were examined as follows:

- skin prick test, following the latest guidelines (11);
- complete respiratory function tests with nonspecific bronchial provocation (Fog test) according to published guidelines (12-13).

Patients were not eligible for the study if they met any of the following criteria:

- age less than 8 or more than 60;
- multiple sensitivities with allergens causing significant interference with assessment of the study endpoints (for example, other perennial allergens, or pollens likely to be encountered during the observation and assessment period, such as birch or other trees);
- FEV1 <80% of the theoretical value;
- severe asthma;
- previous prolonged systemic corticosteroid treatment;
- SIT in the previous three years;
- absolute or relative contraindications to SIT such as pregnancy, use of beta-blockers, cardiopulmonary, autoimmune or neurological diseases, primary or secondary immune deficiencies.

The ITS administration has been carried out according to the most recent Position Paper (14,15).

Clinical endpoints: definition and assessment

Six clinical endpoints were selected and their methodological supports were prepared as specified below. All these endpoints and their assessment scales could be grouped under two main headings for either a positive or a negative overall judgment. Patients attended visits every two months and an overall clinical judgment was drawn up once a year.

Clinical efficacy of treatment

Patients kept monthly diaries, in which they recorded the following items as a basis for assessing this endpoint: itchy nose, runny nose, sneezing, blocked nose, runny eyes, headache, cough, dyspnea. Each symptom was rated as follows: 0 = absent, 1 = mild, 2 = severe, 3 = very severe. At the end of the observation period these scores were evaluated as follows to indicate how much the symptoms had been reduced:

failure:	<25% = 0
poor:	25 - <50% = 1
good :	50 - <75% = 2
excellent:	>75% = 3

Drug intake

A specific monthly diary was also used for this endpoint. In order to achieve some degree of standardization, a multi-step therapeutic approach was used for all patients. This involved:

1. chromones or similar drugs, taken continuously;
2. local or long-acting systemic antihistamines, with beta-2 agonists as needed;
3. nasal or inhaled steroid, with continuous beta-2 agonists;
4. systemic steroid.

At the end of the observation period the findings were classified using the following rating scale:

Failure: systemic steroid needed for more than five days at a time, sometimes with other therapies = 0

Poor: continuous need for antihistamines, topical or systemic steroids or beta-2 agonists for less than five days = 1

Good: non-continuous use (e.g., in cycles) of antihistamines, topical steroids or beta-2 agonists = 2

Excellent: only chromones and/or antihistamines for up to seven days = 3.

Safety

This endpoint was assessed from patients' diaries and by a specific interview at each follow-up visit. The following scale was used for patients receiving SIT:

Inadequate: systemic reactions = 0

Poor: medium/severe local reactions, needing medical therapy = 1

Good: mild local reactions, not needing medical therapy = 2

Excellent: no reaction = 3.

Patients given only pharmacological therapy assessed themselves, using a four-point scale (from 0 to 3), classifying their tolerance as unsatisfactory, fair, good or excellent.

Compliance with treatment

This endpoint was assessed on the basis of diary entries and by checking leftover supplies in relation to planned intake. Compliance was then rated as follows:

inadequate:	<40% = 0
poor:	40 - <60% = 1
good:	60 - <80% = 2
excellent:	>80% = 3

Bronchial hyperreactivity (BHR)

This endpoint was assessed using the fog test, applying the standardized criteria resulting from the literature (12,13). This test was done at the start and end of the observation period and the patients were classified as normal, hyperreactive, or asthmatic. The course of symptoms was assessed over time, and a judgment was made whether respiratory function had improved (normalization), or worsened (hyperreactivity or asthma).

Response to drug therapy alone

This endpoint was assessed in patients responding after the first year of pharmacological therapy, who then continued for another three years. These patients were assessed applying the clinical criteria set out above.

