Immunotherapy in Bronchial Asthma

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ABSTRACT

Immunotherapy and allergenic avoidances are the only etiological treatments we can offer the allergy patient to change the natural course of his disease. Immunotherapy efficacy and safety in bronchial asthma are two aspects considered to be very controversial. Based on different clinical studies that have been performed with a randomized double blind design controlled with a placebo group, we are going to verify how, in fact, both immunotherapy efficacy and safety are two important facets of the therapy. These facets are undoubtedly perfectly demonstrated and supported by the exhaustive and objective analysis represented by the positive results gathered by a Meta-analysis, which also concludes that at least 33 clinical trials with a negative result would be necessary to negate the good conclusions reached by it.

KEY WORDS: Bronchial asthma, immunotherapy efficacy, immunotherapy safety.

INTRODUCTION

Our main objective when attempting to reach an exact etiological diagnosis of a disease is to establish a specific treatment for it. Along these lines, once the agent responsible for the allergy pathology suffered by the patient is known, we should begin the etiological treatment. At present, allergenic avoidance and immunotherapy are the only etiological treatments we can offer the allergy patient.

We define immunotherapy as the art of slowly and progressively immunizing a patient in which a predominately IgE mediated abnormal immune response against the allergens present in the environment has already been initiated. Its objective is to induce a state of clinical tolerance against the allergen administered in the subject.

Basically referring to the immunotherapy administered parenterally, **we are going to demonstrate its importance as an unquestionable cornerstone in the treatment of the patient affected by extrinsic primary bronchial asthma (allergic) as long as we have an adequately standardized extract of the responsible allergen.**

I - EFFICACY OF IMMUNOTHERAPY

As we begin this exposition, we wish to make our opinion clear on the regime we consider the best one to follow when we decide on the subjects to be included in the review. Review articles are frequently found in which the author reports on a series of original papers without knowing the selection protocol of these papers or without having subsequently performed a statistical analysis of the data gathered in them, is common. In addition, it often appears that there is no real independence in this selection because the data are obtained by only one evaluator, a blind tabulation of them is not performed, etc. By the above, we are not trying to say that we are not going to perform a narrative analysis of the papers we consider worth mentioning because of one or several of their data. However, our final conclusions will be based on a meta-analysis, a method invented to integrate clinical trials, in which we know what the inclusion protocol of the papers was (for example, among others, double blind/placebo) and a statistical analysis will then be performed on the data and conclusions given. Going deeper into this question, it would be best if the authors of this meta-analysis were impartial, that their paper had already been published in an English-speaking journal having a great index of international impact and of course, that it had been seen by reliable critics or reviewers prior to its publication.

A - Clinical studies

We review the descriptive bibliography referring to the different fundamental allergens:

1° Animal epithelia

Regarding the immunotherapy performed with animal dander extracts, we have selected the papers listed in references 27 to 37. Table I shows their most significant results of them.

Memberships of Immunotherapy's Committee of AAAI*, EAACI*#, SEAIC*# and ESPACI*

AAAI: American Academy of Allergy and Clinical immunology

EAACI: European Academy of Allergy and Clinical Immunology

SEAIC: Sociedad Española de Alergologia e Inmunologia Clinica

ESPACI: European Society Paediatric of Allergy and Clinical Immunology.

Table I - Immunotherapy and asthma from animal epithelia

Author	Allergen	Symptoms	Skin Tests	Challenge	
				Non-specific	Specific
Taylor	Cat				Improvement
Ohman	Cat	Improvement		NS	Improvement
Sundín	Cat/Dog	NS		C: Improvement	C: Improvement
Valovirta	Dog			D: NS	D: NS
Alvarez-Cuesta	Cat	Improvement	Improvement	NS	Improvement
Rohatgi	Cat/Dog			NS	C: NS D: Improvement
Van Metre	Cat			NS	Improvement
Bertelsen	Cat/Dog				Improvement
Lilja	Cat/Dog	NS		C: Improvement D: NS	C: Improvement D: Improvement

NS: Non-significant; C: Cat; D: Dog

We are going to carefully analyze the study performed by Alvarez-Cuesta et al.[37] as it was the first one to be published in which immunotherapy is performed with a biologically standardized allergenic extract and quantified with monoclonal antibodies. This is a randomized double blind study controlled with a placebo group in which 28 patients diagnosed of atopic bronchial asthma (cat epithelium), 14 of which were treated with immunotherapy (group A) and the remaining 14 with the placebo (group B), were selected. The immunotherapy efficacy was evaluated on the basis of clinical (reduction of symptoms and medication needs) and paraclinical (prick-test, conjunctival and bronchial challenge tests with cat epithelium extract and methacholine) parameters. The immunotherapy treatment was begun with a 0.004 µg dose of Fel d I and reached a final maintenance one of 13.2 µg.

