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Specific immunotherapy in asthma: Is it effective?

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BHR Nonspecific bronchial hyperreactivity

FEV₁ Forced expiratory volume in 1 second

PD₂₀ Provocative dose causing a 20% fall in

SIT Specific immunotherapy

Asthma and allergies are among the most common chronic diseases. Although the role of inhalant allergens has been clearly demonstrated in the pathogenesis of asthma, the importance of specific immunotherapy (SIT) in its treatment is still controversial. ^{1, 2} Asthma is an inflammatory disease in which allergic triggers are often involved (especially in young subjects with asthma), but such triggers are not always the major cause of

inflammation. The efficacy of SIT in asthma was contested some years ago,³ but significant progress has been made with the availability of standardized allergen extracts,⁴ and SIT for asthma was revisited.⁵ However, when these potent extracts were used, allergen injections initially resulted in a greater number of systemic reactions.^{6 7} Thus SIT for asthma is no longer used in the United Kingdom and is seldom used in the Nordic Countries, but it still has considerable acceptance in other European countries and, to a lesser extent, in the United States. The appropriate use of standardized extracts, however, leads to an acceptable rate of mild systemic reactions, making SIT with such extracts an efficient form of treatment.¹ It is therefore essential to carefully select the patients and consider several factors in order to appreciate the respective value of SIT in comparison with other available therapeutic methods, including allergen avoidance and pharmacotherapy.^{8 9} These factors are:

1. Potential severity of the condition to be treated
2. Efficacy of available treatments
3. Optimal use of SIT with standardized extracts, high-quality modified extracts, or purified components of known composition and efficacy
4. Cost and duration of each type of treatment
5. Risk incurred by the patient from the allergic disease and the treatment
6. Modification of the course of the disease by each type of treatment

To minimize risk and improve efficacy, SIT needs to be prescribed by specialists and administered by or under the close supervision of physicians trained to manage acute systemic reactions if anaphylaxis occurs.

Objectives of Immunotherapy

TOP

Asthma is a multifactorial and complex disease in which allergic factors and nonallergic triggers (viral infections, irritants, exercise, drugs, aspirin, occupational factors, stress, air pollution) interact and result in bronchial obstruction and inflammation.¹⁰ The role of inhalant allergens in asthma exacerbations has been clearly demonstrated both for indoor allergens such as house dust mites, animal danders, or insect dusts and for seasonal allergens such as grass pollens or molds.^{11 13}

The inhalation of allergens leads to a complex activation of various cell types and the release of inflammatory and neurogenic mediators, but two different situations seem to exist. Although very few pollen grains can reach the lower airways, these allergens, which are borne on submicronic particles, frequently elicit asthma by an IgE-mediated mechanism. Pollen-induced allergic reactions prolonged over several days almost always lead to nonspecific bronchial hyperreactivity (BHR), which is usually transient in patients who are only allergic to pollens and lasts from a few weeks to a few months after the cessation of the pollen season.¹⁴

On the other hand, house dust mites and other perennial allergens induce a long-sustained inflammation of the bronchi, leading to a variable degree of BHR, and symptoms are caused by allergens, inflammation, and BHR.¹⁵ It has been shown that patients with chronic asthma have a subepithelial fibrosis of the bronchi caused by collagen deposition beneath the basement membrane¹⁶ and alterations of the elastic fiber network of the airways, suggesting the concept of airway remodeling in asthma.¹⁷ 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 ongoing chronic asthma,¹⁸ as well as permanent bronchial wall alterations as shown by computed tomographic scans.¹⁹ It is therefore proposed that immunologic and antiinflammatory treatments should be combined, but after a long course of the

disease, inflammation is a major cause of symptoms, suggesting that the immunologic treatment should be replaced by antiinflammatory drug treatment. However, the airway remodeling in asthma may differ according to the cause of the disease. It has been recently shown that patients with intrinsic asthma have a steeper rate of decline in pulmonary function than those with extrinsic asthma.²⁰

The natural history of asthma in children is not completely known, but a large proportion of children with episodic or mild asthma will outgrow their symptoms within several years, whereas in those with a more severe disease, asthma will persist later in life.^{21 22}

These considerations suggest that (1) SIT may be more rapidly effective in patients with grass pollen allergy than in those sensitized to perennial allergens; (2) that after a long course of the disease, patients with perennial asthma may have permanent airway abnormalities, which cannot be reversed by SIT; and (3) grass pollen allergy may be an adequate model with which to study the effects of specific SIT in patients with normal bronchi, whereas SIT in mite allergy may be used to examine the effects of the treatment in patients with a variable degree of bronchial inflammation and damage.

