Acta Dermatovenerol Croat 2006;14(4):230-240 CLINICAL ARTICLE

Specific Immunotherapy in Atopic Dermatitis – Four-Year Treatment in Different Age and Airborne Allergy Type Subgroups

Magdalena Czarnecka-Operacz, Wojciech Silny

Department of Dermatology and Allergic Diseases Diagnostic Center, University of Medical Sciences, Poznań, Poland

Corresponding author:
Professor Magdalena Czarnecka-Operacz, MD, PhD
49 Przybyszewskiego Str.
60-355 Poznań,
Poland
czarneckam@op.pl

Received: May 16, 2005
Accepted: March 10, 2006

SUMMARY Atopic dermatitis (AD) is a common inflammatory disease involving the skin and frequently other organs and systems such as respiratory system. The recently recognized atopic nature of the skin inflammation in AD has raised a growing interest in the treatment with allergen-specific immunotherapy (SIT). In this study, the efficacy of SIT was evaluated in a group of 37 AD patients aged 5-44 years: 14 allergic to house dust mites (HDM), 17 to grass pollen allergens, and 6 allergic to grass and mugwort pollen allergens. IgE-mediated airborne allergy was well documented in all cases. SIT was performed with Novo Helisen Depot allergy vaccines of appropriate composition. Control group included 29 patients with AD and confirmed IgE-mediated airborne allergy to analogous allergens: HDM, 14 patients; grass pollen allergens, 11 patients; and grass and mugwort pollen allergens, 4 patients. Conventional methods of AD treatment were used in the control group. Clinical evaluation of patients was performed with W-AZS index after 12, 24, 36 and 48 months of therapy. SIT was found to be an efficacious and safe method of treatment for selected patients with AD and IgE-mediated airborne allergy. The efficacy of this therapeutic method was significantly higher than that recorded by conventional methods used in the control group in all 3 age subgroups and all 3 types of airborne allergy (HDM, grass pollen, and grass and mugwort pollen). It is concluded that SIT may be a highly promising method of controlling skin inflammation in AD with the potential to prevent the development of AD into respiratory allergy.

KEY WORDS: atopic dermatitis; allergy; specific immunotherapy; treatment

INTRODUCTION

According to the definition presented at the Second International Consensus Conference on Atopic Dermatitis (ICCAD II) (1), "atopic dermatitis (AD) is a pruritic, inflammatory, chronic skin disease that typically begins in early childhood and may continue to recur as adult disease. While various patterns of expression may eventually be shown to represent different genetic subtypes,

Acta Dermatovenerol Croat
2006;14(4):230-240

there is no current distinction between adult and childhood atopic dermatitis". The following set of consensus statements on AD represent our updated knowledge (2):

- AD is a common chronic inflammatory skin disease. It is characterized by intense itching, dry skin, inflammation and relapses, and it causes physical and emotional distress in patients and their families.
- AD is often familial and frequently associated with asthma, food allergy, allergic rhinitis, and recurrent skin infections.
- Trigger factors such as stress, irritants, microbes and allergens should be identified and avoided.
- In the absence of cure, early effective treatment should be initiated to reduce the signs, symptoms and recurrences, and to prevent progression of the disease.
- Emphasis should be put on long-term control rather than just reactive management of relapses.
- Topical corticosteroids provide effective, acute control but provoke safety concerns when used continuously; furthermore, patients do not always use steroids as prescribed by their physicians.
- There is a need for safe, effective therapy for early control and long-term maintenance.
- The new class of topical calcineurin inhibitors may fulfill this unmet need.

Treatment of AD is still a challenge for physicians and in many cases the disease is poorly controlled. Topical corticosteroids are responsible for various side effects, rebound phenomenon, while the lack of confidence in steroid safety also adversely affects compliance and undertreatment of children with AD. Systemic treatment is associated with potentially severe adverse effects and is generally not recommended except as a last resort (3). Phototherapy is inconvenient and may carry a risk of future skin cancers or/and photoaging. Immunosuppressants such as cyclosporine or azathioprine require appropriate monitoring because of their potential effects on organ toxicity, increased risk of infections and possibly lymphoma, and may interfere with immunization in childhood. And finally allergen-specific immunotherapy (SIT) should be mentioned, because clinical benefit of this method has been shown in the treatment of AD patients (2). SIT in selected cases of AD patients with IgE-mediated airborne allergy was one of our main interests for the last few years. In our opinion SIT fulfills therapeutic objectives for AD because it:

- reduces the signs and symptoms of the disease,
- prevents or reduces recurrences,
- provides long-term management by preventing exacerbations, and
- modifies the course of the disease.

This paper presents our results on SIT performed as an open study over a 4-year period, and discusses differences recorded in patient subgroups divided according to age and type of airborne allergy. It is a part of a complex project on SIT in AD, which includes a double blind placebo controlled 12-month study.