The final results, that were statistically significant, demonstrated the efficacy of the immunotherapy.

1° Improvement of group A in relation to group B (placebo) of both the clinical manifestations presented and the need to use symptomatic medication.

2° Marked decrease in skin and conjunctival sensiti-vity in group A in regards to group B.

3° Intense improvement of the specific bronchial hyperreactivity against cat allergens in group A in regards to group B demonstrated by the specific bronchial challenge test.

No statistically significant changes were observed in the non-specific bronchial hyperreactivity between both groups. It was also clear that a good maintenance dose for immunotherapy with biologically standardized cat extract whose major allergen (Fel d I) is quantified with monoclonal antibodies could be 13.2 µg of Fel d I/dose.

2° Pollens

Regarding immunotherapy efficacy in the treatment of atopic bronchial asthma (pollens), we wish to underline the importance of publications numbers 38 to 54 in our bibliography. Table II shows the principal conclusions of some of these studies.

We are going to briefly summarize the paper published by I. Dolz et al. in 1996. In order to evaluate the efficacy of the immunotherapeutic treatment, a double blind, randomized study controlled with a placebo group was performed. In this study, there was a three year follow-up of 30 patients diagnosed of bronchial asthma due to IgE mediated hypersensitivity to grass pollen. The patients were randomly distributed into two groups -- groups A and B, with a 2:1 ratio respectively, and were treated with specific immunotherapy and placebo as well as with the symptomatic medication required. To evaluate the treatment results, both clinical and paraclinical

Table II - Immunotherapy and asthma due to pollen

Author	Allergen	Symptoms	Skin Tests	Challenge	
				Non-specific	Specific
Reid	Grass pollen	Improvement			
Kuna	Grass pollen	Improvement		Improvement	
Armentia	Grass pollen	Improvement	Improvement	Improvement	Improvement
Rak	Betulaceous	Improvement	Improvement	Improvement	
Van Bever	Grass pollen			NS	I.R.: NS
Creticos	Ambrosia	Improvement	Improvement	NS	Improvement
Dolz	Grass pollen	Improvement	Improvement		Improvement

I.R.: Initial Reaction; NS: Non-significant

Table III - Immunotherapy and asthma due to dust mites

Author	Allergen	Symptoms	Skin Tests	Challenge	
				Non-specific	Specific
Aas	Mites	Improvement			Improvement
D' Souza	Mites	Improvement			
Gaddie	Mites	NS			
Marqués	Mites	Improvement			
Newton	Mites	NS			Improvement I.R.
Warner	Mites	Improvement			Improvement L.R.
Pauli	Mites			NS	
Price	Mites	Improvement			
Bousquet	Mites			NS	Improvement I.R. Improvement L.R.
Mosbech	Mites	Improvement		NS	NS
Wahn	Mites				Improvement I.R.
Van Bever	Mites				Improvement I.R. Improvement L.R.
Van Bever	Mites	Improvement			Improvement I.R. Improvement L.R.
Haugaard	Mites	Improvement	Improvement	NS	Improvement I.R. Improvement L.R.

I.R.: Immediate raction; L.R.: Late reaction; NS: Non-significant

parameters were used. The following results were obtained:

1° Progressive decrease of the clinical symptoms and the use of symptomatic medications during the first two years in group A. These patients were asymptomatic during the third year and did not need antiasthma medication.

2° In group A, the antigenic concentration necessary for the conjunctival challenge and bronchial challenge tests to be positive increased 250 BU/ml and 1000 BU/ml respectively after immunotherapy treatment was completed. In addition, a marked decrease in skin sensitivity to the grass pollens was observed.

3° No statistically significant changes in the serum values of total IgE or specific IgG and IgE were observed between both groups after Group A and B patients completed three years of immunotherapy treatment.