The major objectives of immunologic treatment are, in the short term, to reduce the allergic triggers' precipitating symptoms and, in the long term, to decrease bronchial inflammation and BHR when it is not too severe and when bronchial damage is not prominent. Moreover, at present, SIT appears to be the only treatment that might modify the course of the disease either by preventing the development of new sensitivities or by altering the natural history of asthma.

Efficacy and Safety of Sit in Asthma

TOP

Pollen asthma

Efficacy

Only a few controlled studies have investigated the efficacy of SIT in grass pollen asthma. Some studies have consistently demonstrated that patients receiving SIT had an improvement of the provocative dose causing a 20% fall in forced expiratory volume in 1 second (PD₂₀) to allergen,^{23 25} and, in some cases a reduction of the late phase reaction.²⁶ Most recent studies carried out during the pollen season with the use of aqueous or standardized extracts or formaldehyde allergoids have shown that SIT has a beneficial effect on bronchial symptoms but only under optimal conditions (■Table I).^{27 40} These conclusions were restricted to grass and birch pollen allergy, but similar favorable results were more recently observed in ragweed pollen–induced asthma in the National Institutes of Health collaborative study.^{39 40} Oral SIT with a mugwort extract was found to reduce asthma symptoms.⁴¹

TABLE I. Results of double-blind placebo-controlled studies in pollen-induced asthma

Study	Species	<u>Patient number</u>		Extract	Dose schedule	Protocol	Duration	Symptoms studied	Symptom-medication scores
		A	P						

Armentia et al. ²⁷	Bermuda grass	15	15	Standardized	Rush	Preseasonal	1 yr	B	sc: $p < 0.001$, challenge $p < 0.001$
Bousquet et al. ²⁸	Grass	18		Standardized	Rush	Pre + co-season	1 yr	N,O,B	$p < 0.01$
	Grass	15	14	Formald. allergoid	Clustered	Pre + co-season	1 yr	N,O,B	$0.05 < p < 0.01$
	Grass	13	14	HMW-allergoid	Clustered	Pre + co-season	1 yr	N,o,B	$p < 0.01$
Frankland and Augustin ³⁰	Grass	39	18	HMW-allergoid	Clustered	Pre + co-season	1 yr	N,B	$0.005 < p < 0.01$
		50	50	"Pollaccine"	Classical		1 yr	N,B	$p < 0.001$
		50	50	Purified antigen	Classical			N,B	$p < 0.001$
Hill et al. ³¹	Grass	11	9	Aqueous	Rush	Pre + co-season	4 mo	B	NS
Leng et al. ⁴¹	Mugwort	9	9	Aqueous	Oral	Preseasonal	1 yr	challenge	$p < 0.01$
McAllen ³³	Grass	47	23	Allpyral	Classical	?	1 yr	N,B	NS
		40		Depot preparation	Classical	?	1 yr	N,B	$p = 0.05$
Machiels et al. ³⁴	Grass	37	12	Ag-Ab complexes	Classical	Pre + co-season	3 mo	N,B	$p < 0.03$ & $p < 0.001$
Ortolani et al. ²⁴	Grass	8	7	Standardized	Classical	Preseasonal	1 yr	challenge	PD ₂₀ FEV ₁ : NS
Pastorello et al. ³⁵	Grass	10	9	Alum-allergoid	Classical	Pre + co-season		N,O,B	$p < 0.01$, $p < 0.05$, & $p < 0.05$
Pence et al. ³⁶	Mountain cedar	17	15	Aqueous	Classical	Preseasonal	1 yr	N,B	$p < 0.001$ for all symptoms
Rak et al. ³⁷	Birch	20	20	Standardized	Classical	Preseasonal	1 yr	B	NS to $p < 0.01$
Varney et al. ³⁸	Grass	20	20	Standardized, alum	Classical	Pre + co-season	1 yr	N,B	$p < 0.01$

A, Actively treated group; P, placebo group; Ag-Ab, antigen-antibody; B, bronchial; N, nasal; O, ocular; NS, not significant.

