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Specific Immunotherapy in Atopic Dermatitis

Magdalena Czarnecka-Operacz, Wojciech Silny

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

Corresponding author
Prof. Magdalena Czarnecka-Operacz, MD, PhD
Allergic Diseases Diagnostic Center
Department of Dermatology
University of Medical Sciences
49 Przybyszewskiego Str.
60-355 Poznań
Poland
czarneckam@op.pl

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SUMMARY Despite the existence of various scientific research on the beneficial effect of specific immunotherapy with specific airborne allergens in the treatment of atopic dermatitis, this method has not been easily accepted, as the methodology and the valuation of the studies were heterogeneous. Over the last few years, meta-analysis technology has been developed as a useful tool to globally value the results of different research trials related to one specific scientific problem. When meta-analyses are carried out correctly, they are accepted as the most appropriate way to express the results obtained from different studies. Not many studies have been published in the case of atopic dermatitis and specific immunotherapy.

In this paper, we attempt to present and discuss results obtained by various authors on this topic, beginning with the publication of Strauss and Kligman in 1957. It should be noted that for patients with IgE-mediated airborne allergy, especially children, specific immunotherapy as an early treatment in cases of atopic dermatitis could have an additionally preventive nature in terms of protection against the development of a respiratory atopic problem. Specific immunotherapy should therefore be at least considered in the treatment of selected cases of atopic dermatitis patients presenting airborne IgE-mediated allergy.

KEY WORDS: atopic dermatitis, specific immunotherapy, airborne allergens, IgE

INTRODUCTION

Atopic dermatitis (AD) is defined as a chronic and recurrent skin inflammatory disease. Patients suffering from AD with skin eczematous lesions as the only apparent symptom in up to 60-80% of cases present positive results of bronchial provocation test, indicating the preclinical existence of minimal persistent respiratory inflammation (1-5). Therefore, AD is an atopic, inflammatory disease that may involve not only skin but also other organs and systems, and it seems obvious that the rational therapeutic approach should be a combination of topical and systemic methods. It is also obvious that such a complex treatment may only be successful in case of a well-defined and understood pathological process. Unfortunately, the etiopathogenesis of AD is still obscure. It is believed to be a multifactorial disease with a strong genetic predisposition and a wide variety of immunological and non-immunological abnormalities. Among environmental factors, airborne allergens like house dust mite and plant pollen allergens as well as moulds and animal epithelium allergens seem to be of great importance for the manifestation of AD. Some authors report a high percentage

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of positive skin prick tests and elevated antigen specific IgE (asIgE) serum levels directed against airborne allergens, especially to house dust mite allergens (*Dermatophagoides pteronyssinus* – *Dp* and *Dermatophagoides farinae* – Df) (6,7). Also, atopy patch testing (APT) with environmental allergens like house dust mites may provoke eczematous lesions in AD patients (8-10), inducing an IgE-mediated contact reaction in an extrinsic/allergic type of the disease (11). Furthermore, a clear correlation has been shown between an exacerbation of AD and increased exposure to house dust mite allergens in patients' homes with an improvement of the clinical score following careful avoidance of these airborne allergens (12,13). A recent viewpoint on AD immunopathogenesis proposes a biphasic cytokine expression pattern as a model of disease progression from early acute to chronic lesions (14). So it seems that IFN-γ/IL-12 dependent Th2→Th1 switch is responsible for AD progression to chronic stages of the disease. Knowing that Th2→Th1 immune deviation due to upregulation of IFN-γ-producing cells (15-17) has been previously proposed as a mechanism of specific immunotherapy (SIT), we can conclude that it should be at least helpful in the treatment of selected AD patients.

