

Specific immunotherapy

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Specific immunotherapy was introduced in 1911 for the treatment of pollinosis. It consists of administering to patients increasing doses of allergens which have been shown to elicit allergic reactions. The most common form of administration is the subcutaneous route but oral or nasal immunotherapy may also be effective. Immunotherapy is highly controversial since most protocols have been devised empirically, many allergens are still poorly defined, the mechanisms of action are not yet clear, properly conducted trials are still sparse and allergen injections expose to life-threatening reactions. However, specific immunotherapy is one of the most common treatments in children and adolescents in many parts of the world and is effective under optimal conditions including a demonstrated IgE mediated disease, a high quality extract and proper dose and a correct indication. Moreover, immunotherapy cannot be replaced by any other treatment in venom allergy.

Mechanisms

The mechanisms of action of immunotherapy are still unclear and several possibilities have been proposed since the twenties.

For decades it has been postulated that allergen-specific IgG present in serum and secretions may block allergens before their interaction with cell bound IgE. This blocking activity may have some relevance in the protective effect of venom immunotherapy but is unlikely to act as a major mechanism with inhalant allergen although it may exist (20). IgG subclasses have been extensively examined

but, to date, there is no definite conclusion since in some studies IgG4 was associated to a poor efficacy of immunotherapy (12) whereas in others the contrary was observed (1). Recent studies on the idiotypic network have highlighted the putative role of specific IgG explaining possibly the decrease in IgE production after immunotherapy (15).

The evolution of allergen-specific IgE was also largely examined. In the seventies it was postulated that immunotherapy might induce a reduction in IgE synthesis but this only occurs after several months of treatment and cannot explain the early clinical efficacy of the treatment (45). Animal studies have provided evidence that a series of modified extracts elicited a suppressive activity of the IgE response. However, most of these studies were done on primary or secondary responses and rarely on ongoing ones (37). Many of these extracts have been used in humans, and although they had a protective activity, specific IgE was unaffected (19, 28).

In the thirties, there were some studies showing that skin tests with allergen were decreased during specific immunotherapy but no explanation could be given. These studies were almost forgotten until recent years. Since 1980, many experiments performed with pollens, mites, animal danders or molds have consistently found that skin tests, conjunctival tests, nasal and bronchial challenges are decreased after treatment (3, 5-9, 13, 14, 23, 32). It was observed that these changes in sensitivity were allergen-specific and may appear within hours after the onset of immunotherapy when the appropriate dose has been administered. Studies with nasal

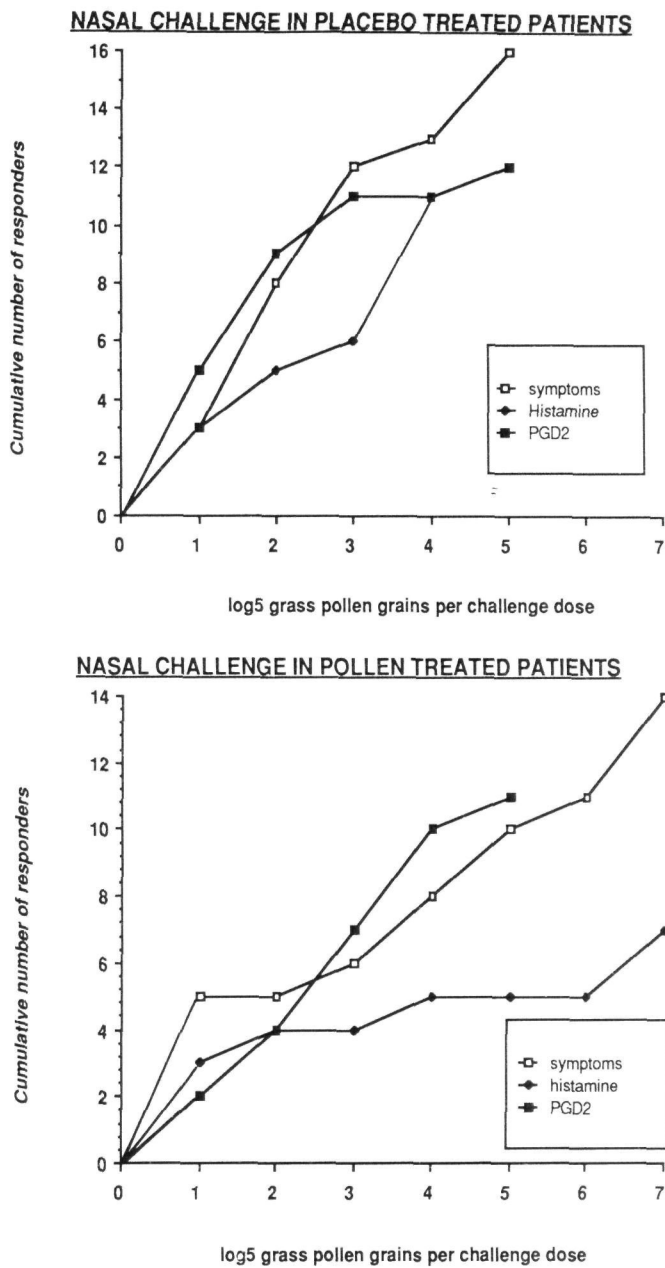


Fig. 1. Nasal challenge with pollen grains. From Bousquet et al. (unpublished results), 30 patients were treated.