During the pollen season, patients with asthma often have increased BHR. The effect of SIT on bronchial

reactivity measured by methacholine was investigated in patients with asthma and birch pollen allergy.³⁷ Untreated patients had a decreased methacholine PD₂₀, whereas those who received SIT did not have a significant decrease in PD₂₀. In this study it has also been shown that eosinophilic inflammation was decreased in subjects receiving SIT.

Sensitization of the patients

The benefits of SIT are specific for the allergen(s) used in treatment, and some studies have shown that SIT with a single extract provides incomplete relief of symptoms.³² This may be due to the failure to immunize with the relevant allergens because many patients have multiple sensitivities, but it has also been shown that these polysensitized patients appear to have an IgE immune response that is different from that of monosensitized patients. Patients sensitized to a single allergen species have significantly lower total serum IgE levels than those allergic to multiple allergen species.⁴² The lymphocyte reactivity of these two groups of patients is also different because the cells of the monosensitized group release significantly lower levels of IgE, interleukin (IL)-4, and CD23 than cells from the polysensitized group. On the other hand, the production of interferon- γ is similar in both groups.⁴³ This study suggests that monosensitized and polysensitized subjects are different in terms of IgE immune response and regulation. A double-blind placebo-controlled study compared the efficacy of SIT in these two groups of patients.⁴⁴ Patients allergic to grass pollen were treated with an optimal maintenance dose of a standardized orchard grass pollen extract, whereas those allergic to multiple pollen species received the same biologically equivalent dose of all standardized allergens to which they were sensitized. The results of the study indicated that patients with grass pollen allergy, but not polysensitized patients, were significantly protected. With a higher allergen dose, it might be possible to show efficacy in the polysensitized group, but the rate of systemic reactions with standardized extracts would have been unacceptable with the rush protocol used.

Safety

Life-threatening reactions are not uncommon with high quality extracts, and some deaths have been reported.⁷ It is, however, difficult to have an exact figure of systemic reactions occurring in the treatment of pollen-induced asthma because most if not all patients were first seen with rhinitis during the pollen season. Moreover, in ragweed pollen SIT most studies have examined patients with rhinitis only. The rate of systemic reactions during the first phase of SIT, when doses are being increased, may be greater with standardized pollen extracts than with either nonstandardized extracts or high-molecular-weight preparations but does not differ from SIT performed with standardized extracts of other allergen species.⁴⁵ It has been observed that patients with asthma during the pollen season have bronchial symptoms more often during SIT than those with rhinoconjunctivitis only.⁴⁶ With less aggressive schedules and premedication, it has been shown that SIT with standardized pollen extracts may be better tolerated.^{46 47}

When the maintenance dose has been reached, the rate of systemic reactions occurring with standardized extracts is usually very low because of the batch-to-batch reproducible potency of the extracts.⁴⁶

Duration

Duration of SIT after its cessation is another matter of debate. In the case of inhalant allergy, more data are needed to support any definite conclusion, but it appears that a long-term treatment, for at least 3 years, is required. For nasal symptoms, it is suggested that the effect of grass pollen SIT lasts several years after its cessation,^{48 49} but prospective controlled studies are lacking, and no definite conclusion can be made yet.

Availability of suitable extracts

International Reference Preparations and International Standards have been prepared under the auspices of the Allergen Subcommittee of International Union of Immunological Societies/World Health Organization. They include many pollens (e.g., timothy and Bermuda grass, short ragweed, birch, and mugwort). Standardized extracts of many grass, weed, and tree pollens are available in many parts of the world. These extracts are of known potency, and although they may be more difficult to administer than low-potency extracts, they should be preferred. Standardized extracts adsorbed on alum are available in Europe. Polymerized extracts have been used for trials, but except in some European countries, these are not available.

House dust mite asthma

Bronchial challenges

Bronchial challenges with mite extracts confirmed symptom scores, because the threshold dose eliciting an immediate bronchial obstruction was increased in many studies after treatment and the late phase reaction was inhibited in most^{50 55} but not all studies.⁵⁶ These studies suggest that SIT is effective and may decrease inflammation because the late-phase reaction was decreased.