Two fundamental conclusions can be drawn from the results presented: 1°: Specific immunotherapy with biologically standardized allergenic extracts is an effective treatment for atopic bronchial asthma (pollens); 2°: Analytic parameters (total IgE, specific IgE and IgG) are not useful for immunotherapy follow-up but the cutaneous tests have a manifest suitability for the follow-up and evaluation of immunotherapy efficacy without having to periodically subject the patients to other specific challenge tests (conjunctival or bronchial challenge), that are much longer and bothersome.

3° House dust mites

In relation to the efficacy of immunotherapy performed with house dust mite allergenic extracts, we have selected bibliographic references 55 to 73. Table III presents the most significant results of some of these studies.

Let us study the paper by Haugaard et al.[72] published in 1993 in greater detail. In this paper, 74 asthmatic patients allergic to house dust mites were included in a double blind, randomized placebo controlled study whose objectives were to evaluate the therapeutic efficacy of immunotherapy and to determine what the optimum maintenance dose would be when adequately standardized extracts are used. These patients were randomly included in four different groups that we will call I, II, III, and IV. The first three groups received a maintenance dose of 0.7 µg, 7 µg and 21 µg respectively of Der p I, but group IV that acted as a control did not receive specific immunotherapy. Clinical and paraclinical parameters were recorded during the 24 months that the study lasted.

The efficacy of immunotherapeutic treatment becomes clear when the following is observed: 1° A marked decrease in both their symptoms and the need for medication to control them in patients treated with immunotherapy in comparison to those forming part of the placebo group (IV); 2° Decreased skin sensitivity together with an increase in the concentration of Der p I needed in the conjunctival challenge test to obtain a positive response in the three groups of patients who received immunotherapy

Table IV - Immunotherapy and asthma from fungi

Author	Allergen	Symptoms	Specific bronchial challenge
Malling	Cladosporium	Improvement	
Malling	Cladosporium		
Dreborg	Cladosporium	NS	Improvement
Horst	Alternaria	Improvement	Improvement

treatment compared to the placebo treated group; 3° An increased dose-dependent tolerance to Der p I in bronchial challenge in each one of the immunized groups (group I: two fold change; group II: 5-9 fold change; group III: 4-5 fold change) and no change in bronchial sensitivity in the control group.

The greater incidence of systemic reactions seen in those patients who received a maintenance dose of 21 µg Der p I per dose (7.1%) compared to those who received 7 µg (3.3%) and those treated with 0.7 µg (0.56%) together with the above mentioned results in the specific bronchial challenge test led to the conclusion that a dose of 7 µg Der p I should be recommended as the optimum maintenance dose.

4° Fungi

In relation to immunotherapy with fungus extracts, we have selected the papers included in references 74 to 80. Table IV gathers the most significant results.

We are going to carefully consider the paper by Horst et al.[80] in which 24 patients who were monosensitized to Alernaria and were included in a double blind randomized study and controlled with a placebo group were studied for one year to evaluate the efficacy of immunotherapeutic treatment with a biologically standardized extract. The group submitted to immunotherapy treatment (group A) and the group treated with a placebo (group B) were formed by 13 and 11 patients respectively.

Once the follow-up of the patients was completed, immunotherapy efficacy was clear on observing that, in relation to group B patients, those included in group A showed a statistically significant improvement in their appreciation of the intensity of the symptoms suffered and the need to use symptomatic medication. This subjective improvement was verified when a marked decrease in cutaneous reactivity and the need for a greater concentration of the extract to reach a positive nasal challenge test was seen in this same group of patients (treated with immunotherapy).

B - Meta-analysis

Having briefly reviewed the narrative bibliography that we consider to be of greatest interest, we should analyze the meta-analysis previously published by Abramson et al. with greater care before establishing our final conclusions. These authors exclusively selected those papers that fulfilled a preestablished protocol: the fundamental point being studies designed in a double blind fashion, controlled with a placebo group. A total of 20 papers were selected for analysis (9 on mites, 5 on pollens, 5 on animal epithelia and 1 on fungi). The variables analyzed in each one of the studies chosen were: 1° Improvement of symptoms; 2° Decrease in medication usage; 3° Bronchial hyperreactivity; 4° Lung function and 5° Side effects.