challenges showed that the release of mediators participating in the allergic inflammation was decreased after treatment (Fig. 1) and that these changes were correlated to the efficacy of immunotherapy. Moreover, in vitro studies using histamine release from blood basophils or platelets have also found a decreased sensitivity of these cells to the allergen after immunotherapy (24). These changes in cell sensitivity may be due to cytokines (40). Recently it has been shown that after 3 days of venom immunotherapy, a serum factor decreases the sensitivity of platelets to venom. Moreover, during pollen immunotherapy mononuclear cells synthesize

less histamine-releasing factors. Finally, eosinophils and mast cells participating in the allergic inflammation may not be attracted during the allergen exposure in treated patients (31, 36).

Changes in cell sensitivity may better explain the efficacy of immunotherapy than variations in serum antibodies but both mechanisms may operate at different times of immunotherapy or with different allergens.

Efficacy

The efficacy of immunotherapy is now widely documented in optimally designed controlled trials. More specifically, immunotherapy with venoms protects over 90% of allergic individuals (11, 18). Immunotherapy with honey bee venom appears to be less effective than that of Vespidae venoms. In inhalant allergy, grass and ragweed pollen extracts are efficient in rhinoconjunctivitis (2, 5, 6, 8, 9, 14, 16, 17, 19, 30, 33) and recent studies have confirmed the efficacy of the treatment in grass pollen asthma (6, 9). Other pollen species have rarely been studied and it is postulated that immunotherapy is effective but proper trials have to be done. Immunotherapy for mite asthma is also effective but the inflammation of the airways should be considered before starting it (3, 7, 10, 21, 27, 44). The sustained allergic reaction in the bronchi of mite allergic asthmatics leads to a severe inflammation and bronchial hyperreactivity. After a natural course of two to three decades, many patients present an irreversible airways obstruction and the response to immunotherapy is usually poor. It was therefore observed that children respond more favourably to mite immunotherapy than adults (7). Specific immunotherapy was proposed in animal dander allergy and results are not completely clear. Results of provocative challenges have found that allergen injections reduce the bronchial sensitivity to allergen but symptoms were not always reduced in patients living with animals (38, 42). Finally, only pilot studies have been started with molds and interesting results have been produced (13, 23).

Double-blind controlled studies have therefore confirmed the efficacy of immunotherapy

but pharmacologic treatment is also available for the treatment of allergic diseases. This was improved in recent years since it is more effective and side reactions have been significantly decreased so that before starting immunotherapy the relative efficacy and risk of immunologic and pharmacologic treatments should be carefully compared (Table 1).

Indications

For indications other than venoms, relative benefits, risks, costs and inconvenience of pharmacologic and immunologic treatments have to be considered before starting the injections; and immunotherapy should only be started when serious attempts at allergen avoidance have been made.

Immunotherapy has been shown to be more effective in children and young adults than later in life, so that in old age the indications of immunotherapy are restricted. Before 5 years of age, immunotherapy may be started but it is desirable to evaluate more closely its benefits. During pregnancy, the severity of allergic diseases is often modified and, immunotherapy should not be started except in case of highly exposed patients allergic to venom.

Before starting immunotherapy each patient

should be carefully informed of risks, duration and effectiveness of this treatment and, cooperation and compliance to the treatment are absolutely required before starting it.

The specific indications have been extensively studied. It is commonly accepted that immunotherapy is indicated in severe pollinosis, especially when asthma complicates rhinoconjunctivitis, in mite allergy (but severe asthmatic patients should be excluded owing to possible untoward side reactions) and in life-threatening reactions due to *Hymenoptera* venoms. This form of treatment may be started in some selected cases of animal dander allergy but allergen avoidance is favoured. Mold extracts might be used in the future but, at present, high quality extracts are merely unavailable in practice. Immunotherapy with house dust, *Candida albicans* or bacterial vaccines was largely used in the past but it is not advisable any more. Some anecdotal data gave the impression that foods or occupational allergens might be used to treat patients but these extracts should be restricted to controlled trials.

Contraindications

Absolute contraindications include patients with other serious immunopathological conditions,

Table 1
Comparison between immunotherapy and the pharmacologic treatment of allergic diseases

	Venom allergy	Pollen rhinitis		Pollen asthma	Mite asthma
		mild	severe		
<i>Efficacy</i>					
IT drugs	high none*	high high	usually good usually fair	high high	non to high fair to high
<i>Side effects</i>					
IT drugs	possibly severe	possibly severe none to mild		possibly severe none to mild	possily severe none to severe
<i>Duration</i>					
IT drugs	3-5 yr	3 yr- life span life span		3 yr- life span life span	3 yr- life span life span
<i>Cost of health care</i>					
IT drugs	expensive	expensive lower cost		expensive lower cost	expensive may be expensive

*: no preventive drugs, adrenaline may not be given early enough to cure anaphylaxis.
IT: immunotherapy

malignancies, poor compliance, severe psychological disorders and/or treatment with beta-blocking agents.

