

EAACI/PTA Symposium Reviews

Risk and safety of immunotherapy

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The risk and safety of specific immunotherapy (SIT) has been the subject of many well-designed studies since it was introduced. Most authors consider SIT an efficient and safe mode of treatment despite the occurrence of life-threatening anaphylactic reactions. They emphasize the importance of a proper selection of patients as well as the requirement for highly qualified physicians to provide the treatment. Another problem associated with the safety of SIT is the potential enhancement of the synthesis of immune complexes after the treatment. SIT causes a decrease in allergen-specific IgE which is slower in circulating immune complexes than in the serum. No data are available to show that SIT induces immune-complex diseases, in either the immunologic or the clinical sense. As far as anaphylactic reactions are concerned, new alternative methods different from the conventional parenteral mode of delivery seem to be safe. Our increased understanding of the altered functions of the immune system justifies the assumption that the more specific the method of SIT administration, the more effective and safe it is.

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Immunotherapy is in the forefront of immunology. Specific immunotherapy (SIT) is perceived to be a selective suppression of the allergen-specific hyperergic reactions which determine the symptoms and clinical presentations of allergic disorders. This therapy was introduced at the beginning of this century and is still in use today worldwide. It is intriguing that in spite of some 80 years of experience in the use of SIT, its mechanism of action has not yet been entirely clarified. Although extensive research during the last quarter of a century has provided important data on various immunologic changes resulting from or attendant upon treatment, it still remains unknown which of these changes directly cause reduction and/or relief of symptoms. It is not known either whether any parameter provides an index of allergic disease activity more reliable than the others (1-5).

Among several major factors that should be taken into account when undertaking SIT, efficacy and safety require special attention. However, it is difficult to estimate the risk and safety of any mode of therapy whose mechanism of action is not fully understood. Many well-designed studies have proven SIT to be safe under appropriate conditions, but controversies over its beneficial or adverse effects

persist (1, 5-11). The safety of SIT could be disputed for two main reasons:

- 1) during the treatment, systemic reactions, including those life-threatening, may occur
- 2) SIT, which may be perceived as an immunostimulating treatment, may induce various immunologic alterations which have not been precisely described until now.

A high-dose regimen of SIT has been recommended. The development and use of more potent allergen extracts increases the risk of side-effects. This raises the question of the safety of SIT. On the other hand, it is clear that proper diagnosis of allergy and efficient treatment of patients by SIT are possible only with the use of allergen extracts with consistent potency and composition (3, 5).

However, it has not been suggested that some allergen preparations are more likely to induce adverse reactions than others. It is known that aqueous preparations induce systemic reactions more frequently than depot ones. Rush immunotherapy is more risky than a conventional regimen (2, 4, 12).

The safety of SIT for allergic diseases has been the subject of many well-designed studies, beginning

virtually with its introduction in 1911. There is general agreement that, provided the management is optimal, the risk of adverse events is low and fatal reactions are extremely rare. However, hypsensitization may be dangerous.

After conventional high-dose immunization with allergen extracts, three types of allergic reactions have been observed:

- 1) wheal and erythema at the injection site
- 2) late-phase subcutaneous swelling with itching
- 3) anaphylaxis.

Unlike the first two reactions, which do not represent any serious risk and can be controlled by an adjustment dosage, anaphylaxis is always life-threatening and requires highly professional management for both its treatment and the prevention of recurrence.

It is well known that in the UK, in 1957–86, 26 deaths caused by anaphylaxis or bronchospasm occurred after SIT (2, 13). In the USA, in nearly the same period (1959–84), 46 deaths (12 from intradermal skin tests and 36 from anaphylaxis due to administration of SIT) were reported (14).

It is worth emphasizing that these fatalities were caused by either a mistake in dosage, incorrect timing of injections, unrecognized and untreated complications, lack of equipment for emergency management, application of allergen extracts to patients with unstable asthma, or exacerbations of the allergic symptoms. It is argued by many authors that unstable asthma is a major risk factor for induction of adverse reactions to immunotherapy (15–18). According to Lockey et al.'s survey (14), 77% of the fatalities were patients with asthma. The British Committee on the Safety of Medicines registered 62% of such fatalities as being asthma patients (13). The incidence of systemic reactions in patients receiving allergen SIT for asthma has been reported by Bousquet et al. (17) as 5–35%. Bousquet & Michel (16) and Du Buske (18) emphasize that allergen extract should not be administered to patients with FEV₁ under 70% of predicted value or to patients who have unstable or symptomatic asthma. Furthermore, according to the British Society for Allergy and Clinical Immunology working party on allergen immunotherapy, until the data of studies comparing immuno- and pharmacotherapy are available, the use of SIT in asthma patients can be regarded only as an experimental therapy (2, 3).

