

Retrospective Study of Specific Immunotherapy – What Should Be Done in the Future

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SUMMARY In this retrospective study, data on 241 atopic patients treated with specific cutaneous immunotherapy during the 1985-2006 period at Allergy Clinic, University Department of Dermatology and Venereology, were reviewed. The following diagnoses were recorded: atopic dermatitis, pure or in combination with allergic rhinitis or allergic bronchitis, or allergic bronchitis and asthma, allergic rhinitis, allergic conjunctivitis, urticaria, and Quincke's edema. The aim was to retrospectively analyze clinical efficacy and laboratory findings in atopic patients undergoing specific immunotherapy. Before specific immunotherapy administration, eosinophil count, immunoglobulins, skin prick test, total IgE (RIST) and specific IgE (IgE UniCAP) were determined. The following allergens were included in specific immunotherapy: *Dermatophagoides pteronyssinus*, house dust mite (mixed or separately), mixed and single pollens (grass, tree, weed), feather, and animal dander. The most frequent allergens in 241 atopic patients were grass pollen mixture, *Dermatophagoides pteronyssinus*, ragweed, tree pollen mixture, cocksfoot, birch, animal dander, and feather. Treatment efficacy was demonstrated after 3 years of continuous therapy by clinical evaluation and with the same diagnostic procedure. After several months of therapy, initial clinical improvement was noticed in atopic dermatitis patients as well as in patients with respiratory diseases that were sensitive to airborne allergens. According to literature, specific immunotherapy was used as a treatment option, which may affect the natural course of allergic diseases. It reduces development of asthma in patients with allergic rhinitis and prevents the onset of new sensitizations.

KEY WORDS: airborne allergens, atopic dermatitis, specific immunotherapy

INTRODUCTION

Allergen specific cutaneous immunotherapy (SCIT) is the first-line management in atopic patients sensitive to airborne allergens. In this retrospective study, we evaluated the efficacy

of SCIT in different groups of atopic patients as well as in pure atopic dermatitis patients as a valuable option for a selected group of atopic patients (1).

Recently, immune mechanisms underlying clinical efficacy of SCIT in human allergic diseases have aroused considerable interest. In the last years, it has been demonstrated that SCIT may influence a deviated immune response of allergic patients towards normal immunity (2). In this study, serum total and specific IgE directed against common airborne allergens were evaluated, and serum eosinophil count, total immunoglobulins (IgA, IgM, IgG) and correlation between the skin prick test (SPT) and IgE in atopic patients were determined.

MATERIAL AND METHODS

During the 1985-2006 period, 241 atopic patients underwent SCIT at Allergy Clinic, University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine. According to clinical diagnosis, SCIT was administered in patients with atopic dermatitis (AD), pure or in combination with allergic rhinitis (AR) and/or allergic bronchitis (AB), allergic bronchitis and asthma, allergic rhinitis (AR+AB), allergic conjunctivitis (AC), urticaria, and Quincke's edema (U+QE) (Fig. 1). Atopic patients were clinically evaluated, free from disease relapses and without any immunotherapy procedure (1,3). The SCIT AD group of patients consisted of 88 AD pure patients, 30 AD+AR and 3 AD+AB patients in comparison with 87 AR, 16 AC, 12 AB and 4 U+QE respiratory allergy patients. All AD patients had intense pruritus, excoriated skin lesions and moderate disease.

Before treatment, the following measurements were performed: immunoglobulins, eosinophil count, SPT, total IgE and specific IgE, according to standard procedure. SPT standardized allergens were supplied by Zagreb Institute of Immunology,

according to the European standard. A standard procedure of SPT was performed (3-5).

The immediate type hypersensitivity was demonstrated with allergens for SPT. We started with histamine as positive control and buffer solution as negative control. After 20-25 minutes, we read positive reactions: weal and flare, from +1 to +4 (3).

In this study, serum total IgE and specific IgE antibodies directed against common airborne allergens were evaluated before and after 36 months of SCIT therapy by use of the Radio Immunosorbent Test (RIST), FluoroImmuno Assay (FIA), FluoroEnzymeImmunoAssay-CAP System (FEIA-CAP), and RadioAllergosorbent Test (RAST) and CAP System RAST for determination of specific IgE antibodies (3).