Material and methods

The study included two groups of AD patients: SIT group of 37 patients (25 female and 12 male, age range 5-44, mean age 18 years) with moderate to severe disease activity evaluated by W-AZS index: 94.5±39.7 points (4,5) (Tables 1 and 2). All patients had excoriated skin lesions with intensive pruritus. IgE-mediated airborne allergy was confirmed in all patients (clinical evaluation, skin prick tests with aeroallergens, total IgE, and IgE against aeroallergens); 17 patients were allergic to grass pollen allergens, 6 patients to grass and mugwort pollen allergens, and 14 patients to house dust mite allergens (*Dermatophagoides (D.) pteronyssinus* and *Dermatophagoides (D.) farinae)*. This group of patients were administered SIT with Novo-Helisen Depot vaccines over a 4-year period. Control group consisted of 29 AD patients (19 female and 10 male, age range 5-41, mean age 17 years) with moderate to severe disease activity as assessed by W-AZS index: 86.9±24.0 points. Before therapy, there was no significant between group difference in the clinical activity of AD. Control group patients met all the criteria for SIT but did not want to receive allergy vaccination. Eleven of these patients were allergic to grass pollen allergens, four to grass and mugwort pollen allergens, and 14 to house dust mite allergens (*D. pteronyssinus* and *D. farinae*). In this group of patients conventional methods of treatment were used during the 4-year period.

Specific immunotherapy

Novo-Helisen Depot allergy vaccines were used in the treatment of the SIT group. The composition

of vaccines was selected individually according to the clinical and allergological characteristics of patients. The following allergy vaccines were used:

1. grass pollen allergens 100% in 17 patients
2. grass pollen allergens 80% and mugwort pollen allergens 20% in 6 patients
3. house dust mite allergens *D. pteronyssinus 50%* and *D. farinae 50%* in 14 patients

Novo-Helisen Depot allergy vaccines were administered perennially by the classic subcutaneous route in all three types of airborne sensitization. The following concentrations of allergen extracts were used:

- concentration 1, 50 TE/mL
- concentration 2, 500 TE/mL
- concentration 3, 5000 TE/mL (TE=therapeutic unit)

SIT was performed according to the classic protocol, starting with 0.05 mL of concentration 1 (50 TE/mL). Injections were then administered every 7-14 days with gradually increasing doses of allergen extracts to the maintenance dose (1 mL of concentration 3, 5000 TE/mL). Finally, the maintenance dose was repeated every 4 weeks for the total SIT period of 4 years. The total dose administered throughout this period was approximately 188000 TE (47000TE per year). In case of seasonal sensitization during the pollination season the dose was reduced according to clinical picture (by 20%-50% of the planned dose).

Conventional treatment consisted of antihistaminic drugs (generation I and II), antipruritic agents, anti-inflammatory agents, topical steroids, moisturizing and greasing agents.

Clinical assessment was performed before and after 12, 24, 36 and 48 months of treatment in both study groups. W-AZS index was used on clinical evaluation of patients (Tables 1 and 2).

Table 1. W-AZS index

I EVALUATION OF PRURITUS AND LOSS OF SLEEP IN PATIENTS WITH ATOPIC DERMATITIS.

A. PRURITUS EVALUATION:

	POINTS
No pruritus	0
Pruritus is present:	
Extensiveness:	
1. Single or multiple localization of pruritus	2
2. Extensive pruritus involving whole body surface	6
Frequency:	
1. Short episodes of pruritus - less than 30 minutes	2
2. Longlasting pruritus episodes	4
3. Constant pruritus	8
Severity:	
1. Scratching is not necessary	2
2. Scratching is necessary	4
3. Anxiety and irritation caused by pruritus	8

B. LOSS OF SLEEP EVALUATION:

1. No loss of sleep	0
2. Problems in falling asleep	3
3. Night awakening caused by pruritus	6
4. Sleeplessness	12

TOTAL (A + B) ..... + ... = I

Table 2. W-AZS index

II EVALUATION OF EXTENSIVENESS AND SEVERITY OF SKIN INFLAMMATION IN PATIENTS WITH ATOPIC DERMATITIS

Extensiveness of skin lesions A	Severity of skin inflammation: erythema edema	vesicles erosions	crusts scaling	lichenization pigmentation B	A x B 10
1. Face and neck ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
2. Scalp and nucha ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
3. Trunk (anterior surface) ( )x4=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
4. Trunk (posterior surface) ( )x4=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	....
5. Right arm ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
6. Right forearm and hand ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
7. Left arm ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
8. Left forearm and hand ( )x1=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
9. Right thigh ( )x2=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
10. Right shank and foot ( )x2=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
11. Left thigh ( )x2=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
12. Left shank and foot ( )x2=	( )x3 +	( )x3 +	( )x2 +	( ) = ...	.....
				TOTAL	II

- Score extensiveness of skin lesions 0-3:
  - 0 = not present
  - 1 = 1-10% of skin surface involved
  - 2 = 11-30% of skin surface involved
  - 3 = 31-100% of skin surface involved
- Score severity of skin inflammation 0-3:
  - 0 = not present
  - 1 = mild
  - 2 = moderate
  - 3 = severe

TOTAL W-AZS : I + II

Statistical analysis

Statistical evaluation was performed by use of Student's t-test, ANOVA/MANOVA polydimensional analysis, Wilcoxon test and Mann-Whitney U test. For evaluation of correlations, Spearman rank correlation coefficient was calculated for statistical significance.