It is worth bearing in mind that the relevance of the UK and US records for the general experience is in question because most of the fatalities reported were associated with unexpectedly gross and usually avoidable mistakes. However, our knowledge of factors contributing to side-effects is not complete.

Many authors have provided convincing evidence of the safety of SIT when applied under appropriate conditions. In the prospective studies of 419 patients, mostly asthmatics, who underwent SIT with *Dermatophagoides pteronyssinus* and grass-pollen extracts according to a conventional schedule, Tabar et al. (19) reported local reactions in 10.5% and systemic reactions in 4.8% of subjects who responded rapidly and fully to the treatment. Only 0.37% of the injections administered were associated with systemic side-effects, mainly late and mild ones. No life-threatening reactions were observed.

An extensive study of Luigi et al. (7) confirms the safety of SIT. From 1968 to 1993, 300 086 injections were administered to 6319 patients suffering from allergic asthma and/or rhinitis. Over the whole period, 184 (0.061%) systemic reactions in 131 subjects (2.1%) were reported, comprising

- 1) urticaria (59.3%)
- 2) mild asthmatic attacks (23.9%)
- 3) asthma and urticaria (9.7%)
- 4) rhinitis (7.1%).

No incidence of anaphylaxis was reported. In Matloff et al.'s (8) study of 27 806 injections (inhalant or venom allergen extracts), 143 (0.57%) systemic reactions occurred. It is worth noting that the symptoms were usually only subjective ones which did not always correspond with the presence of objective signs.

SIT as applied by all these authors fulfilled criteria established and proposed by the Immunotherapy Subcommittee of the European Academy of Allergology and Clinical Immunology (EAACI) (5). A proper selection of patients and ensuring that SIT is conducted in a specialized setting under the supervision of well-trained physicians following the EAACI recommendations are vital for maximization of the benefit-to-risk ratio.

SIT may be seen as a prolonged stimulation of the immune system probably associated with the enhancement of the production of immune complexes. This underlies another important safety problem of the therapy which is confusing for some clinicians. Already in the 1980s, researchers were intrigued by the problem of the possible increase of immune-complexes synthesis during the course of hyposensitization. This reaction was then considered to pose a risk of the induction of immune-complex-mediated disease in this form of treatment.

Although Cano et al. (20) were able, in 1977, to demonstrate an increased concentration of circulating immune complexes (CICs) after a 5-year period of immunotherapy by determining exogenous C1q expenditure, other researchers failed to

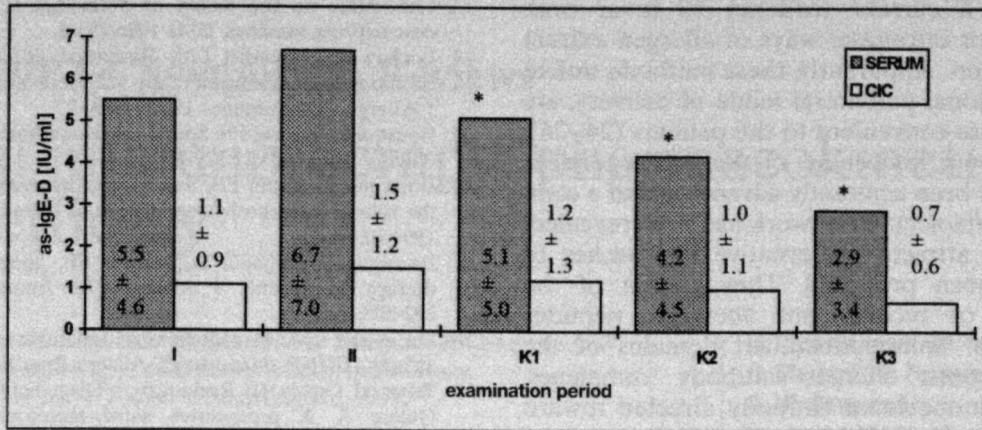


Fig. 1. Allergen-specific IgE (as-IgE-D) concentration in serum and in CICs in patients with allergy to *Dermatophagoides pteronyssinus* during SIT. Statistically significant differences between I and K1, K2, and K3 periods ($P < 0.05$; Wilcoxon rank sum test).