The Pharmacia UniCAP system FEIA reagents were used for quantitative measurement of serum total or specific IgE antibodies, with reading in classes 0 to 6. Normal total IgE range was 100 kU/L. Specific IgE range (kUA/L) was from class 0 to 6 (Table 1).

Immunoglobulins (IgA, IgM, IgG) were determined by the immunoturbidimetric method (Cobas Roche 600). Eosinophil count was determined in percentage of blood count.

Table 1. Specific IgE range (kU/l) – UniCAP

Class	Concentration	Normal values
0	<0.35	<0.35
1	0.56	0.35-0.70
2	2.20	0.70-3.50
3	10.70	3.50-17.50
4	36.70	17.50-50.00
5	66.70	50.00-100.00
6	111.20	>100.00

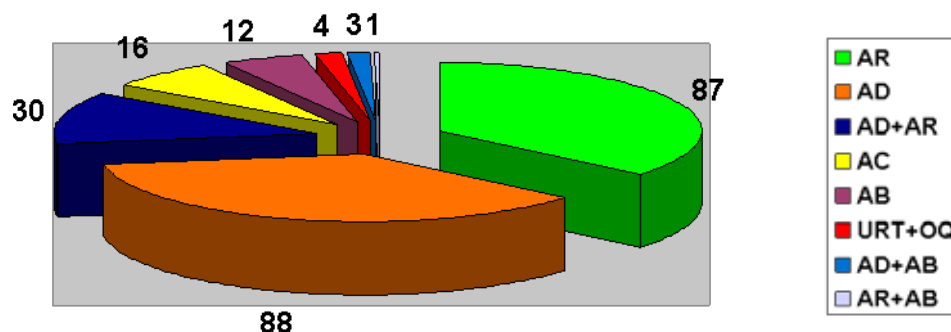


Figure 1. Distribution of 241 atopic patients according to clinical diagnosis.

AR= allergic rhinitis

AB=allergic bronchitis

AD=atopic dermatitis

URT+QE=urticaria + Quincke's edema

AC=allergic conjunctivitis

The following allergens were used for specific immunotherapy according to WAO taskforce (4):

- *Dermatophagoides pteronyssinus*, house dust mite (mixed or separately),
- mixed pollens (grass, tree, weed)
- single allergens:
 - o grass (cocksfoot, timothy, rye)
 - o tree (hazel, birch, black pine, locust, plane-tree, poplar, lime, olive, elder, willow, oak)
 - o feather, animal fur

RESULTS

In this retrospective study including data on 241 atopic patients, results of clinical evaluation and laboratory tests confirmed the efficacy of SCIT. We analyzed correlation between SPT, total and specific IgE UniCAP tests (Table 3, Fig. 3). The results showed the correlation of SPT with specific IgE for grass and weed pollen to be better in patients with allergic rhinitis, conjunctivitis and bronchitis. There was good correlation in all three tests. Patients with atopic dermatitis sensitive to *Dermatophagoides pteronyssinus* showed better correlation of SPT with total IgE and clinical efficacy. In all AD patients, there was a long period with relapse of skin lesions (10-15 months).

As shown in Figure 2, the most frequent allergens in 241 atopic patients were grass pollen mixture, *Dermatophagoides pteronyssinus*, ragweed, tree pollen mixture, cocksfoot, birch, animal dander, and feather.

Therapeutic efficacy (less or free from symptoms in almost all patients) was noticed after a minimum of 3 years of therapy. Very good clinical outcome was noticed in patients with atopic respiratory diseases as well as in those with atopic dermatitis allergic to aeroallergens (*Dermatophagoides*, mixed pollens: grass, tree, weed). In these

groups of patients, therapeutic efficacy was first proved several months of therapy initiation, as also reported by Canonica *et al.* (4).

In one patient, a systemic adverse event was recorded (bronchospasm, wheals). Parenteral anti-allergic therapy was successfully administered; however, specific immunotherapy was discontinued.

Due to marked erythema on the photoexposed areas (face, neck and hands), two patients gave up specific immunotherapy and switched to local immunomodulator.

There was a significant decrease in serum total IgE and specific IgE to *Dermatophagoides*. The values of eosinophil count and immunoglobulins were within the normal limits both before and after SCIT.