Statistical analysis

In line with the main international references on this topic, we assessed the results of this observational program after patients had been treated for 36 months (14,15). A descriptive, non-parametric approach was taken for the main demographic variables. For symptoms, drug consumption, safety and compliance we used the scores relating to the improvement observed, classifying patients in four categories: failure = 0; poor = 1; good = 2; excellent = 3. Patients were then further divided into two categories: those with a substantially negative assessment (failure or poor) and those with a substantially positive assessment (good or excellent). The chi-squared test was used to compare these findings with controls.

The BHR findings at the start and end of the observation period were analyzed by non-parametric analysis comparing all treatment groups, and assessing the outcome as improvement (normalization) or worsening (appearance of BHR or asthma).

Descriptive non-parametric statistics were used to analyze patients who became non-responders to pharmacological therapy, and the progress of their pathology.

RESULTS

Patient population (Tab. I)

The population enrolled corresponded fully to the criteria set out in the decisional tree (Fig. 1). A total of 256 patients were observed, 135 of them admitted to the SIT follow-up program. Of these 95 received SIT (36.3% of the initial total), and 40 (16.4%) decided to continue taking drugs (controls). The main demographic variables (Table I) did not differ significantly in the three treatment groups (Allerkin, Lais or sc SIT).

Assessment of efficacy (symptoms and drug intake)

As shown in Figs 2 and 3, data analysis after 36 months of observation showed significant differences in all three SIT groups compared to the controls. The efficacy of the SIT appears to be confirmed by the substantial similarities between symptom reduction patterns and drug intake.

Safety and compliance

No severe adverse reactions were reported in any of the treatment groups and no patients dropped out during follow-up on account of serious adverse events. The group treated with nasal immunotherapy reported local rhinorrhea-like reactions during the induction phase with the highest doses but these regressed after some months of maintenance therapy. Four patients recorded persistent rhinorrhea, needing premedication with disodium chromoglycate. Six of the patients given sc SIT reported mild local edema and swelling at the injection site, which subsided within three days' treatment with topical steroids and/or systemic antihistamines. One of the patients given sublingual SIT complained of urticaria which responded to five days' antihistamine course.

Statistical analysis found no significant differences between the treatment groups and controls. Compliance was better than 80% for almost all patients, with no significant differences between the treatment groups and controls.

Bronchial hyperreactivity (Tab. II)

Among patients treated with intranasal SIT, 14% had an asthma-like response at the end of therapy, and 10% had BHR. This indicates an approximately 20% progression of the respiratory

Tab. I. *Patients' main data.*

TREATMENT	PTS	PATHOLOGY*	SEX	AGE
Group A (SIT)	32	32AR	21M/11F	26.4±13.6
Control group A	10	10AR	7M/3F	25.9±13.45
Group B (ALLERKIN)	34	34R	23M/11F	26.6±12.99
Control group B	18	18R	13M/5F	26.5±13.38
Group C (LAIS)	29	29AR	20M/9F	24.2±11.78
Control group C	12	12AR	9M/3F	22.9±11.65

Group A = subcutaneous SIT (maintenance phase 84.000 U/per year) plus pharmacological treatment.
Group B = intranasal SIT (Allerkin) (maintenance phase 25.000 AU/per year) plus pharmacological treatment.
Group C = sublingual SIT (Lais) (maintenance phase 100.000 AU/per year) plus pharmacological treatment.
Control group A, B and C, = treatment with only proper pharmacological treatment.
SIT = Allergen Specific Immunotherapy.
**PATHOLOGY: AR= asthma and rhinitis/conjunctivitis.*
R = rhinitis/conjunctivitis.