The results of the evaluation of the variables mentioned are expressed by the odds ratios (OR), which mean how many patients improve with the treatment studied in regards to the control (probability of success due to the treatment received). If the treatment being studied does not benefit the patients more than the control, the OR would be equal to or similar to 1, and should have a value of >1 in order to consider that the efficacy of the established treatment is adequate. This efficacy is greater, the higher the OR value. Table V gathers the OR values obtained after analysis of the studies performed and its combined definitive values obtained from the joint analysis of all of them.

The final conclusion obtained is that immunotherapy is an effective treatment for bronchial asthma. In the group of patients who received immunotherapy treatment compared to the control group (placebo), the following was observed:

* A three fold decrease in the intensity of the symptoms perceived.
* A four fold decrease in the need for symptomatic treatment.
* A six fold decrease in the specific bronchial hyperreactivity.

These conclusions are strongly supported by the assertion made in Abramson's paper that at least 33 studies with negative results, performed with the same scientific precision as those reviewed here, are needed to neutralize the positive conclusions obtained. Finally, we state that most of the studies chosen in this meta-analysis have not been performed with standardized antigens; it is logical to think that if these had been used, the results shown would be greater.

C - A very important aspect to consider is not only that of the already demonstrated efficacy of immunotherapy but also if **it is maintained in the long run**. We wish to

Table V - Abramson et al. ODDS RATIOS

	House dust mite	Other	Combined
PSE	2.7	4.8	3.2
SMS	4.2	–	4.2
BHR	13.7	5.5	6.8

PSE: Patient's self evaluation; SMS: Sympto-medication scores; BHR: Bronchial hyperreactivity

make special mention of the paper by Des Roches et al. (Allergy 1996) in which 40 asthmatic subjects divided into two groups received immunotherapy with mite extract from house dust for a period ranging from 12 to 35 months for those included in group I and from 36 to 60 months for those in group II. Once the immunotherapy was discontinued, a follow-up of all the patients was performed for three years and in this way, the duration of the immunotherapy efficacy was evaluated. The results obtained were the following:

* All the patients were asymptomatic for a period of time greater than one year, which can be explained because, as in the other investigations performed, all of the patients received treatment for a time interval that was not less than one year.
* The duration of the immunotherapy efficacy after its suspension was directly proportional to the maintenance time of it.
* The evolution following the skin tests in both the active treatment period as well as the later follow-up has an important predictive value about the length of the efficacy of the immunotherapy performed.

Table VI - Modification of the late responses by immunotherapy

Reference	Antigen	Population	Late response	Improvement of symptoms
Metzger, 1985	Alternaria	Adults	⇓ Pulm. (50%)	Yes
Warner, 1987	Mites	Children	⇓ Pulm. (50%)	Yes
Van Bever, 1989	Mites	Children	⇓ Pulm. (60%)	?
Pienkowski, 1985	Ambrosia	Adults	⇓ Cutaneous	Yes
Fling, 1989	Cedar	Adults	⇓ Cutaneous	Yes
Varney, 1991	Phleum	Adults	⇓ Cutan. (57%)	No

D/ Finally, the effect of the immunotherapy treatment on the late phase of the asthmatic reaction, a circumstance which corroborates the clinical improvement of the patient, is summarized in Table VI.

II - SAFETY OF THE IMMUNOTHERAPY

We want to begin by emphasizing that a fatal adverse reaction has never been described in original research manuscripts published since 1911.

The observation that the efficacy of immunotherapy was dose-dependent led many investigators to design very aggressive protocols with excessively high maintenance doses accompanied by a relatively high number of adverse reactions. The later development of biologically standardized allergenic extracts in which, thanks to the use of monoclonal antibodies, it was possible to know the exact concentration of major allergens, has made it possible to solve this problem. It has thus been possible to use high optimum maintenance doses with a high safety index and when these doses are accompanied by adverse reactions, they are generally local and easily controlled with common treatments without requiring their administration to be interrupted.