Allergy vaccines in the treatment of AD patients

Allergy vaccines in selected cases of AD patients with a well-documented airborne allergy have been long regarded as a potential tool for successful control of the disease. Conventional specific immunotherapy (SIT), i.e. the subcutaneous injections of allergen extract, is known to be a curative treatment for special forms of IgE-mediated allergies. It is particularly effective in patients suffering from rhinitis and asthma elicited by pollens (18-23), house dust mite allergy (23-27) and Hymenoptera venom (28,29). SIT is the only treatment that may affect the natural course of allergic diseases, as it may prevent the onset of new sensitizations and influences the natural course of the atopic disease it reduces development of asthma in patients with allergic rhinitis (30,31). Therefore, SIT can also be regarded as a preventive method. It seems to be exceptionally important in AD patients who are at high risk of allergic respiratory signs and symptoms. It seems that SIT may lead to a noticeable clinical improvement in AD patients involving somehow different immunological events than in allergic rhinitis or bronchial asthma, and further clarification of this problem is obviously needed.

Nowadays, SIT is rarely used in the management of AD, although it has been attempted in selected cases over many years. In 1957, Strauss and Kligman were the first to publish their data indicating the possible use of SIT in the treatment of AD patients (32). In 1974, Kaufman and Roth (33) performed a controlled trial on a group of 26 patients with AD. A water-soluble alum-precipitated pyridine extracted complex was used in the treatment of 16 patients. The composition of allergy vaccines was dependent on the results of skin testing, and respective reacting airborne antigens were diluted from independently prepared materials so that appropriate concentrations of antigens were in each patient's SIT therapy set (house dust mite allergens, plant pollen allergens, animal epithelium allergens). The remaining 10 AD patients received placebo. The first 16 doses were given at one-week intervals, and thereafter injections were given every three weeks throughout the 24-month study period. There was a clinical improvement in 13 out of 16 AD patients treated with an active vaccine, and 4 of 10 treated with buffered saline. There was a significant difference in the clinical improvement between the treated group and the placebo group of AD patients.

Further investigations were conducted by Di Prisco, De Feuenmayer and Champion in 1979 (34). The authors selected 15 patients from over 3,000 cases of AD patients, aged 6-14 years with a mean of 25 years. The inclusion criteria were: a history indicating that exposure to the suspected aeroallergen repeatedly caused itching and an exacerbation of skin lesions; a positive skin prick test, in a few cases confirmed by a RAST test; the aeroallergen could not be readily avoided; symptoms were severe enough to warrant the difficulties and cost of treatment; and, finally, all patients with the first four essential criteria had a similar clinical picture. Most patients were severely affected and had failed to respond to conventional therapy, including in-patient treatment. The most important aeroallergens were house dust mite – 9 patients, and grass pollen allergens – 4 patients. The vaccines used were alum-precipitated pyridine extracted. Significant improvement occurred in 33.3% of patients, improvement in 26.7% and slight improvement in 40% of AD patients. Improvement usually started after the fourth or fifth injection. In some cases, it lasted for only a few weeks, usually some months, and in a few cases a single course seemed to achieve an improvement maintained for years. It should be stressed that 7 of the patients had a single course of 8 or

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more injections at weekly intervals, 4 patients had repeated courses and 4 were being maintained on a long-term continuation course of monthly injections of the maximum dose given in the initial standard course. It seems that surely in the last group of patients SIT could be the most effective. The authors concluded that SIT has a place in selected AD patients with a severe course of skin inflammation and can obviously be expected to ameliorate only the allergic component of this multifactorial disease. There was some additional research in the late 1970's on the possible use of SIT in allergic skin disorders (35-37).

In 1982, Ring (38) presented his paper on successful SIT in monozygotic twins with AD. Two sisters (monozygotic twins) suffering from severe AD with seasonal exacerbation during early summer were treated with either grass pollen extract (Alum-precipitated extract ADL) or saline. After 2 years of treatment, the clinical score of the patient treated with grass pollen extract improved significantly, while the placebo caused minimal change in her twin. The therapeutic effect was paralleled by a greater decrease in total serum IgE (from 4.200 to 1.3000 KU/l) in the pollen treated patient (compared with 3.500 to 2.580 KU/l) in the control group.