RESULTS

Clinical efficacy according to age subgroups

Patients with AD were divided into three age subgroups: subgroup 1, children aged 5-14 years (n=16); subgroup 2, patients aged 15-21 (n=9); and subgroup 3, patients aged >21 (n=12). In the control group, the respective figures were 14, 5 and 10.

Mean values of W-AZS score for particular age subgroups and statistical analysis of results are presented in Tables 3 and 4, and Figure 1. In the SIT age subgroup 1, the mean W-AZS score decreased from 84.0±39.3 points before treatment to 5.4±5.2 points after 48-month therapy. At 24, 36 and 48 months of treatment, the disease severity decreased significantly ($p<0.001$) in comparison with the initial status. In the SIT age subgroup 2, the mean value of W-AZS score was 102.0±38.7 points before and 21.2±35.3 points after 48 months of SIT. A statistically significant clinical improvement from the initial status was recorded at 24 months ($p<0.05$) as well as at 36 and 48 months ($p<0.001$) of therapy. In the SIT age subgroup 3, the mean value of W-AZS score was 102.9±41.1 points before treatment to decrease to 11.2±10.9

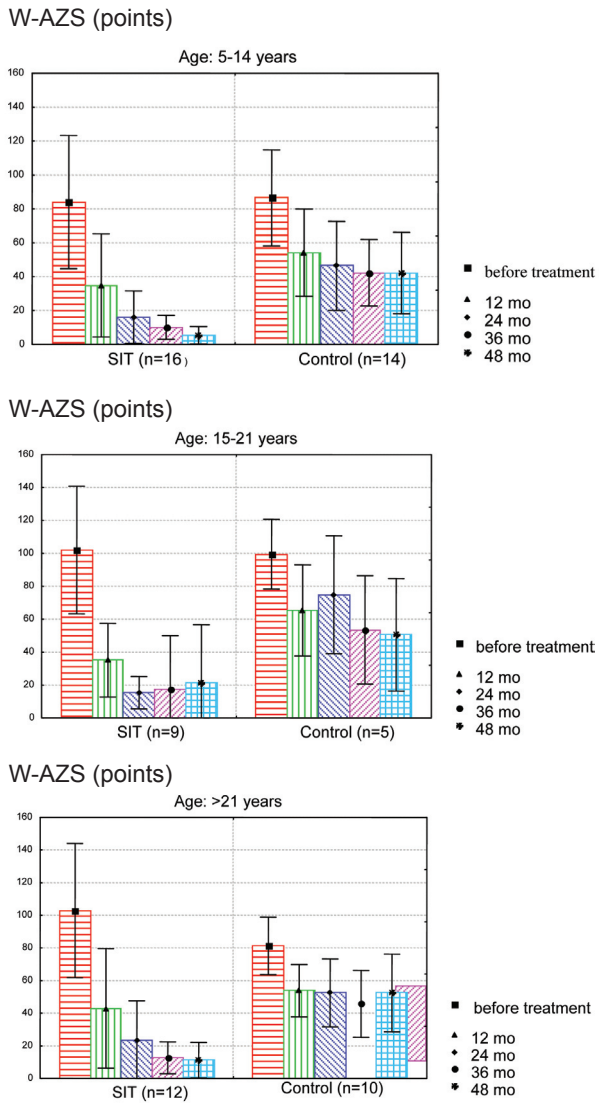

Figure 1. Mean values of W-AZS score ±SD in the SIT and control groups according to age groups

points after treatment. The 24-, 36- and 48-month SIT resulted in a significant clinical improvement ($p<0.01$ at 24 months, and $p<0.001$ at 36 and 48 months). In the control group, patients aged 5-14 showed a mean pretreatment W-AZS score of 86.4±28.4 points, which decreased to 42.2±24.0 points after 48 months. A significant improvement was recorded at 24, 36 and 48 months of therapy ($p<0.001$, $p<0.01$ and $p<0.001$, respectively). Patients aged 15-21 treated with conventional methods showed a pretreatment W-AZS score of 99.5±21.2 points, which decreased to 50.6±34.2 points after 48 months of treatment. A statistically significant difference in the clinical score in comparison with the initial status was only recorded at 48 months of treatment ($p<0.05$). In the control subgroup aged >21 the clinical score was as follows 81.3±17.6 points before and 52.4±23.8 points at 48 months of conventional therapy. After 12, 36 and 48 months of therapy clinical improvement was statistically significant in comparison with the initial status ($p<0.01$, $p<0.001$, and $p<0.05$, respectively).