In relation to immunotherapy safety, we emphasize the following papers:

* M.J. Reid et al. who in 1993 published the results of a survey made among the members of the American Academy of Allergy and Immunology, gathering a total of 27 deaths associated to the use of immunotherapy. These deaths represented one per 2 million doses administered, 76% of them corresponding to patients with unstable asthma and 26% to subjects in treatment with betablockers; in both of these circumstances, the use of this treatment is contraindicated.
* A. Tabar et al. (Allergy 1993), in a prospective study on 419 patients affected by asthma due to grass pollen and/or mites, who were administered a total of 9482 doses, found local reactions in 10.5% of the patients and systemic reactions in 4.8% of them. These reactions corresponded to 0.37% of the total doses administered and it was not necessary to discontinue treatment in any case.
* E. Alvarez-Cuesta et al. in his study on cat dander extract standardized with monoclonal antibodies and in spite of reaching a high maintenance dose (13.2 µg of Fel d I), only observed the appearance of adverse reactions in 1.91% of the total doses administered, 1.5% corresponding to local reactions and 0.41% to systemic reactions. It was not necessary to discontinue treatment in any of the cases.

III - COST OF THE IMMUNOTHERAPY

Although some medical colleagues insist on the inconvenience of the cost of immunotherapy without counting on adequate bibliographical support, we believe that this section has much less importance than some have tried to emphasize. It must be assumed by both us and the patient that immunotherapy, together with allergenic avoidance, is the only etiological and preventive treatment that we can offer the allergy patient to stop the natural evolution of his disease. When speaking about specific immunotherapy, we must not forget that we are dealing with a treatment that should be individually adjusted to the needs of each patient, that is, we are speaking of a "**TAILOR MADE SUIT**" and not ready made clothes. Finally, when referring to immunotherapy costs, we must remember, as Abramson et al. have demonstrated in the meta-analysis analyzed, that thanks to immunotherapy, the use of symptomatic medications is reduced more than four times.

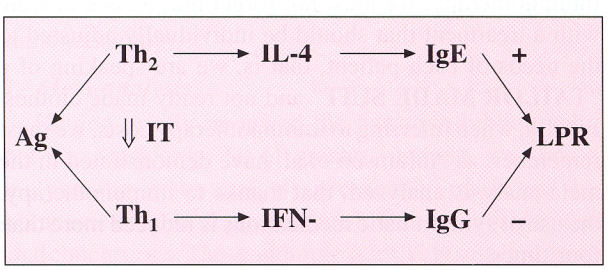
IV - ACTION MECHANISM OF IMMUNOTHERAPY

When, after allergenic stimulation, interaction of the allergen with the antigen-specific IgE molecules joined to FceRI (high affinity) and FceRII (low affinity) receptors of the mastocyte and macrophage surface respectively is produced, the series of events of phenomena characteristic of hypersensitivity type I reactions begins. These have an immediate phase followed by a late phase at 4-6 hours which, as we have already mentioned, is the most directly related to the severity of the disease in the long run. The T cell that is activated is a CD_4+ cooperating cell (Th_2), which produces IL-4, IL-5 and GM-CSF (granulocyte-macrophage colony stimulating factor) that predominately collaborates in the synthesis of IgE.

On the contrary, in the non-allergic subjects, the CD_4+ (Th_1) cells, producing IL-2, IL-3, IFN-γ and GM-CSF predominate.

A point of immunotherapy to consider in the treatment of allergic diseases is its interference with the mechanisms responsible for the release of mediators. After immunotherapy treatment, both a decrease in the T lymphocytes infiltrates as well as in the pattern of lymphokines produced by them, with a greater synthesis of IFN-γ at the cost of a decrease in the IL-4 and IL-5 is observed in the cellular clones of the allergy patients. This means there is a predominance of the Th_1 cells over the Th_2 ones. The decrease in the number of the latter cells, favored by the immunotherapy whose principal final effect is the inversion of the Th_1/Th_2 ratio, would cause the reduction of the synthesis of IL-4 and thus of IgE, dependent on the former as well as a decrease of the activation of the mastocytes secondary to the action of the IL-3 (produced by the Th_2 lymphocytes).

Durham et al. reached the conclusion that the predominance of Th_1 lymphocytes can be related to the activity of the IL-12 fundamentally produced by the activated tissular macrophages. Furthermore, the IFN-γ produced by these cells (figure 1) would act both by inhibiting the IgE synthesis dependent on the IL-4 as well as by inducing the specific IgG_4 blocker antibodies, circumstances that jointly would favor the blockage of the late phase of the type I hypersensitivity reaction and thus modify and avoid the natural evolution of the disease toward the irreversible deterioration of the respiratory function of the patient.