Tab. II. *Bronchial hyperreactivity (No. of patients).*

TREATMENT	PERIOD	NORMAL	ASTHMA	HYPERREACTIVITY
Group A (SIT)	before	0	13	19
	after	11	3	18
Control group A	before	0	8	2
	after	7	1	2
Group B (ALLERKIN)	Before	34	0	0
	after	27	4	3
Control group B	Before	18	0	0
	after	12	3	3
Group C (LAIS)	before	8	14	7
	after	20	3	6
Control group C	before	12	0	0
	after	8	3	1

Group A = subcutaneous SIT (maintenance phase 84.000 U/per year) plus pharmacological treatment.
Group B = intranasal SIT (Allerkin) (maintenance phase 25.000 AU/per year) plus pharmacological treatment.
Group C = sublingual SIT (Lais) (maintenance phase 100.000 AU/per year) plus pharmacological treatment.
Control group A, B and C, = treatment with only proper pharmacological treatment.
SIT = Allergen Specific Immunotherapy.

Tab. III. *Responders to pharmacologic treatment.*

	BASELINE (I year treatment)	1st year follow-up	2nd year follow-up	3rd year follow-up
R	**51**	**3**	**1**	-
A	**24**	**7**	**5**	**4**
R/A	**46**	**2**	**4**	**2**
TOTAL	121	12	22	28
cumulative %		(10%)	(19,2%)	(24,2%)

R= Rhinitis/conjunctivitis; A= Asthma; AR= Asthma and rhinitis/conjunctivitis.