Comparative statistical analysis of clinical results obtained in the SIT and control groups is presented in Table 4. In the 5-14 age group there was a statistically significant difference in favor of SIT group after 12, 24, 36 and 48 months of treatment ($p<0.05$ at 12 months, and $p<0.001$ at 24, 36 and 48 months). In the 15-21 age subgroup there was a significant difference in favor of SIT group after 24, 36 and 48 months of therapy ($p<0.05$). In the >21 age subgroup a significant difference in favor of SIT group was recorded after 24,36 and 48 months of treatment ($p<0.01$ at 24 months, and $p<0.001$ at 36 and 48 months).

Clinical efficacy according to type of air borne allergy

Tables 5 and 6, and Figure 2 summarize results of treatment with allergy vaccines and conventional methods in AD patients with different types of IgE-mediated airborne allergy.

In the SIT group 14 patients were allergic to HDM allergens (*D. pteronyssinus* and *D. farinae*), 17 patients were allergic to grass pollen allergens, and 6 patients were allergic to grass and mugwort pollen allergens. In patients allergic to HDM allergens the mean value of W-AZS score was 98.8±44.3 points before and 14.7±25.8 points after 48 months of treatment. There was a significant difference in the clinical score after 48 months of SIT in comparison with the initial clinical status of patients ($p<0.001$). In the group of patients allergic to grass pollen allergens the mean value of W-AZS score was 100.1±34.1 points before treatment to decrease to 9.3±15.9 points at 48 months of therapy. Results of statistical analysis were similar to those recorded in the previous group. A significant difference was recorded after 48 months of SIT in comparison with the initial clinical score ($p<0.001$). In the group of 10 patients allergic to grass and mugwort pollen allergens the mean value of W-AZS score was 68.6±39.9 points before and 7.9±5.9 points after 48 months of SIT, yielding a statistically significant difference.

In the control group, there were 14 patients allergic to HDM allergens,11 patients allergic to grass pollen allergens, and four patients allergic to grass and mugwort pollen allergens. In patients allergic to HDM allergens the mean value

Table 3. Mean values of W-AZS score in the SIT and control groups of patients with AD according to age groups

	Mean value of W-AZS score (pts) ± SD					
	SIT group			Control group		
	Age (yrs)			Age (yrs)		
	5 - 14 (n-16)	15 - 21 (n-9)	> 21 (n-12)	5 - 14 (n-14)	15 - 21 (n-5)	>21 (n-10)
Before treatment [a]	84.0±39.3	102.0±8.7	102.9±41.1	86.4±28.4	99.5±21.2	81.3±17.6
At 12 months [b]	34.8±30.4	35.0±22.4	43.0±36.6	54.2±25.7	65.3±27.7	53.8±16.1
At 24 months [c]	16.1±15.5	15.4±9.9	23.7± 23.9	46.4±26.4	74.9±35.8	52.4±20.8
At 36 months [d]	10.1±7.1	17.6±32.5	12.7±9.8	42.3±19.6	53.5±32.8	45.7±20.5
At 48 months [e]	5.4±5.2	21.2±35.3	11.2±10.9	42.2±24.0	50.6±34.2	52.4±23.8

SIT group:

age 5-14	a/b; b/c; c/d; d/e (NS)
	a/c; a/d; a/e (p<0.001)
age 15-21	a/b; b/c; c/d; d/e (NS)
	a/c (p<0.05)
	a/d; a/e (p<0.001)
age >21	a/b; b/c; c/d; d/e (NS)
	a/c (p<0.01)
	a/d; a/e (p<0.001)

Control group:

age 5-14	a/b; b/c; c/d; d/e (NS)
	a/c (p<0.01)
	a/d; a/e (p<0.001)
age 15-21	a/b; a/c; a/d; b/c, c/d, d/e (NS)
	a/e (p<0.05)
age >21	a/b (p<0.01)
	a/c; b/c, c/d, d/e (NS)
	a/d (p<0.001)
	a/e (p<0.05)

of W-AZS score was 80.1±20.2 points before and 45.3±25.8 points after 4 years of conventional treatment. A significant improvement of the clinical score in comparison with the initial status was recorded at 12 months (p<0.01) and 48 months (p<0.001) of therapy. In the 11 patient allergic to grass pollen allergens the mean value of W-AZS score was 94.6±27.6 points before and 47.8±27.7 points at 48 months of therapy. After 48 months of classic treatment there was a significant improve-