DISCUSSION

In this retrospective study including data on 241 atopic patients, we confirmed the efficacy of SCIT, substantiated by our own experience. In a future prospective study we will assess the influence of SCIT on serum level of IFN- γ , IL-4 and IL-5 before and after 3-4 years of therapy. Correlation between clinical score and serum level of cytokines will be determined.

Specific immunotherapy is used for a century now and its efficacy is well documented.

However, as there were no defined standards for performing clinical trials with specific immunotherapy, the World Allergy Organization gathered a group of experts to develop guidelines for the methodology of immunotherapy studies. The recommendations include guidelines for study design, patient selection, appropriate outcomes and statistical processing to be applied in planning and performing clinical studies with allergen specific

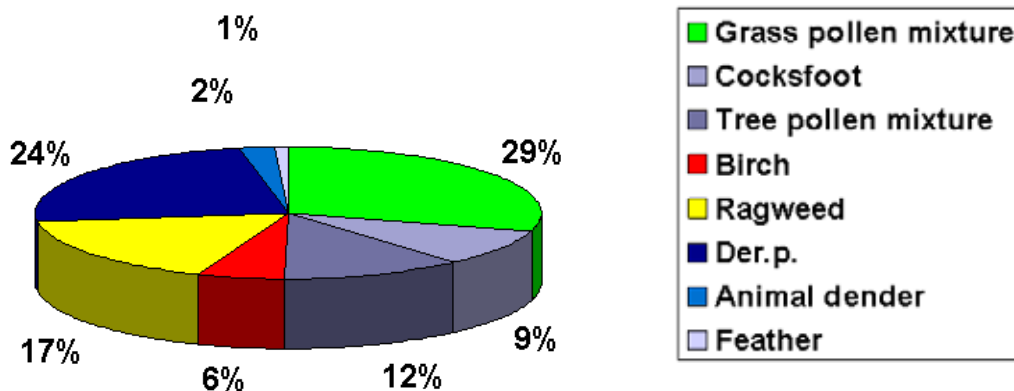


Figure 2. Most common allergens in 241 atopic patients according to skin prick test.

Table 2. Correlation of skin prick test (SPT), total and specific IgE UniCAP tests in 241 atopic patients undergoing specific immunotherapy (1985-2006) before treatment

Number of patients	Diagnosis	Most often positive reactions in SPTs (+1 to +4)	Total IgE value UniCAP (kU/l)	Specific IgE range from +1 to +6
87	AR	Grass pollen +2, +4 Der p +3, +2 Tree pollen +3 Weed pollen +3	441-1034	Grass pollen +2 (1.70) +4 (50.6) Der p +3 (8.66) to +5 (70.0) Tree pollen +3 (12.0) to +4 (21.0) Birch +4 (39.40) Weed pollen +3 to +4 Ragweed +6 (>100.0)
88	AD	Der p +4, +3 Grass pollen +3, +2 Timothy +4, +3 Feather +1 Weed pollen +2, +4 Mugwort +3 Tree pollen +2	154 to >4000	Der p +4 (33.9) to +6 (>100.0) Grass pollen +2 (1.70) to +4 (36.8) Timothy +4 (30.3) Feather 0 (<0.35) Weed pollen +2 (3.13) to +5 (58.2) Ragweed +5 (59.9) Tree pollen +3 (4.54) to +6 (>100)
30	AD+AR	Der p +1 Feather +1, +2 Grass pollen +3 Tree pollen +2 Birch +2, +3 Cocksfoot +3 Weed pollen +4 Mugwort +2	129-2455	Der p +1 (1.42) Timothy +4 (50.6) Weed pollen +6 (>100) Mugwort +4 (60.0) Tree pollen +6 (>100) Birch +2 (2.20) Feather +3 (13.1)
16	AC	Der p +3 Tree pollen +2 Birch +3 Animal dander +2 Grass pollen +3 Cocksfoot +3 Weed pollen +3	46-1072	Der p +3 (8.66) Tree pollen +4 (21.0) Birch +4 (32.4) Animal dander +2 (2.20) Grass pollen +3 (12.0) Cocksfoot +3 (13.1) Weed pollen +3 (10.8) to +6 (>100.0)
12	AB	Grass pollen +2 Cocksfoot +2 Birch +2 Der p +2	29-797	Ragweed +5 (68.2) Cocksfoot +2 (2.69) Oak +3 (4.49) Der p +2 (2.69)
3	AD+AB	Der p +2,+3 Grass pollen +2, +3 Tree pollen +2 Weed pollen +3 Feather +1	36-609	Der p +6 (>100) Grass pollen +4 (36.8) Tree pollen +6 (>100) Weed pollen +2 (3.13) to +5 (58.2)
1	AR+AB	Der. p +3 Weed pollen +2,+3 Grass pollen +2	109	Der.p +6 (>100) Weed pollen +4 Tree pollen +3
4	URT+QE	Grass pollen +1 Weed pollen +2, +3 Tree pollen +2,+3	150- 466	Weed pollen +4 (40.4) do +5 (86.7) Ragweed +3 (10.8) Tree pollen +2 (2.20) to +4 (21.0)

