

Specific Immunotherapy in House Dust Mite Allergy

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Introduction

Specific immunotherapy (SIT) was introduced in 1911 (1) and for many years remained based on empiricism. Extracts of unknown quality and shelf-life (e.g., house dust, *Candida albicans*, bacteria) were used and the efficacy of SIT was seriously questioned. The introduction of standardized extracts made it possible to increase the efficacy of immunotherapy and double-blind placebo-controlled studies have demonstrated the efficacy of this form of therapy in rhinitis, asthma, and conjunctivitis. The increased efficacy of immunotherapy was associated with an increased risk of anaphylactic reactions (2–4), leading again to question the future of SIT (5). International guidelines have been issued to improve the use of SIT (6–8). SIT is the only treatment intervention that may alter the course of allergic diseases and new methods of specific and nonspecific immunotherapy are being proposed and may prove to be efficacious and safe (9).

SIT is still widely used throughout the world. In the future several approaches may be interesting, but all of them are based on the perfect characterization of allergenic molecules and epitopes causing the IgE-mediated immune response. New technologies using molecular biology and genetic engineering have made significant progress in the characterization and preparation of allergens.

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Objects of Immunotherapy

Rhinoconjunctivitis

The treatment of allergic diseases combines immunologic and pharmacologic treatments. In many patients, drugs can relieve nasal and ocular symptoms without side effects. In these patients, SIT is not indicated but in a subset of patients drugs are not sufficiently effective or induce side effects. In these patients SIT may be started.

However, differences between the pharmacologic and immunologic treatments of allergic diseases may not be restricted to safety and efficacy. Drugs only represent a symptomatic treatment and SIT is the only treatment that might cure the disease if it is shown that the effects of SIT last after its cessation. Finally, SIT may prevent the onset of asthma in patients suffering from nasal symptoms, since it was observed in many studies that nasal symptoms often precede bronchial ones.

Asthma

Asthma is a complex disease in which allergic factors and non-allergic triggers (viral infections, irritants, exercise, drugs, aspirin, occupational factors, stress, air pollution) are interacting and result in bronchial obstruction and inflammation. The role of inhalant allergens in asthma exacerbations has been clearly demonstrated both for perennial and seasonal allergens. The inhalation of allergens leads to a complex activation of various cell types and the release of inflammatory and neurogenic mediators. Perennial allergens such as house dust mites induce a long-sustained inflammation of the bronchi leading to airways inflammation and a variable degree of bronchial hyperreactivity. Inflammation and airway remodeling may be involved in the "accelerated decline" of the pulmonary function characterized by a poorly reversible bronchial obstruction appearing after some decades of chronic asthma. After a long course of the disease, inflammation is a major cause of symptoms, suggesting that the immunologic treatment should be replaced by anti-inflammatory drugs (10).

The objective of immunologic treatment is, in the short term, to reduce the allergic triggers precipitating symptoms, and, in the long term, to decrease bronchial inflammation and bronchial hyperreactivity (BHR) when it is not too severe and when bronchial damage is not prominent.

General Considerations

Double-blind placebo-controlled studies have confirmed the efficacy of SIT but clinical efficacy does not mean clinical indication, especially as controlled trials of SIT are optimally designed and may not

always be applicable to daily medical practice and a safe and effective pharmacologic treatment is also available for the treatment of allergic diseases. Thus, before starting SIT it is essential to consider several factors to appreciate the respective value of allergen avoidance, pharmacotherapy, and SIT (11,12).

1. Demonstration that the disease is owing to an IgE-mediated allergy and that high quality extracts are available;
2. Complete allergen avoidance is impossible;
3. Potential severity of the affection to be treated;
4. Efficacy of available treatments, including quality of allergen extracts that are used;
5. Cost and duration of each type of treatment; and
6. Risk incurred by the patient owing to the allergic disease and the treatments.

In patients receiving SIT, both SIT and pharmacotherapy should be used in combination, since few patients will be completely free of symptoms when treated with SIT, but, on the other hand, SIT reduces the needs for medication in severe patients. Moreover, allergen avoidance should always be attempted, even if it cannot be complete.

Specific immunotherapy needs to be prescribed by specialists and done by physicians who are trained to use emergency techniques if anaphylaxis occurs. Before starting SIT, each patient should be carefully informed of risks, duration, and effectiveness of this treatment, and cooperation and compliance to the treatment are absolute requirements before starting it.

Subcutaneous Immunotherapy

Asthma

Efficacy

The review of the literature available indicates that SIT with mites is more effective than with house dust. Although some studies are conclusive (13,14), SIT with house dust extracts should not be used any more owing to the great heterogeneity of house dust and the impossibility of appropriately standardizing house dust extracts. Both asthma and rhinitis have been improved with mite SIT, but there are some inconclusive data, and standardized extracts have been used in a few studies only (15–24) (Table 1). Many studies showed that SIT was able to reduce the bronchial sensitivity to allergen (25–29).