Table 4. Comparative statistical analysis of clinical score (W-AZS) in the SIT and control group

	CLINICAL SCORE W-AZS						Statistical analysis
	SIT group			Control group			
	Age (yrs)			Age (yrs)			
	5-14 (n=16)	15-21 (n=9)	>21 (n=12)	5-14 (n=14)	15-21 (n=5)	>21 (n=10)	Statistical significance
Before treatment	a	b	c	a	b	c	a/a p>0.05 b/b p>0.05 c/c p>0.05
At 12 months	a	b	c	a	b	c	a/a p<0.05 b/b p>0.05 c/c p>0.05
At 24 months	a	b	c	a	b	c	a/a p<0.001 b/b p<0.05 c/c p<0.01
At 36 months	a	b	c	a	b	c	a/a p<0.001 b/b p<0.05 c/c p<0.001
At 48 months	a	b	c	a	b	c	a/a p<0.001 b/b p<0.05 c/c p<0.001

Table 5. Mean values of W-AZS score ± SD in patients with AD treated with SIT and in control group according to type of airborne allergy

		SIT group			Control group		
		D. pteronyssinus D. farinae (n=14)	Grass pollen (n=17)	Grass and mugwort pollen (n=6)	D. pteronyssinus D. farinae (n=14)	Grass pollen (n=11)	Grass and mugwort pollen (n=4)
Before treatment	a	98.8± 44.3	100.1±34.1	68.6± 39.9	80.1±20.2	94.6±27.6	89.8±25.0
At 12 mo	b	36.8± 32.2	35.0± 28.2	46.4± 35.7	57.1±23.4	58.2±25.1	46.0±14.6
At 24 mo	c	18.7±22.7	16.6± 15.1	22.7 ±11.2	53.9±31.3	49.8±26.7	61.1±17.2
At 36 mo	d	16.9± 26.0	7.6±6.7	17.5 ±7.3	45.8±25.1	46.2±22.4	41.7±10.4
At 48 mo	e	14.7± 25.8	9.3±15.9	7.9 ± 5.9	45.3±25.8	47.8±27.7	51.8±22.5

SIT group

- patients allergic to HDM allergens
  - a/b; b/c; c/d; d/e (NS)
  - a/e (p<0.001)
- patients allergic to grass pollen allergens
  - a/b; b/c; c/d; d/e (NS)
  - a/e (p<0.001)
- patients allergic to grass and mugwort pollen allergens
  - a/b; b/c; c/d; d/e (NS)
  - a/e (p<0.001)

Control group

- patients allergic to HDM allergens
  - a/b (p<0.01)
  - a/e (p<0.001)
  - b/c; c/d; d/e (NS)
- patients allergic to grass pollen allergens
  - a/b; b/c; c/d; d/e (NS)
  - a/e (p<0.01)
- patients allergic to grass and mugwort pollen allergens
  - a/b; b/c; c/d; d/e (NS)
  - a/e (p<0.05)

Table 6. Results of comparative statistical analysis of the W-AZS clinical score between SIT and control groups of patients with AD

	SIT group			Control group			Statistical analysis
	D. pteronyssinus D. farinae (n=14) (n-14)	Grass pollens (n=17)	Grass and mugwort pollens (n=6)	*D. pteronyssinus D. farinae* (n-14)	Grass pollens (n=11)	Grass and mugwort pollens (n=4)	Statistical significance
Before treatment	a	b	c	a	b	c	a/a p>0.05 b/b p>0.05 c/c p>0.05
At 12 months	a	b	c	a	b	c	a/a p<0.05 b/b p<0.05 c/c p>0.05
At 24 months	a	b	c	a	b	c	a/a p<0.01 b/b p<0.01 c/c p<0.05
At 36 months	a	b	c	a	b	c	a/a p<0.01 b/b p<0.001 c/c p<0.05
At 48 months	a	b	c	a	b	c	a/a p<0.01 b/b p<0.001 c/c p<0.05