Symptom-medication scores

The review of the literature available indicates that SIT with mites is more effective than SIT with house dust. Although very few studies have been conclusive, SIT with house dust extracts should not be used any longer owing to the great heterogeneity of house dust and the impossibility of appropriately standardizing house dust extracts.^{8 9 57}

When aqueous or standardized *Dermatophagoides pteronyssinus* and/or *D. farinae* extracts were used, many studies demonstrated a significant effect of SIT (■Table II). However, some of the results are not always impressive, and, especially in adults, they are sometimes negative. With other extracts, results are more variable.^{50 52 58 64} Haugaard et al.⁶⁴ examined the dose required to achieve a significant clinical effect. For a maximal dose of 7 µg of *Der p* I, patients showed a significant improvement in PD₂₀, but the maximal effect was observed for a dose of 21 µg of *Der p* I.

TABLE II. Results of double-blind placebo-controlled studies in house dust mite–induced asthma with subcutaneous injections

Study	Allergen No.	Extract	Duration	Symptoms	Bronchial challenge
Bousquet et al. ⁵¹	<i>Der p</i> 27	Standardized, rush	7 wk		$p < 0.01$, EPR & LPR
D'Souza et al. ⁵⁸	<i>Der p</i> 96	Aqueous	1 yr	$p = 0.02$	Improved, EPR
Gabriel et al. ⁵⁹	<i>Der f</i> /HD 66	Aqueous	1 yr	Improved	
Gaddie et al. ⁶⁰	<i>Der p</i> 55	Tyrosine-adsorbed	1 yr	NS	

Machiels et al. ⁵²	<i>Der p</i>	39	<i>Der p</i> –antibody complexes	1 yr	$p < 0.001$	$p < 0.05$
Marques and Avila ⁶¹	<i>Der p</i>	28	Tyrosine-adsorbed	1 yr	Improved	
Newton et al. ⁶²	<i>Der p</i>	14	Alum-pyridine	1 yr	NS	Improved
Pauli et al. ⁶³	<i>Der p</i>	18	Tyrosine-adsorbed	1 yr	NS	
Warner et al. ⁵⁰	<i>Der p</i>	85	Tyrosine-adsorbed	1 yr	$p < 0.01$	Improved, LPR

Der p, *Dermatophagoides pteronyssinus* extract; *Der f*, *D. farinae* extract; *HD*, house dust; *EPR*, early-phase reaction; *LPR*, late-phase reaction.

Bousquet et al.⁶⁵ attempted to identify candidates for mite SIT.⁶⁵ Two hundred and fifteen patients were enrolled in a controlled trial. They were followed up for 1 year by means of symptom-medication scores and pulmonary function tests. One hundred fifty-eight received allergen injections, and the others were employed 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 *D. pteronyssinus*, children showed a significantly greater improvement than adults, and patients with irreversible airflow limitation (FEV₁ below 70% of predicted values after an adequate pharmacologic treatment) did not benefit from SIT. Mosbech et al.,⁶⁶ using either a standardized or a polyethylene glycol–modified extract, did not reach similar conclusions; however, many patients were treated with inhaled corticosteroids during the trial, and the interpretation of the data was therefore more difficult.

Machiels et al.^{52, 67} used allergen-antibody complexes made from allergens of *D. pteronyssinus* and an excess of purified autologous specific antibodies and claimed that this treatment was safe and highly effective, as assessed by symptom scores and bronchial challenge with allergen. The effects of SIT were prolonged after the cessation of SIT. However, the complexes are difficult to prepare, and until human monoclonal antibodies are available, it will be difficult to apply this technique on a large scale.

Local bronchial immunotherapy has been proposed by Crimi et al.⁶⁸ and Tari et al.,⁶⁹ who found in double-blind placebo-controlled studies that this form of administration is safe and effective.

Taken together, these studies suggest that mite SIT is only effective under optimal conditions, including an appropriate selection of patients and the use of high-quality extracts administered with an adequate schedule.

BHR and indirect indices of inflammation

Results of studies examining the evolution of BHR in patients undergoing mite SIT are still unclear. Some studies have demonstrated an improvement in BHR,^{52, 67} whereas others have not.^{1, 53, 70} Although studies in which bronchial biopsies and bronchial challenges are used are still missing, indirect indices of inflammation have been studied. It has been shown that blood eosinophils are decreased in patients with asthma who had effective SIT with standardized mite extracts.