Using aqueous or standardized mite extracts, many studies found that patients treated with mite extract were significantly protected in comparison with the placebo or the control groups. However, the results are not always impressive, or even negative, especially in adults.

Table 1
Results of Double-Blind Placebo-Controlled Studies
in House Dust Mite Asthma Using Subcutaneous Injections

Refs.	No. of patients	Allergen	Extract	Duration	Bronchial Symptoms	Challenge
Bousquet et al. (57)	20	<i>Der p</i>	Standardized, rush	7 wk		$p < 0.01$, epr ^b and Ipr ^c
D'Souza et al. (16)	96	<i>Der p</i>	Aqueous	1 yr	$p = 0.02$	Improved, epr
Gabriel et al. (17)	66	<i>Der f</i> / HD ^d	Aqueous	1 yr	Improved	
Gaddie et al. (18)	55	<i>Dep p</i>	Tyrosine-adsorbed	1 yr	ns	
Machiels et al. (36)	39	<i>Der p</i>	<i>Der p</i> -antibody complexes	1 yr	$p < 0.001$	$p < 0.05$
Marques et al. (20)	28	<i>Der p</i>	Tyrosine-adsorbed	1 yr	Improved	
Newton et al. (21)	14	<i>Der p</i>	Alum-pyridine	1 yr	ns	Improved
Pauli et al. (22)	18	<i>Der p</i>	Tyrosine-adsorbed	1 yr	ns	
Warner et al. (23)	85	<i>Der p</i>	Tyrosine-adsorbed	1 yr	$p < 0.01$	Improved, Ipr

^a*Der p*: *Dermatophagoides pteronyssinus* extract.

^bepr: Early phase reaction.

^cIpr: Late phase reaction.

^dHD: House dust.

Using rush SIT, efficacy was noticeable after a few weeks of treatment (15). Bousquet et al. examined the candidates for mite SIT. Two hundred fifteen patients were enrolled in a controlled trial (30). They were followed up for 1 yr by means of symptom-medication scores and pulmonary function. One hundred fifty eight received allergen injections and the others were taken as a control group. Patients who had other perennial allergies, or aspirin intolerance, and/or chronic sinusitis did not improve. Moreover, among the patients allergic only to *Dermatophagoides pteronyssinus*, children presented a significantly greater improvement than adults, and patients with irreversible airflow limitation (FEV₁ under 70% from predicted values after an adequate pharmacologic treatment) did not benefit from SIT. With tyrosine-adsorbed *D. pteronyssinus* extracts, it was noticed that asthmatic children were significantly protected in comparison to placebo (23), whereas results in adults were not always conclusive (22), and the efficacy was only seen after a long-term allergen administration. A study with PEG-modified extracts was inconclusive (31,32).

The idiotype-anti-idiotype network is an elegant method to decrease the IgE-immune response in allergen-specific responses (33). Anti-idiotypic antibodies (anti-Id Abs) are involved in the regulation of a number of immune responses including the IgE antibody production (34). In atopic patients, the increased synthesis of IgE antibodies could be related to a defective production of regulatory anti-Id Abs. Levels of anti-Id Abs against two anti-*Lol p I* monoclonal antibodies (MAbs; 290A-167, 348A-6) were higher in normal volunteers than in untreated atopic patients. SIT increased the levels of anti-Id Abs to those of normal volunteers (35). These observations suggest a role for the Id-anti-Id network in the regulation of IgE antibody production. Machiels et al (19,36,37) used allergen-antibody complexes made from allergens of *D. pteronyssinus* or grass pollen and an excess of purified autologous specific antibodies to treat patients and claimed that the treatment was safe and highly effective as assessed by symptoms scores and bronchial challenge with allergen. However, the complexes are difficult to prepare and until human MAbs are available it will be difficult to apply this technique on a large scale. However, confirmation is needed and the industrial preparation of extracts and antibodies may prove to be difficult. The use of recombinant allergens and human MAbs may be of interest in some situations (cat and birch pollen allergy where the number of allergens is limited).

Safety

The safety of mite SIT is critical since many, if not most, patients who recently died from an allergen injection were asthmatics and, in these patients, death was caused by an irreversible bronchial obstruction (4,5) (Table 2). Although some investigators suggest that SIT is indicated in severe patients, Bousquet et al. performed a controlled study in over 1000 patients who received the same maintenance dose using a rush or a step procedure (38,39). Most patients with FEV₁ under 70% of predicted values developed asthma during SIT highlighting the importance of avoiding SIT, in severe asthmatics. The age of the patient also appears to be of importance. Children under 5 yr of age present a significantly greater risk of systemic reaction. The symptoms of the systemic reactions were different in pollen- or mite-allergic individuals (39,40). In the latter group, as expected, bronchial symptoms were more prevalent than either urticaria or anaphylaxis, whereas in pollen-allergic individuals asthma was less common. Attempts have been made to reduce systemic reactions, and, as in the case of pollen immunotherapy, it was observed that premeditation and exclusion of severe asthmatics lead to an acceptable rate of mild systemic reactions.