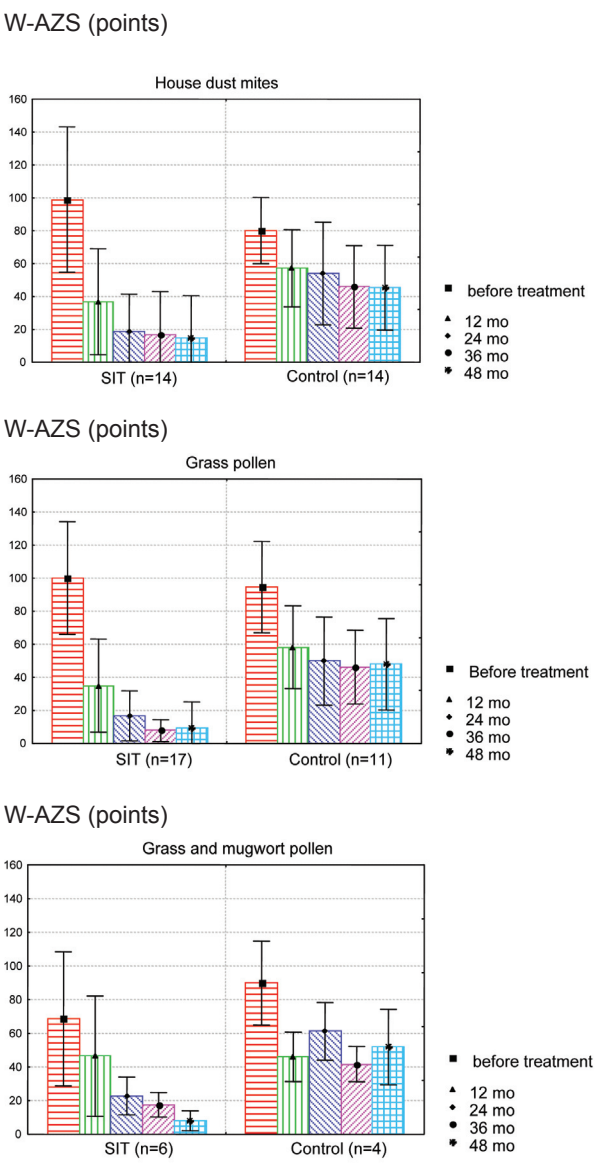

Figure 2. Mean value of W-AZS score ±SD in patients with AD treated with SIT and in the control group according to type of allergy

ment of the clinical score in comparison with the initial score ($p<0.01$). In the four patients allergic to grass and mugwort pollen allergens treated with conventional methods the mean value of W-AZS was 89.8±25.0 points before and 51.8±22.5 points after 48 months of conventional therapy. In this patient subgroup a statistically significant difference was recorded between the initial clinical status and the clinical score obtained at 48 months of therapy ($p<0.05$).

Comparative statistical analysis in the group of patients allergic to HDM allergens (Table 6) revealed a statistically significant difference of clinical score in favor of SIT patients after 12, 24, 36 and 48 months of treatment ($p<0.05$ at 12 months, and $p<0.01$ at 24, 36 and 48 months). In patients allergic to grass pollen allergens there was no significant difference between the SIT and control groups before treatment, however, a significant difference in favor of SIT group was observed at 12, 24, 36 and 48 months of therapy ($p<0.05$ at 12 months, and $p<0.01$ at 24, 36 and 48 months). In patients allergic to grass and mugwort allergens there was no significant between group difference before and after 12 months of therapy, however, a significant difference in favor of SIT group was recorded at 24, 36 and 48 months of treatment ($p<0.05$).

DISCUSSION

The recent viewpoint on AD immunopathogenesis proposes a biphasic cytokine expression as a model of disease progression from the early acute to the chronic stage of skin inflammation. It seems that IFNγ/IL-12-dependent TH2→Th1 switch is responsible for sustained AD progression, and therefore cytokines themselves might be regarded for potential treatment. Controlled studies have shown the safety and efficacy of long-term use of recombinant IFN-γ (rIFN-γ) in the treatment of AD (6-8). Since IFNγ/IL-4 imbalance is commonly accepted to be the central immune defect in atopic allergy, this therapy seems to be very rational and promising. Also considering SIT as the only method which is capable of modifying the natural course of the atopic process by reversing the imbalance of Th2/Th1 subpopulations, this therapy should be considered potentially beneficial. Although scientific research on SIT has been performed for nearly a century (9), its results have only recently and partially been accepted (10). One of the reasons perhaps lies in the meta-analysis technique as well as in the scientific and statistical methodology used for validation of SIT efficacy (11,12). The critical difference between the symptomatic nature of pharmacological treatment and the causal, pathogenic and preventive nature of SIT should be clearly stressed. The indications for SIT in allergic rhinitis and asthma, only limited to cases in which pharmacological treatment is not adequate to control symptoms, raise the question of the equivalence of therapies (13). Also, discussing the clinical efficacy of SIT, we base our selection of studies on the criteria directly extrapolated from that of drug trials. DBPC, a randomized study design, obviously provides highest grade evidence for the efficacy and safety of the investigated drug

that exerts its action in a short time and is poorly influenced by confounding factors (13). Clinical response in case of SIT is time-related and generally a long period is required to limit the inflammatory process. Therefore, well-designed observational studies should also be evaluated for proper analysis of the SIT clinical efficacy, otherwise there is a high risk of the result underestimate. The WHO position paper states that SIT for AD is only accepted for clinical trials, as exclusively two DBPC trials have been evaluated. According to our knowledge, there have been at least 5 such trials and results obtained by the authors are promising (14-18). Therefore, we believe that AD patients with IgE-mediated airborne allergy who do not respond to conventional treatment may be selected for SIT.