A group of Danish investigators performed an evaluation of non-specific and specific immunotherapy in severe cases of AD (39). SIT was performed in a group of 12 adult patients sensitive to house dust mite allergens. Three also suffered from asthma, 3 from rhinitis and 2 patients displayed all three main atopic diseases. However, AD was the major health problem in all patients and the only purpose of treatment. Six out of 12 patients improved, 3 patients showed slight improvement, while 2 patients were unchanged and 1 got worse after the observation period, which lasted from 1.5 to 5 years. In most cases, an initial increase followed by a decrease of total serum IgE was detected during the treatment. There was a similar but less pronounced decrease of asIgE serum levels measured by RAST. What is important from the clinical standpoint is that the consumption of topical steroids was found to be reducing during SIT. In the authors' opinions, based upon their investigation and other reports (Ring, Kaufmann-Roth) in the literature, it may be worthwhile to try SIT in selected cases of severe AD.

In 1992, Glover and Atherton (40) published their results of a double-blind controlled trial of SIT in AD children sensitized to *Dp* allergens. A standard 8-month course of treatment with tyrosine-absorbed Dp vaccine on 24 AD children failed to demonstrate superiority over placebo. In the second phase, however, children initially administered active treatment were randomly allocated to continue with active treatment or switched to placebo for further 6 months. The clinical scores suggested that prolonged hyposensitization may be more effective than placebo and further studies would be justified.

In 1993, Leroy *et al.* (41), in a double blind placebo controlled study (DBPC), treated 24 adults with AD and allergic to *Dp* with intradermal injections of complexes containing autologous specific antibodies and *Dp* allergens. After 4 months of treatment, the placebo group received active therapy for further 8 months. The authors reported improvement after 4 months of treatment only in the active treated group. After 1 year of therapy, 82% of the patients showed a mean improvement of 83%. Although the authors concluded that treatment with allergen-antibody complexes was safe and effective for patients with AD, this method is not often used due to methodological and financial difficulties.

Also in 1993, Mosca *et al.* (42) published their data on the treatment of 41 patients with moderate to severe AD and respiratory symptoms with conventional SIT and 48 patients with sub-lingual SIT (SLIT). All enrolled patients had been responding poorly to conventional methods of AD treatment. The observation period lasted for 3 years, and 75.6% of the patients treated with SIT showed a significant improvement, while 19.5% had side effects. SLIT treated patients improved significantly in 64.4% of the cases, with a prevalence of side effects in 14.6%.

In 1994, Pacor *et al.* (43) investigated 32 AD patients allergic to house dust mite allergens. SIT was performed for 3 years with appropriate allergy vaccines (Bayropharm). Significant clinical efficacy was detected in all investigated patients. In addition, a general tendency of skin prick test negativization as well as a decrease in IgE levels was observed.

In 1994, Galli *et al.* (44) demonstrated in a group of 60 AD patients that oral SIT (Neo-Abello), although without side effects, is rather ineffective and does not affect the natural history of AD. Perhaps these contrasting results are dependent upon the different route - oral SIT - which may be inadequate for AD patients.

In 1996, Zwacka *et al.* (45) conducted a multicenter trial comparing different methods of

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treatment on 212 patients with AD. One group was treated with SIT, one with SLIT and another with conventional methods. To evaluate the efficacy of the treatment, total serum concentrations of IgE and clinical status were compared at the second year of therapy with values obtained before treatment. Significant clinical improvement and a reduction of total IgE were noted in both the SIT and SLIT groups, with no significant differences in the symptomatic drug-treated group of patients.

Some Polish authors also approached the problem of SIT in AD. Rudzki *et al.* (46) conducted SIT in a group of 15 patients allergic to house dust mite allergens as well as Samochocki and Rudzki (47) in a group of 6 patients sensitized to the mentioned aeroallergens. The authors were able to confirm the good efficacy of SIT in AD in most of the investigated cases. Trofimowicz *et al.* (48) were also able to prove the good efficacy of SIT in a 3-year treatment of 22 AD patients. Other authors were also optimistic about this type of treatment in selected cases of AD and published their data on this topic (49).