V - PRACTICAL ASPECTS OF IMMUNOTHERAPY

Our condition as allergologists requires us to know the most important aspects of immunotherapy when it is used to treat allergic diseases. These are given in the following decalog:

1° For immunotherapy to reach its maximum efficacy and safety, it should be **individually adapted** to the characteristics and needs of each patient. It should always be considered as a "tailor-made suit" and never as a "prêt à porter."

2° **Conditions for an efficient immunotherapy**. Maximum efficacy is reached by using adequate antigenic extracts administered at the optimum dose.

* An adequate antigenic extract is that which contains all the active allergens in their native form in the adequate proportion and with the optimal strength. The following should be expressed on the label: the total allergenic activity in biological units, the concentration of the major allergens in µg/ml and the expiration date.

* Optimum dose is that which is associated to the maximum safety and efficacy for treatment and should be adjusted for each specific extract and for each patient individually. It generally ranges from 6 to 12 µg/ml.

3° **Allergenic extracts.**

* Aqueous. They are partially purified extracts because of the elimination of the low weight molecular non-allergenic substances. They are best used to apply rapid regimes and clusters. They have the inconvenience that the allergens rapidly degrade but they make it possible to reach the maintenance dose faster, a circumstance that can be important for the patient's life and they have the advantage that few subcutaneous nodules appear on the administration site.

* Modified. They are widely accepted as they are considered safer than the previous ones. They are characterized by a **reduction in their allergenicity** (capacity to induce an IgE mediated reaction), and maintain their immunogenicity (capacity of activating the immune system). Their adequate standardization should include: 1° The standardization of the initial material used to elaborate the extract; and 2° The documentation of the modification process reproductivity.

The modifications can be:

* Physical: Several substances are used as transporters (aluminum hydroxide, calcium phosphate, etc). They are the extracts called depot.

+ Chemical: Extracts modified with formaldehyde and alginate. They are called "polymerized."

* Mixed. They include the extracts modified with glutaraldehyde and tyrosine.

4° **Indications of the immunotherapy.**

Atopic subject with predominance of IgE mediated component:

- Not controlled with environmental measurements and sporadic medications that are well tolerated and of low risk.
- Progressive severity.
- Induced by mites and/or pollens.
- Induced by animal epithelium, but only under the following circumstances:
  - Frequent visits to places in which contact with the animal cannot be avoided.
  - Occupational disease.
  - Unknown exposure and/or crossed reactivity.
- Induced by fungi. We only use immunotherapy in those cases in which we have adequately standardized extracts.

5° **Contraindications of immunotherapy.**

* Absolute:

1st Malignant or associated immunopathological diseases.

2nd Contraindications of adrenalin. Immunotherapy should not be used in those patients in whom adrenalin (treatment of choice of the possible adverse reactions) could be dangerous or not very efficacious (hyperthyroidism, high blood pressure, treatment with betablockers, etc).

3rd Difficult correct administration (psychiatric patient and/or uncooperative one).

* Relatives:

1st Age under 5 years

2nd Pregnancy. Although no teratogenic effects of the immunotherapy have been observed at any time, this should not be initiated during pregnancy to avoid the risk of undesirable effects secondary to both possible adverse reactions as well as the treatment of them. If the immunotherapy, already in the maintenance phase, is well tolerated, there is no indication for it being discontinued. We will ALWAYS discontinue it in the face of any doubt of the patient.

3rd Patients over 50 years, since the IgE mediated component can have less importance in them, the benefit/risk ratio being less favorable. These are frequently very advanced processes with irreversible deterioration of the lung function in which the immunotherapy would be ineffi-cacious.

4th Severe atopic dermatitis. Immunotherapy can worsen the cutaneous outbreaks, a circumstance in which it should be immediately suspended.

6° **Immunotherapy administration form.**

* In relation to its chronology, we differentiate:

Perennial - Ideal form of administration since, in this way, the total dose received by the patient is greater and thus the clinical results better.

Pre-seasonal - It is used by some specialists, in certain circumstances.

* In relation to the administration, we differentiate:

Conventional regime: During the initial phase, we administer growing doses at weekly intervals so that, once the optimum dose is reached, it can be repeatedly administered at intervals of 21-30 days.

Rapid regime. Shorten the duration of the initial phase by administering the immunotherapy several days a week, applying more than one injection per day. After reaching the optimum doses, the same will be done as in the previous regime. During the initial phase, aqueous extracts are used which, if they are properly standardized (expressing the exact amount of major allergens in µg/ml and with the adequate proportion between them), when the maintenance dose is reached, they can be directly substituted for depot allergenic extracts having the same characteristics.