confirm their results. Using the method with Raji cells because of the high density of Fc receptors, Yang (21) estimated CICs concentration in a trial of 95 patients suffering from inhalant allergy who had undergone SIT and 45 subjects who had been treated pharmacologically. He did not observe any influence of this form of treatment on the value of determined CICs.

Theoretically, hyposensitization may induce a synthesis of CICs composed of allergen and blocking activity of IgG. However, this hypothesis can hardly be validated. Firstly, the manifestation of allergic diseases is a consequence of exposure to a vestigial amount of allergen. As emphasized by Platts-Mills et al. (22), an asthma attack may be induced by exposure to 10 µg of mite allergen.

Secondly, during conventional immunotherapy, very small amounts of allergen may get into the circulation. Koehler (23) disputed the idea that the complexes originated from an allergen and antibody during SIT. He showed mathematically that in the course of SIT no more than 1 µg of an allergen is detectable in the circulation. Such quantities of the allergen together with the relevant antibody could give rise to complexes too small to be detected by current research methods. It can be assumed that those CICs which constitute the combination of an allergen with an antibody are small. They undergo phagocytosis and are eliminated from the circulation.

In our study*, the decrease of allergen-specific serum level after SIT of house-dust-mite-sensitized patients with allergic rhinitis and/or asthma has

been observed only after 1 year of treatment. However, the absolute content of allergen-specific IgE in CICs was significantly lower not earlier than after 3 years of therapy. The binding rate of these antibodies in immunocomplexes increased during the course of SIT (Fig. 1).

CICs were isolated from patient sera by precipitation with a solution of polyethylene glycol. Total and allergen-specific IgE was estimated in the serum and in immune complexes by fluoroimmunoassay (Bio-Whittaker FAST System). The estimation was not preceded by an attempt to dissociate the complexes so as to avoid the destruction of IgE epitopes. The assay for allergen-specific IgE requires free Fab endings of the IgE molecule; thus, proving the presence of allergen-specific IgE in the composition of CICs isolated from serum shows that they do not contain allergen. It can be assumed that the CICs determined in our study are the real contributors to the combination of IgE with its antibody (IgE/anti-IgE). These observations provide evidence of the pathophysiologic role of CICs in atopy, a role which is different from the well-known conception of immune complexes in classical immune-complex-mediated diseases. However, the comprehensive explanation of the alterations observed requires further studies (the precise estimation of CICs composition in relation to their function *in vivo* and *in vitro*).

Hitherto, no data have been available to determine whether SIT induces the immune-complex diseases, in either the immunologic or the clinical sense.

Introduced at the turn of the century, SIT is still widely used by physicians. At the same time, its use continues to decrease, mainly because the risk-to-benefit ratio is not acceptable when compared to optimal pharmacologic management of allergic disorders.

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There is a current tendency to favor oral, sublingual, or intranasal ways of allergen extract administration. Apparently, these methods, unlike the conventional parenteral mode of delivery, are safe and more convenient to the patients (24–26).

Recently, our knowledge of the IgE-dependent reactions has been constantly advancing, and a complex cellular/molecular network has been revealed. Thus, other attractive alternative approaches to SIT have been proposed. They consist of the application of recombinant allergens, peptides derived from immunodominant domains of the major allergens, allergen-antibody complexes, humanized monoclonal antibody directed toward an epitope in the CH3 heavy-chain domain of the IgE molecule, active immunization with small IgE epitopes, and immunization with DNA-encoding protein allergens (27–33).

These methods do not pose any risk of anaphylaxis, but they have not been fully established yet. Although clinical studies of their overall effects are not yet completed, it is believed that the efficacy of treatment and low risk of adverse effect on the integrity and vital function of the immune system can be secured only by the highly accurate methods of immunointervention.

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