Regardless of all the studies and publications, SIT in the treatment of AD remains a controversial problem. A WHO position paper (50) clearly states that immunotherapy for AD is accepted only for clinical trials, as two DBPC trials have been evaluated exclusively (40,41). As we have just presented, there were at least five such trials, and such studies are not ideal from clinical and ethical standpoints. The necessity of DBPC trials in evaluating the efficacy of SIT appears to be directly borrowed from that of other drug investigations. A DBPC randomised study design gives rise to evidence of the highest grade as to the safety and efficacy of a drug that by definition exerts its action in a short time and is poorly influenced by confoundings. The biological effects of SIT in terms of antiallergic and anti-inflammatory modes of action obviously require a long time period to be recognised, and well-designed observational studies should also be considered for final conclusions. Otherwise, the under-valuation of this therapeutic approach is certain.

In our Department of Dermatology and Allergic Diseases Diagnostic Center, SIT is being performed in over 113 AD patients, and our observations of its clinical efficacy and safety are promising. We have performed a 48-month observational study (51) followed by a DBPC trial (12 months) (results in press).

The basic aim of the observational study was to evaluate the efficacy of specific immunotherapy performed with Novo-Helisen Depot allergy vaccines in a group of 37 patients with AD, allergic to house dust mites (n-14), grass pollen allergens (n-17) or grass pollen and mugwort pollen allergens (n-6). IgE-mediated airborne allergy was confirmed in all cases, and SIT was performed with allergy vaccines of appropriate composition: *Dermatophagoides pteronyssinus* 50%, *Dermatophagoides farinae 50%*, grass pollen allergens 100%, grass pollen allergens 80% and mugwort pollen allergens 20%. The control group consisted of 29 patients with AD and confirmed IgE-mediated allergy to analogous airborne allergens (house dust mites – 14 patients, grass pollen allergens – 11 cases, grass pollen and mugwort pollen allergens – 4 cases). In the control group, conventional methods of treatment of AD were applied, i.e. antihistaminic drugs, antiinflammatory and antipruritic medications or topical glucocorticosteroids.

Patients recruited for the SIT and control groups presented similar clinical scores and similar allergological and immunological status. A clinical evaluation of the severity and extensiveness of skin inflammation in AD patients was performed using the W-AZS index before treatment and after 12, 24, 36, and 48 months of therapy. The clinical efficacy of SIT and conventional methods was evaluated according to W-AZS values during the course of therapy. SIT was found to be an effective method of treatment of selected patients with AD and IgE-mediated airborne allergy. The efficacy of this therapeutic method was significantly higher than the efficacy of conventional methods applied in the control group in all 3 age compartments analyzed and in cases of patients allergic to house dust mites, grass pollen and mugwort pollen allergens. In the group of patients treated with Novo-Helisen Depot vaccines, asymptomatic status was observed after 48 months of therapy in 12 cases (32.4%), significant improvement in 21 patients (56.8%), improvement in 2 cases (5.4%) and no improvement or slight improvement in 2 patients (5.4%). In the control group, asymptomatic status was registered in 2 cases (6.9%), significant improvement in 9 patients (31.0%), improvement in 10 cases (34.5%) and no improvement in 8 patients (27.6%).

Comparative assessment of the clinical efficacy of both therapeutic approaches revealed a significant difference to the advantage of SIT after 12 months ($p<0.05$), 24 months ($p<0.001$), 36 months ($p<0.001$) and 48 months ($p<0.001$) of treatment. It seems that the effectiveness of SIT is related to the proper selection of patients and the adequacy

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of vaccines, and detailed clinical evaluation and proper allergological diagnostic are therefore necessary. SIT appeared to be a safe method of treatment, and the development of allergic respiratory symptoms was found relatively rarely in comparison to the control group.

There were significant differences between the group of patients treated with allergy vaccines and the control group in the results of allergological and immunological investigations (skin prick tests, serum levels of total IgE, asIgE, ECP, IL-4, IL-5, IL-10, IFN-γ, sIL-2R). In the SIT group, the negativization of skin prick tests, a decrease in the serum level of total IgE (directed against respective allergens), ECP ($p<0.001$) and sIL-2R ($p<0.01$) were noticed after 48 months of therapy. On the contrary, in the control group there were no tendency for the negativization of skin prick tests, and we observed an increase of serum levels of total IgE, asIgE, IL-4 ($p<0.01$) and IL-5 ($p<0.05$) after 48 months of therapy.