Safety

The safety of mite SIT is critical because many if not most patients who recently died as a result of an

allergen injection had asthma, and in most cases, death was caused by an irreversible bronchial obstruction. Although some investigators suggest that SIT is indicated in patients with severe asthma, Bousquet et al.⁷¹,⁷² performed a controlled study in over 1000 patients who received the same maintenance dose with a rush or a step procedure. During the first phase of SIT, when doses are increased, in most patients with FEV₁ below 70% of predicted values asthma developed during SIT, highlighting the importance of avoiding SIT in patients with severe asthma. The symptoms of the systemic reactions were different in individuals with pollen allergy and those with mite allergy. In the latter group, as expected, bronchial symptoms were more prevalent than either urticaria or anaphylaxis, whereas in subjects with pollen allergy asthma was less common. Attempts have been made to reduce systemic reactions, and it was observed that premedication and exclusion of patients with severe asthma led to an acceptable rate of mild systemic reactions. This study showed that SIT with standardized extracts may be safe, but the selection of patients is critical.

During maintenance injections, when standardized extracts are used, systemic reactions are uncommon, although they may always occur,⁶⁶ ⁶⁷ especially if symptoms of asthma are not totally controlled. It is therefore essential that any patient with asthma should have his or her peak flow rate measured before any injection.

The age of the patient also appears to be of importance. Children under 5 years of age have a significant greater risk of systemic reaction.⁷¹

Duration

The duration of SIT with mite extracts is still a subject of debate. Price et al.⁷³ stopped SIT after a year of treatment in half of the children enrolled in a double-blind placebo-controlled study and noticed that most children who stopped SIT had a relapse within a year. Using SIT with standardized extracts, Hejjaoui et al.⁷⁴ studied the duration of efficacy of SIT after its cessation in patients with perfectly controlled asthma. The rate of relapse was dependent on the duration of SIT. When SIT was performed between 18 and 35 months, the rate of relapse was 65% compared with 35% in patients with SIT duration of over 36 months. The estimation of duration of SIT efficacy was done with the Kaplan-Meier test. The mean duration of efficacy was 16.0 ± 21.7 months in patients with SIT duration under 35 months and 32.2 ± 25.2 months ($p < 0.03$) in patients with a duration of SIT of over 36 months. These results are in accord with those of Machiels et al.⁶⁷ who observed that most patients treated for 3 years with immune complexes (allergen-IgG) and who stopped SIT for 1 year did not experience a relapse. However, more studies are needed to gain a better insight into the duration of efficacy of SIT after its cessation.

Availability of suitable extracts

D. pteronyssinus International Standard is available. In many countries standardized extracts from *D. pteronyssinus* and *D. farinae* are available. These extracts are usually in lyophilized or aqueous form, but in Europe, they are often adsorbed on alum.

Allergy to animal proteins

Clinical efficacy

Some studies show that SIT is effective in improving the threshold dose inducing positive bronchial challenges with cat or dog dander extract in subjects with asthma, but very few studies have confirmed the clinical efficacy of this form of treatment in patients who kept an animal at home.⁷⁵ ⁷⁷

Availability of suitable extracts

In many countries standardized extracts of cat and dog are available. They are sometimes labeled in weight or units of major allergen.

Allergy to mold

Clinical efficacy

Molds are major allergen triggers of asthma, but they often induce polysensitizations, and the quality of extracts available in the early 1980s was far from being adequate, so that it was proposed to avoid use of mold SIT.^{[78](#)} However, SIT with standardized *Cladosporium*^{[79](#)} and *Alternaria* extracts^{[80](#)} was found to be effective in the treatment of asthma.

Availability of suitable extracts

Cladosporium and *Alternaria* standardized extracts are available in some countries. However, other extracts are not standardized, and their quality is usually poor, which seriously limits use of SIT for asthma caused by molds.

Other forms of allergy or other forms of SIT

Although SIT may be administered by oral or sublingual routes, there is as yet no controlled study showing that it is definitively effective in the treatment of asthma. Some controlled trials have been started, and results should be available soon. SIT with extracts of undefined allergens (e.g., bacterial, foods, *Candida albicans*, insects, dust) should not be used any longer in clinical practice, but controlled trials, in which only standardized extracts are used, could be started.^{[8](#)},^{[9](#)},^{[57](#)}

Can Immunotherapy Alter the Course of Asthma?