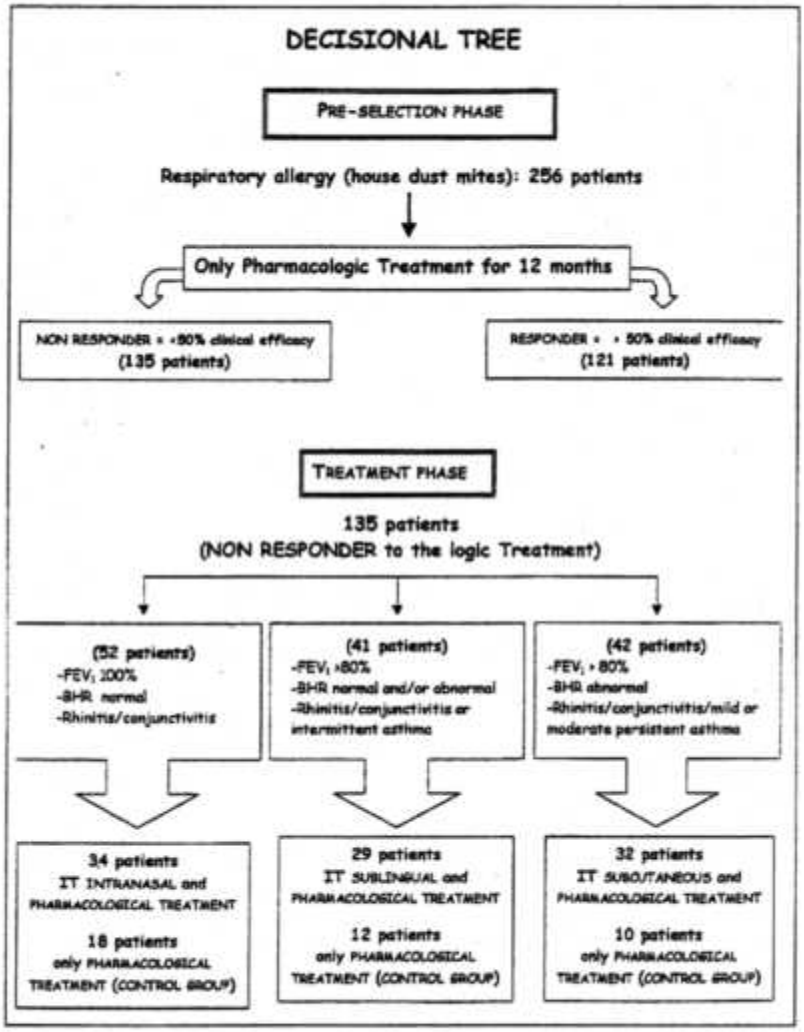

Fig. 1. *Decisional tree.*

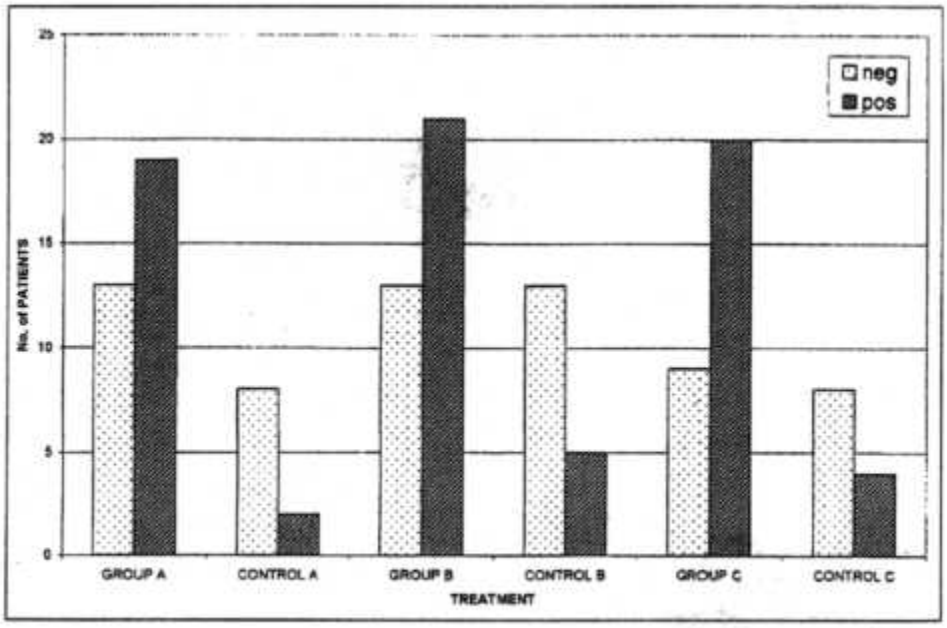

Fig. 2. *Clinical efficacy: patient's assessment of symptoms after 36 months of immunotherapy plus pharmacological treatment (group A = subcutaneous SIT, group B = intranasal Allerkin, group C = sublingual Lais) or only pharmacological treatment (control group A, B, C).*
neg = failure or poor clinical efficacy - pos = good or excellent clinical efficacy.