No significant correlation of serum cytokine concentrations with clinical status of patients was shown. There was also no correlation of skin prick test results with serum asIgE levels, but significant correlations of serum concentrations of asIgE for house dust mites and grass pollen allergens (in appropriate groups of allergens) were noticed. It therefore seems that allergological diagnostic in patients suffering from atopic dermatitis should consist not only of skin prick tests but should also include an evaluation of serum asIgE directed against main suspected allergens. This is especially important when SIT is planned for the treatment of patients.

In our DBPC trial, SIT was performed for 12 months. Twenty patients with AD and monovalent

Table 1. Main trials performed on SIT in AD

PROJECT	NUMBER OF PATIENTS	TYPE OF SIT	TIME OF SIT	RESULTS	FIRST AUTHOR
DBPC	26	SC	2 years	+	Kaufman HS 1974 (33)
OBSERVATION	15	SC	12 months	+	Di Prisco de Fuenmayor 1979 (34)
DBPC	2	SC	2 years	+	Ring J 1982 (38)
OBSERVATION	17	SC	12 months	+	Samochocki Z 1990 (47)
OBSERVATION	15	SC	12 months	+	Rudzki 1990 (46)
DBPC	24	SC	8+6 months	+/-	Glover MT 1992 (40)
DBPC	24	ID	4+8 months	+	Leroy BP 1993 (41)
OBSERVATION	41	SC/SL	3 years	+	Mosca M 1993 (42)
OBSERVATION	32	SC	3 years	+	Pacor ML 1994 (43)
OBSERVATION	60	ORAL	3 years	-	Galli E 1994 (44)
OBSERVATION	32	SC	3 years	+	Trofimowicz A 1995 (48)
OBSERVATION	212	SC/SL	2 years	+	Zwacka G 1996 (45)
OBSERVATION	35	SL	2+4 years	+	Mastrandrea F 2000 (49)
OBSERVATION	37	SC	4 years	+	Czarnecka-Operacz M 2000 (51)
DBPC	20	SC	12 months	+	Silny W 2003 (55)
OBSERVATION	36	SC	36 months	+	Silny W 2005 (52,53,54)

airborne allergy (house dust mites or grass pollens) were enrolled in the study (age: 5-40 years). SIT was performed with Novo-Helisen Depot allergy vaccines prepared for the controlled conditions by the Nexter-Allergopharma pharmaceutical company. We evaluated the clinical efficacy of the treatment based upon the W-AZS index, and we measured the serum concentration of total IgE asIgE and other selected immunological parameters (ECP, sIL-2R, IFN-γ, IL-4, IL-5, IL-10). Before treatment, the mean value of the W-AZS index was 87.6±15.8 pts. in the SIT group and decreased to 38.8±34.4 pts. after 12 months of therapy ($p<0.01$). In the placebo group, the mean value of the W-AZS index was 86.3±15.7 pts. before treatment, and after 12 months of therapy it increased to 111.9±41.7 pts. Comparative statistical analysis indicated a significant difference between the two investigated groups to the advantage of patients treated with active allergy vaccines ($p<0.01$). Serum levels of asIgE in the SIT group showed a clear tendency to decrease, although we were not able to indicate the statistical significance of this phenomenon due to the small size of the investigated population. On the contrary, the concentration of asIgE serum in the placebo group tended to increase. We also monitored serum concentrations of selected immunological parameters (ECP, sIL-2R, IFN-γ, IL-4, IL-5, IL-10).

In conclusion specific immunotherapy is an effective method of treatment in selected cases of atopic dermatitis patients with well documented IgE-mediated airborne allergy. It seems to be strongly beneficial in the case of children and teenagers (52) in terms of clinical picture and modification of the natural course of atopic march.

We have listed the main trials performed on SIT in AD in Table 1.

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