AR, allergic rhinitis; AD, atopic dermatitis; (AD+AR), atopic dermatitis and allergic rhinitis; AC, allergic conjunctivitis; AB, allergic bronchitis and asthma; (AD+AB), atopic dermatitis and allergic bronchitis and asthma; (AR+AB), allergic rhinitis and allergic bronchitis and asthma; (URT+QE), urticaria and Quincke's edema

immunotherapy (4). Although the real role of IgE in the efficacy of SCIT is not quite clear, it seems that IgE is involved in AR, venom allergy and AD treated with SCIT.

SCIT is a causal treatment for IgE-mediated allergic diseases. It induces long-term tolerance to

the applied allergens through several immune effects. Its preventive aspects, especially reduced development of bronchial asthma and less new allergic sensitizations, have been ever more taken in consideration when deciding on SCIT, as also proven in this study.

Table 3. Correlation of skin prick test (SPT), total and specific IgE UniCAP tests in 241 atopic patients undergoing specific immunotherapy (1985-2006) after 36 months of treatment

Number of patients	Diagnosis	Most often positive reactions in SPTs (+1 to +3)	Total IgE value UniCAP (kU/l)	Specific IgE range from +1 to +5
87	AR	Grass pollen +1, +3 Der p +2, +1 Tree pollen +1 Weed pollen +1	220-800	Grass pollen +1 to +2 Der p +1 to +3 Tree pollen +1 to +2 Birch +2 Weed pollen +2 Ragweed +3
88	AD	Der p +2; +1 Grass pollen +1, +1 Timothy +2, +1 Feather 0 Weed pollen +1, +2 Mugwort +1 Tree pollen +1	80 to >2500	Der p +2 to +3 Grass pollen +1 to +3 Timothy +2 Feather 0 Weed pollen +1 to +5 Ragweed +2 Tree pollen +1 to +2
30	AD+AR	Der p 0 Feather 0, +1 Grass pollen +1 Tree pollen +1 Birch +1, +2 Cocksfoot +1 Weed pollen +2 Mugwort +1	50-1210	Der p 0 Timothy +2 Weed pollen +3 Mugwort +3 Tree pollen +3 Birch +1 Feather +1
16	AC	Der p +1 Tree pollen +1 Birch +1 Animal dander +1 Grass pollen +1 Cocksfoot +1 Weed pollen +1	22-600	Der p +1 Tree pollen +2 Birch +2 Animal dander 0 Grass pollen +1 Cocksfoot +1 Weed pollen +1 to +3
12	AB	Grass pollen +1 Cocksfoot +1 Birch +1 Der p +1	20-200	Ragweed +3 Cocksfoot +1 Oak +1 Der p +1
3	AD+AB	Der p +1, +1 Grass pollen 0, +1 Tree pollen +1 Weed pollen +1 Feather 0	10-300	Der p +3 Grass pollen +2 Tree pollen +3 Weed pollen +1 to +3
1	AR+AB	Der. p +1 Weed pollen +1, +1 Grass pollen +1	60	Der.p +3 (>100) Weed pollen +3 Tree pollen +2
4	URT+QE	Grass pollen 0 Weed pollen +1, +1 Tree pollen +1, +1	128-250	Weed pollen +2 to +3 Ragweed +1 Tree pollen +1 to +2