Extracts

Many different extracts have been proposed since the introduction of immunotherapy. Aqueous extracts are effective when standardized but they expose to a high rate of systemic reactions so that it was proposed to attempt decreasing the allergenicity (reduction of side effects) without modifying the immunogenicity (similar efficacy). Among the various preparations, adsorbed extracts on aluminium, tyrosine or calcium phosphate are commercially available and were shown to decrease the incidence of side reactions (43) but they only represent a first attempt. Extracts polymerized by formaldehyde (8, 9, 25) or glutaraldehyde (17, 34) are effective and high molecular weight preparations are safer than the aqueous extracts. PEG-modified extracts represent another interesting approach. In animals, they were shown to suppress the IgE production. In humans this property was not so clear but they appear to be effective and safer than aqueous ones (19, 28, 37).

Dose of maintenance injections

The maintenance dose of immunotherapy is still a matter of debate. Initially, it was proposed to give a high dose to patients but owing to severe and fatal reactions, other investigators following the concept of Dr. Rinkel proposed low doses after so-called skin test titration. However, this technique has been found ineffective and should not be used any more (26). Then, it was proposed to give to patients the "highest tolerated dose" with potent extracts (30). Once again, severe untoward reactions were observed and lower doses (but not low doses) were administered. We proposed to use *optimal doses* i.e. doses inducing a change in cell sensitivity but giving a low and acceptable rate of systemic reactions. We started by serially studying skin tests after allergen administration and defined a dose inducing a decrease in skin test end point.

Then we confirmed that the dose was able to decrease the $PD_{20}FEV_1$ of mite allergen and to increase the mean numbers of pollen grains during nasal challenge (3, 5–9). Finally, we also demonstrated that this optimal dose achieved protection in patients suffering from pollen-induced rhino-conjunctivitis and asthma. Using a ten fold greater dose we increased the number of side reactions without major changes in efficacy (5). However, a much greater increase might enhance the effectiveness of immunotherapy but side reactions are likely to be greater and unacceptable.

For venom allergy, the maintenance dose was empirically proposed as being twice the content of a bee venom sack (18). Hopefully, this dose was effective in over 85 % of allergic individuals but when single venoms are used it is advised to increase the monthly maintenance dose to 200 μ g if serum venom-specific IgG does not increase enough (11).

Routes of administration and schedules

The usual route of administration of immunotherapy is the subcutaneous one. Recent studies have, however, nicely shown that oral (2, 39) or nasal immunotherapy (16) are effective when the appropriate extracts are given at a high dose. Systemic or local reactions were rather low with local administration of extracts. Oral immunotherapy with current extracts is not cost-effective since very large doses of extracts are required. Nasal immunotherapy can only be given with modified extracts.

Many protocols have been proposed empirically. Weekly or biweekly injections before the maintenance dose has been reached represent the classical form of the treatment. In 1930, Freeman proposed a rush procedure increasing doses several times a day. This rush regimen was only used for drugs until the seventies. It is now widely accepted for venoms and gains acceptance for many inhalant extracts since it makes it possible to reach the maintenance dose in 2–4 days.

The interval between two maintenance injections is also another matter of debate. Most investigators propose a monthly injection but in

the case of immunotherapy with aqueous extracts in the treatment of perennial allergy, many patients require injections at 2-3 weeks' intervals. Adsorbed and modified extracts may be given at 6 weeks' intervals.

Finally, some studies have shown that a passive administration of hyperimmune serum may protect the patient against systemic reactions and such an approach has been attempted in venom allergy (4).

Side reactions

Life-threatening reactions are not rare with high quality extracts, and deaths have been reported (29, 46). Thus, before any injection, patients should be monitored carefully and the treatment delayed if the patient presents any symptom of asthma or infection. Injections should only be given under the close supervision of a trained physician, in settings where anaphylactic reactions can be immediately corrected. The patient should be followed for up to 30 minutes after the shot. Systemic reactions occurring after allergen injection should be regarded as possibly serious and adrenaline (and oxygen therapy) should be immediately administered if necessary.

Monitoring

After some weeks to a few months of treatment, patients receiving immunotherapy should be reassessed and the treatment be stopped if not effective. In vivo and in vitro methods have been proposed to evaluate the efficacy of immunotherapy. Provocative challenges are the best approach but they are difficult to perform routinely in clinical practice.

Patients receiving immunotherapy often require an additional pharmacological treatment, especially in asthma, but the immunologic treatment often makes it possible either to reduce drugs or to improve the control of the disease.

Duration

Duration of immunotherapy is another matter of debate. Our best current knowledge is for

venom immunotherapy for which it is accepted that injections can be safely stopped when skin tests and RAST to venom become negative or very low (41). Some investigators have discontinued venom immunotherapy after five years but the results of these studies are not completely available.

In the case of inhalant allergy in atopic individuals data are lacking to support any conclusion, but it appears that a long term treatment (35), at least three years, is required. For perennial allergens, immunotherapy might be required for the life span.

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