This paper present results of clinical evaluation of SIT performed for 4 years in selected cases of AD. We aimed to analyze any possible differences according to age and type of airborne allergy. We expected SIT to be most effective in youngest AD patients with higher adaptive properties of the immune system. In fact, these children presented the lowest mean W-AZS score after 48 months of SIT; however, the highest score was not recorded in the oldest age subgroup but in patients aged 15-21 (the medium age group). SIT resulted in a gradual and continuous clinical improvement in all three age subgroups (5-14, 15-21 and >21 years). Clinical improvement was recorded already at 12 months of treatment, but it did not reach statistical significance (all three subgroups); after 24, 36 and 48 months it was statistically significant. In youngest patients (age subgroup 1) the clinical score improved more significantly after 24 months of SIT in comparison with the other two age subgroups and it was another age-related difference. In the patients treated with conventional methods we also recorded clinical improvement in all three age subgroups. In age subgroup 1 (5-14 years), clinical improvement was not significant at 12 months, but reached statistical significance at 24, 36 and 48 months. In age subgroup 2 (15-21 years) a statistically significant clinical improvement was only recorded at 48 months of conventional treatment. In age subgroup 3 (>21 years) clinical improvement was observed at 12, 36 and 48 months of therapy in comparison to the initial score. Therefore, the improvement of clinical status in the control group was not as steady and continuous as in the SIT group.

Comparative statistical analysis of the SIT and control group treatment efficacy revealed significant difference in favor of SIT patients in all age subpopulations. In the youngest patients this difference was statistically significant after 12, 24, 36 and 48 months of treatment, and in the other two subgroups it was significant after 24, 36 and 48 months of treatment.

In conclusion, SIT was more effective than conventional treatment of AD patients in all age subgroups, with the best result in youngest patients. The children aged 5-14 exhibited better response already at 12 months of SIT and the best clinical score at the end of the study.

Another parameter taken into consideration in terms of clinical efficacy of SIT was the type of IgE-mediated airborne allergy (HDM, grass pollen, grass and mugwort pollen). The patients allergic to HDM treated with allergy vaccines (Novo-Helisen Depot allergy vaccines: *D. pteronyssinus* 50%, *D. farinae* 50%, n=14) showed clinical improvement already at 12 months of SIT, however, significant difference was recorded at 48 months of treatment. In the group of patients allergic to grass pollen allergens treated with allergy vaccines and those allergic to grass and mugwort pollen allergens clinical improvement was gradual and continuous, and was observed already at 12 months of SIT, to reach statistical significance at 48 months of treatment. The only exception was observed in the group of patients allergic to grass pollen allergens during the last year of treatment, when their mean W-AZS score slightly increased (by 1.7 points). The results obtained in the control group were somehow different in all three subpopulations. In the patients allergic to HDM allergens clinical improvement was significant already at 12 months of treatment and then at 4 years of therapy, although the final clinical score in the control group was much worse in comparison with the SIT group (45.3 vs 14.7). The patients allergic to grass pollen allergens and those allergic to grass and mugwort pollen allergens exhibited significant clinical improvement only after 48 months of treatment.

Comparative statistical analysis of the SIT and control groups yielded a statistically significant difference in favor of SIT group after 12 months of therapy in the patients allergic to HDM and those allergic to grass pollen allergens. After 24, 36 and 48 months of treatment a statistically significant difference in favor of SIT group was recorded in all three allergy type subpopulations (patients allergic to HDM, to grass pollen allergens, and to grass and mugwort pollen allergens). It is therefore concluded that SIT is more effective than

classic treatment of AD irrespective of the type of IgE-mediated airborne allergy. However, in case of the most complex type, grass and mugwort pollen allergy, a statistically significant difference in W-AZS score in comparison with the control group was observed later than in the other two allergy type subpopulations.

Allergen specific immunotherapy has been recognized by the WHO as the only therapeutic modality that can affect the natural course of allergic diseases (10,19) because of the proven clinical efficacy and specific immune changes thus induced. At Department of Dermatology and Allergic Diseases Diagnostic Center of the University of Medical Sciences in Poznań, this method of treatment has been carefully studied in AD patients for years (20-28). In our opinion, SIT may be an effective and promising method of treatment in selected patients with AD and IgE-mediated airborne allergy. This type of systemic therapy is administered to correct the immune derangement underlying AD and should be considered as one of the elements of complex therapeutic strategies in AD.