Cluster regime. During the initial phase, although the immunotherapy is administered weekly, several doses are injected each day with intervals of 30 to 120' between them. We will act the same in the maintenance phase as in the previous regimes.

7° **Duration of immunotherapy**

How long immunotherapy should be prolonged is a question that has yet to find an adequate response in our days. Several clinical studies have demonstrated the prolonged duration of protection given by immunotherapy with Hymenoptera venom and inhalants (Des Roches et al 1996) once this has been discontinued after continuous administration of 3-5 years. Heeding the previous reflections and following the recommendations of the Immunotherapy Committee of the EAACI, we consider that the immunotherapeutic treatment should last for no less than three years at which time it can be discontinued if the patient remains:

* Symptom free for two years with negativization of the skin tests and specific IgE.

* Symptom free for two years with a marked decrease in the skin tests and the sensitivity of the shock organ.

8° Suspension of the immunotherapy

Immunotherapy should be interrupted in the following suppositions:

* Development of some contraindications already seen after the onset of treatment.
* In patients who show no clear clinical improvement after one year of treatment, a new allergologic evaluation should be performed. This apparent therapeutic failure is generally related to: erroneous etiological diagnosis, that there is no indication for its use, that it is not acting properly on the environmental antigenic load, that new sensi-tizations have been produced and to excessive and/or premature therapeutic perspective by the patient.

9° Practical management of immunotherapy.

It should be prescribed, without exception, by an allergy specialist, should be administered by an experienced nurse and should always be done under the supervision of an attending physician (ideally, an allergologist). The parenteral immunotherapy is administered subcutaneously, using a one-time use syringe with a 26-27 mm needle, which should be applied on the external face of the arm at a mean distance between the shoulder and the elbow, alternating between both arms. The needle should form a 45° angle with the skin and its bevel directed upwards. The zone should not be massaged after application.

Prior to its administration, the following should be done:

* Evaluate the clinical condition of the patient to avoid administration in those situations in which it is not advisable.
* Question the patient about the tolerance of the last dose administered, thus being able to control the presentation of a possible adverse reaction and adjust the new dose to be administered. Chart I shows the principal orientations of the Immunotherapy Committee of the EAACI in relation to the modifications of the dose.
* Delay the injection several days when there is: respiratory infection in the last week, maximal expiratory flow 20% inferior to the common basal values, recent unstable asthma and/or recently exacerbated atopic dermatitis and present treatment, presumably short, with betablockers.

Once the dose is administered, the patient should remain for at least 30' in the health center and should be evaluated by a physician before leaving it. It should be recommended that no intense physical exercise should be performed or warm baths, saunas taken, etc. for several hours after the administration of the extract.

Chart 1: Recommendations of the EAACI on modifications of the dose

The last dose administrated is maintained if:	The doses to be administered is reduced if:
* Immediate local reaction Adults: >5cm diameter Under 12 years: >3cm diameter	* Systemic Reactions * Co-seasonal treatment coinciding with high environmental antigenic load
* Late local reaction >8cm in diamenter or less if it is very bothersome	* When the administration of a bottle from a different batch than the previous one is initiated during the maintenance phase
* Excessive time interval from the last dose.	* Excessive time interval from the last dose.

10° Follow-up of the immunotherapy

At least once a year and in the same period in which the first preimmunotherapeutic evaluation was performed, the patient should be seen by the same specialists who initially prescribed it. For greater information on this subject, refer to reference number 8.

VI - CONCLUSIONS

1° Because of the development of standardized allergenic extracts in which both the strength as well as the concentration and proportion of its major allergens (thanks to the application of monoclonal antibodies in the field of immunotherapy) are well known, we can reach definite diagnostic and therapeutic achievements which make it possible for the clinical allergologist to convert the "art" of allergy into an exact medical practice.

2° The results of all the studies analyzed and predominantly of the meta-analysis performed by Abramson et al. make it possible to solidly support and defend the importance of immunotherapy as a cornerstone of the extrinsic bronchial asthma treatment whenever the causal allergen is identified and there is an allergenic extract that is adequately standardized for the treatment.

ACKNOWLEDGEMENTS:

We thank Barbara Shapiro for her help in the translation of this paper.

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