TOP

Antiinflammatory effects

Although there are few studies in asthma,^{[37](#)},^{[81](#)}-^{[84](#)} studies have been carried out in rhinitis showing that SIT reduces the release of inflammatory mediators and cells (eosinophils) in nasal secretions during early- and late-phase reactions after allergen challenge.^{[44](#)},^{[84](#)},^{[85](#)}

Prevention of asthma

One of the major goals in the next few years will be to determine whether early administration of SIT in patients with rhinitis can prevent the onset of asthma. A retrospective study suggested that this might be possible in patients allergic to grass pollens (Bousquet et al., unpublished data). However, there is no controlled study available, although a large multicenter study has been started in Europe (Preventive Allergy Treatment).

Prevention of the development of new sensitivities

It has been proposed that SIT with one allergen may prevent the development of new sensitivities. If this is the case, SIT should be started very early in life, as soon as an allergic sensitization develops. A study was

carried out in our group to determine whether SIT administered in children under 6 years of age could prevent the onset of new sensitivities. Unfortunately, there was no significant difference between children who received SIT and those who did not (Bousquet, unpublished data). However, some patients who had SIT very early after the onset of symptoms completely lost their allergenic sensitivity (negative skin test, IgE, and nasal challenge results).

Duration of efficacy after cessation of immunotherapy

Recent evidence suggests that after a course of several years, the efficacy of SIT persists after its cessation. However, the numbers of studies are still low, and most data are retrospective.

Indications for Avoidance and Immunotherapy in Asthma According to Recent International Guidelines TOP

In the *Guidelines of the International Consensus on the Diagnosis and Management of Asthma*, some recommendations for the use of SIT in asthma have been recently proposed.⁹ They are based on reports from the World Health Organization/International Union of Immunological Societies⁸ and European Academy of Allergy and Clinical Immunology.^{57, 86} In all of the recommendations the quality of the extract to be administered was stressed. Optimally, these extracts should be standardized with the most modern techniques.⁴

The indication for SIT should be carefully proposed in highly selected patients (■Table III). Doctors should always discuss the length and cost of the treatment with their patients because compliance to antiasthmatic treatments and SIT is often poor.⁸⁷ To minimize risk and improve efficacy some suggestions have been made (■Table IV). Absolute contraindications include the presence of other serious immunopathologic conditions, malignancies, poor compliance, severe psychologic disorders, and/or treatment by β-blocking agents, even when administered topically.

TABLE III. Considerations for initiating immunotherapy
Table not available

TABLE IV. Recommendations for minimizing risk and improving efficacy of SIT in asthma
Table not available

Before initiating SIT, avoidance of exposure to the allergen(s) causing asthma should always be attempted. Except in the case of animal dander, most common aeroallergens cannot be avoided completely, and this is particularly true for patients who are allergic to house dust mites and those who are allergic to multiple allergens.

Allergy to house dust mites may be influenced by mite avoidance measures, which should always be applied. If such measures fail and if pharmacotherapy is incompletely effective or leads to side effects, SIT may be considered, but only if mites are the only perennial allergen. The indications for SIT in mite allergy have been extensively examined, but a definite conclusion cannot be made until the results of the large study performed by the American Academy of Allergy and Immunology and the National Institutes of Allergy and Infectious Diseases are available. At present it is suggested that SIT is effective in children and young adults who are only allergic to mites and in whom FEV₁ after pharmacologic treatment is above 70% of predicted values.

Pollen-induced asthma is a good indication for SIT, especially if the patient is allergic to few or a single allergen species.

In animal dander allergy, allergen avoidance is the best choice, but SIT to cat or dog may occasionally be an alternative in occupational allergy and in some children for whom the eviction of the animal may be an intense shock.

In mold-induced asthma, the elimination of indoor allergen is favored, and SIT may be restricted to patients who are allergic to only *Alternaria* and/or *Cladosporium* species.

Conclusions

[TOP](#)

In 1990, although the importance of SIT has been seriously disputed, it should still represent one of the treatments for allergic asthma, but its indications must be restricted to highly selected cases.

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Development of a quality-of-life assessment for the allergic child or teenager with multisystem allergic disease

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