References

1. Hanifin J, Saurat JH. Proceedings of the International Consensus Conference on Atopic Dermatitis. Rome, Italy, November 5-6, 1999. J Am Acad Dermatol 2001;45: S1-68.
2. Ellis C, Luger T. International Consensus Conference on Atopic Dermatitis II (ICCAD II). Chairman's introduction and overview. Br J Dermatol 2003;148:3-10.
3. Sidbury R, Hanifin JM. Systemic therapy of atopic dermatitis. Clin Exp Derm 2000;25:559-60.
4. Silny W, Czarnecka-Operacz M, Gołębka E, Silny P. W-AZS a new scoring index for patients with atopic dermatitis. Przegl Dermatol 1999;86:215-22.
5. Czarnecka-Operacz M, Bator-Wegner M, Silny W. Atopy patch test reaction to airborne allergens in the diagnosis of atopic dermatitis. Acta Dermatovenereol Croat 2005;13:3-16.
6. Hanifin JM, Schneider LC, Leung DYM, Ellis CN, Jaffe HC, Izu AE, *et al.* Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 1993;28:189-97.
7. Schneider LC, Baz Z, Zarcone C, Zurakowski D. Long-term therapy with recombinant interferon-gamma (rIFN-gamma) for atopic dermatitis. Ann Allergy Asthma Immunol 1998;80:263-8.
8. Jang IG, Yang JK, Lee HJ, Yi JY, Kim HO, Kim CW, *et al.* Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. J Am Acad Dermatol 2000;42:1033-40.
9. Noon L, Cantab BO. Prophylactic inoculation against hay fever. Lancet 1911;1: 1572-3.
10. Bousquet J, Lockey RF, Malling HJ. WHO position paper. Allergen immunotherapy – therapeutic vaccines for allergic diseases. Allergy 1998;53:1-42.
11. Boquete M, Carballada F, Exposito F, Gonzalez A. Preventive immunotherapy. Allergol Immunopathol 2000;28:89-93.
12. Sendin I. Evaluation of pediatric aspects of the WHO document and meta-analysis of immunotherapy. Allergol Immunopathol 2000;29:82-9.
13. Mastrandrea F. Immunotherapy in atopic dermatitis. Exp Opin Invest Drugs 2001;10:49-63.
14. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. Clin Exp Allerg 1992;22:440-6.
15. Leroy BP, Lachapelle JM, Somville MM, Jacquemin MG, Saint-Remy JM. Injection of allergen-antibody complexes is an effective treatment of atopic dermatitis. Dermatologica 1991;182:98-106.
16. Kaufman HS, Roth HL. Hyposensitization with alum precipitated extracts in atopic dermatitis: a placebo controlled study. Ann Allergy 1974;32:321-30.
17. Ring J. Successful hyposensitization treatment in atopic eczema: results of a trial in monozygotic twins. Br J Dermatol 1982;93:597-602.
18. Silny W, Czarnecka-Operacz M. Specific immunotherapy in the treatment of patients with atopic dermatitis – results of double blind placebo controlled study. In press.

19. Theodoropoulos DS, Lockey RF. Allergen immunotherapy: guidelines, update and recommendations of the World Health Organization. Allergy Asthma Proc 2000;21:159-66.
20. Silny W, Czarnecka-Operacz M. Specific immunotherapy in the treatment of atopic dermatitis. Alergia Astma Immunol 1999;4 (Suppl 2):85-7.
21. Silny W, Czarnecka-Operacz M. Specific immunotherapy in the treatment of patients with atopic dermatitis. Rev Fr Alergol 1999;56 (Numero special):87-8.
22. Silny W, Czarnecka-Operacz M. Possible application of specific immunotherapy in the treatment of atopic dermatitis – modulation of immune response. Alergia Astma Immunol 2000;5 (Suppl 1):31-4.
23. Czarnecka-Operacz M, Silny W. Specific immunotherapy in selected cases of atopic dermatitis. Przewodnik Lekarza 2001;3:118-21.
24. Silny W, Czarnecka-Operacz M. Atopic dermatitis – new methods of treatment. Przewodnik Lekarza 2002;3:48-56.
25. Czarnecka-Operacz M. Specific immunotherapy in the treatment of patients with atopic dermatitis. Poznań: Poznańskie Zakłady Graficzne SA, 2000.
26. Czarnecka-Operacz M. Allergy vaccines in the treatment of atopic dermatitis. Int Rev Allergol Clin Immunol 2001;7:5-8.
27. Czarnecka-Operacz M. Total IgE and antigen specific IgE in patients with atopic dermatitis and airborne allergy treated with specific immunotherapy. Int Rev Allergol Clin Immunol 2001;7:16-26.
28. Czarnecka-Operacz M, Silny W, Sobieska M. Serum levels of IFN-γ, IL-2R, IL-4, IL-5 and IL-10 in the course of specific immunotherapy of patients with atopic dermatitis. Int Rev Allergol Clin Immunol 2001;7:27-33.

Cover of “Svijet” magazine; year 1929.
(from the collection of Mr. Zlatko Puntijar)