AR, allergic rhinitis; AD, atopic dermatitis; (AD+AR), atopic dermatitis and allergic rhinitis; AC, allergic conjunctivitis; AB, allergic bronchitis and asthma; (AD+AB), atopic dermatitis and allergic bronchitis and asthma; (AR+AB), allergic rhinitis and allergic bronchitis and asthma; (URT+QE), urticaria and Quincke's edema

SCIT is indicated in patients with IgE-mediated sensitizations with clinical symptoms to allergens which do not permit allergen avoidance and are available as suitable extracts. Children tolerate and benefit from its immunomodulatory effects most (5). New routes of administration currently

considered include sublingual immunotherapy (SLIT), demonstrated to be equally efficacious and with less side effects and good compliance (6).

As the high prevalence of allergic adverse events during treatment remains one of the main

problems, there are some approaches to reduce the allergenicity of immunotherapy preparations while maintaining immunogenicity. Peptide immunotherapy (short synthetic peptides) represents major T-cell epitopes of the allergen. The possible benefits might be reduction of both the capacity to cross-link IgE molecules and activation of mast cells and basophils as well as the ease of manufacture and standardization (7).

SCIT or SLIT in atopic dermatitis (AD) is still a controversial issue. In our AD patients, SCIT was beneficial. A WHO position paper states that immunotherapy for AD is only acceptable for clinical trials. However, SCIT seems to be beneficial in children and teenagers in particular, for modification of the natural course of atopic march. As for the immunologic parameters in the sera of patients with AD, a significant decrease in total IgE and IgE against aeroallergens was recorded in the course of SIT. Our results confirmed this finding. Czarnicka-Operacz and Silny followed ECP, IFN- γ , IL-12, IL-4 and IL-5 before and after SCIT (8).

SLIT treatment for 6 months was clinically effective in decreasing asthmatic symptoms and medication use in children with mild-to-moderate asthma due to mite sensitivity. After 6 months of treatment, there was a significant difference in nighttime asthma symptom scores and specific IgG4 between the SLIT group and placebo group (9). In addition, daytime symptom and medication scores, total IgE, eosinophil count, FEV1 and mean evening peak expiratory flow rate reached significant differences in SLIT group. No severe adverse events were reported (9).

Another study in children with house-dust mite (HDM) induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures indicated that SLIT did not provide additional benefit, despite a significant reduction in allergic response to HDM (10). However, the authors emphasize that the results of this study must be viewed in the context where allergen SIT is known to modify and induce reduction of asthma onset in patients with allergic rhinitis. On the other hand, long-term inhaled corticosteroid therapy in children does not have a disease-modifying effect. Therefore, children with early onset of allergic asthma not treated with inhaled steroid therapy could be potential candidates for SLIT (10).

The usefulness of SCIT in patients with atopic dermatitis allergic to HDM and allergic sensitization to HDM was confirmed in a multi-center, randomized, dose-response study conducted by Werfel *et al.* They showed that SIT to HDM

preparation for one year improved eczema in patients with atopic dermatitis sensitized to HDM allergens and reduced the need of topical corticosteroids (11). A similar observation was noted in our study.

CONCLUSION

It is difficult to evaluate the possible effect of SCIT; however, its efficacy has been demonstrated in many study groups of atopic patients as well as in our retrospective study. The issue will be additionally investigated in future trials.

Atopic and allergic diseases are increasing in the last decades. Atopic dermatitis is prevalent worldwide and *Dermatophagoides pteronyssinus* is the leading causative allergen (2,11). The disease itself is difficult to treat, especially in combination with respiratory allergy, and is disturbing for the patient and his family. At the moment, SCIT seems to be a valuable treatment that can both prevent new sensitizations and modify the course of atopic march. Therefore, we support SCIT as the method of choice in atopic patients, as it represents a worthwhile therapeutic option not only for children with respiratory allergy but also for adolescents sensitive to aeroallergens. According to our experience, SCIT should better be administered twice a year (spring and autumn) with pollen allergens, and once a year for other inhalant allergens. We intend to launch a prospective study with a more extensive spectrum of immunologic parameters (IFN- γ , IL-4 and IL-5) before and after three years of SCIT to demonstrate the advantages of this therapeutic method.

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