Table 2
Safety of Specific Immunotherapy with House Dust Mite Extracts^a

Refs.	Allergen	No.	Extract		Percent SR/ patient	Percent SR/ injection
Blainey et al. (41)	<i>Der p</i>	17	Tyrosine-adsorbed	Rhinitis	5.8	
Corrado et al. (45)	<i>Der p</i>	33	Alginate-conjugated	Rhinitis	3 (mild)	
D'Souza et al. (16)	<i>Der p</i>	96	Aqueous	Asthma	10.6 (mild)	
Ewan et al. (44)	<i>Der p</i>	19	Standardized	Rhinitis		15.0
Hejjaoui et al. (39)	<i>Der p</i>	290	Standardized, rush	Asthma	36.2	3.8
		160	Standardized, rush, premedication	Asthma	16.2	2.0
		479	Standardized, rush, premed, precautions	Asthma	7.3	0.8
		223	Standardized, step premed, precautions	Asthma	5.4	0.6
Machiels et al. (36)	<i>Der p</i>	39	<i>Der p</i> -antibody complexes	Asthma	0	
Marques et al. (20)	<i>Der p</i>	28	Tyrosine-adsorbed	Asthma	3.6	
Mosbech et al. (31)	<i>Der p</i>	18	Standardized-alum adsorbed	Asthma	83.3	9.0
		19	PEG-modified	Asthma	63.2	5.1
Pauli et al. (22)	<i>Der p</i>	18	Tyrosine-adsorbed	Asthma	0	
Warner et al. (23)	<i>Der p</i>	85	Tyrosine-adsorbed	Asthma	0	

^aSR, systemic reactions.

Rhinitis

Few double-blind placebo-controlled studies have been performed in rhinitis with house dust mites and showed that SIT was effective (41–46; for review, see ref. 47). With mite allergens, the indications of SIT are still vague but can be envisaged especially if the patient presents asthma. In rhinitis, a course of topical steroids is often required at the beginning of SIT since symptoms are owing to both allergy and inflammation.

Atopic Dermatitis (AD)

A double-blind controlled trial of hyposensitization with tyrosine-adsorbed *D. pteronyssinus* (Dpt) vaccine in 24 children with atopic

eczema and immediate hypersensitivity to Dpt failed to demonstrate superiority over placebo after a standard 8-mo course of treatment (48). Leroy et al. (49) attempted to determine whether the administration of allergen-antibody complexes would improve the symptoms of 24 adults with AD and hypersensitivity to Dpt. After 4 mo, placebo-treated patients started receiving active treatment. All patients were treated for a full year. Symptoms of AD subsided within a few weeks after starting therapy, with significant reduction after 4 mo in treated patients only. After 1 yr, 82% of the patients exhibited a mean improvement of 83%, associated with reduction of Dpt-specific IgG antibodies. The treatment of Dpt-sensitive patients with AD by injections of allergen-antibody complexes was found to be safe and effective in a majority of patients. However, before proposing to use such a treatment in AD, more data are needed.

Indications

The indication of SIT in mite allergy is not easy to propose and definite indications will not be available until the National Institutes of Health (NIH) sponsored study on mite allergy has been published. From the current studies the following recommendations may be proposed (11).

1. Only patients with house dust mites as perennial allergens should be treated.
2. Patients with aspirin intolerance or nonspecific triggers of asthma such as chronic sinusitis should not receive SIT.
3. Efficacy and safety studies suggest that patients with irreversible airflow obstruction (FEV_1 under 70% of predicted after an adequate pharmacologic treatment) should not receive SIT.
4. The age of the patient should also be considered.

On one hand, children and young adults usually respond more efficiently to SIT, but, on the other hand, children under 5 yr of age may not receive SIT because of an increased risk of systemic reactions, an increased severity of the systemic reactions, and also because the sensitivity of young patients may vary.

Other Routes for Allergen Administration

The usual route of administration of SIT is the subcutaneous one. However, recent studies have shown that oral (50), nasal (51), bronchial (52–54) or sublingual (55) SIT have been shown to be effective. Systemic or focal reactions were rather low with local administration of extracts. The addition of oral SIT to boost parenteral SIT may be effective but more data are required.

These alternative routes of SIT need more data to be fully documented (56), but they may be of interest since oral and sublingual routes are usually perfectly tolerated. Thus, although they are likely to present a lower level of efficacy, they may reduce the needs for an aggressive pharmacological treatment. In particular, such SIT may improve the control of asthma in young children.

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