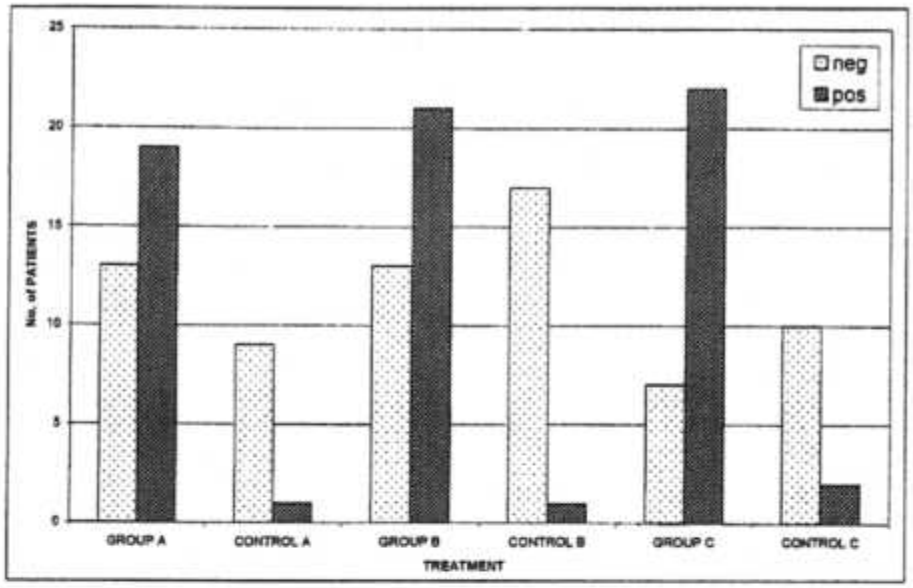

Fig. 3. *Clinical efficacy: patient's assessment of drug intake after 36 months of immunotherapy plus pharmacological treatment (group A = subcutaneous SIT, group B = intranasal Allerkin, group C = sublingual Lais) or only pharmacological treatment (control group A, B, C). neg = failure or poor clinical efficacy - pos = good or excellent clinical efficacy.*

pathology from rhinitis to asthma in four years. In the group given sc SIT 34% showed normalization at the end of therapy, and asthma had dropped from 40% to 10%. Overall analysis therefore showed a substantial improvement in respiratory function, although the difference from controls was not significant. Improvement in the sublingual immunotherapy group reached 41%, but again the difference from controls was not statistically significant.

Patients using only pharmacological therapy (Tab. III)

During the three-year observation period there was a gradual rise in the proportion of patients giving no clinical response to pharmacological therapy (Table III). After three years, therefore, about a quarter of the patients in this study fulfilled the criteria for inclusion in the SIT program. This is a clinically noteworthy proportion, especially among patients with asthma.

DISCUSSION

This study was carried out to establish a CPI system for use in allergology. This involved certain basic steps: drawing up a decisional tree; use of an observational methodology reflecting routine clinical practice; establishing a control group; measuring specific clinical endpoints, and statistical analysis of the results according to a preset plan. From the strictly methodological viewpoint the population was homogeneous as regards etyopathogenesis, as they all had respiratory allergies due to house dust mites, and were followed for a four-month "window" from November to February for a total of about five years. The decision to work in this "window" was based on the need to make the population as homogeneous as possible as regards exposure to the allergen, and to permit a more clear documentation of all the main clinical endpoints.

The selection of the control population, which expressed a preference for proper pharmacological therapy, was based on practical considerations to respect the observational method. The populations enrolled were thus homogeneous enough to be clinically significant even though the lack of randomization procedure and analysis of confounding factors means we cannot draw any generalized conclusions, applicable to all patients with respiratory allergy.

We decided to work on an observational basis because the study's main aim was to develop investigational methods that could be used in allergological practice, and because the study relied on observation of a large, selected case list followed for at least 36 months. As has been widely noted,

the long observation period required in an allergy study means it is difficult to arrange randomized double blind vs placebo clinical trials on large populations. In addition the patients who received SIT in this study were by definition "difficult cases", who had failed to respond to pharmacological therapy alone in the previous year. The proportion of patients given SIT thus seems higher than would be encountered in routine clinical practice. One explanation might be that patients attending specialized allergy centers are often those whose diagnostic-therapeutic path has not been in line with the latest medical guidelines. This population is therefore selected, but at the same time, since these are difficult cases, they can be more significant from a clinical viewpoint.

With these points in mind, the results of this observational study do confirm the safety and efficacy of all three treatments studied: intranasal, sublingual and sc according to previous published data (10,16-22). The BHR findings indicate a possible protective role when SIT is administered by the sublingual or subcutaneous route, in line with previous clinical trials (23,24).

Findings on compliance with treatment indicate, even bearing in mind the methodological limitations of the study, especially as regards assessment of the pharmacological therapy, that an appropriate follow-up schedule of the patient can result in excellent levels of compliance. For SIT this appeared significantly better than in other trials whose findings have been published (25,26). Analysis of responders to pharmacological therapy showed that with the years the proportion drops significantly, probably at least partly on account of problems in complying with treatment for asthma.

In conclusion, the present CPI program indicates that dividing patients up and prescribing SIT by different routes, can give gains in terms of cost/benefit results.

The results of the study can suggest also a possible use of the immunotherapy in patients with poor compliance to drug therapy.

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