# Allergen-specific immunotherapy in atopic dermatitis

**Marek Jutel, Katarzyna Solarewicz-Madejek, Agnieszka Węgrzyn**

Department of Clinical Immunology, Wroclaw Medical University, Poland
Head: Prof. Marek Jutel MD, PhD

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**Abstract**

Allergen-specific immunotherapy (SIT) is the only known causal allergy treatment. Although used for over 100 years, its mechanisms are still the subject of investigation. The safety and efficacy of SIT have been demonstrated in children and adults in many clinical trials, which showed the essential role of SIT in prevention of both new allergy diseases (especially asthma) and new sensitizations. This method is currently recommended in the treatment of IgE-mediated aeroallergens and hymenoptera venom allergy. However, SIT treatment of airborne and food allergy in atopic dermatitis (AD) patients is the subject of investigation. The reported frequency of sensitization to aeroallergens in AD is close to 80% and the clinical significance of avoidance measures has been demonstrated in AD patients. Although initial reports on the efficacy of SIT in AD are somewhat conflicting, new evidence appears to support SIT as a practical and effective method in achieving symptom control in AD. However, new controlled studies including larger patient samples are necessary for further proof of the efficacy of SIT as well as in the development of optimal treatment schedules and preparations for SIT.

**Key words:** atopic dermatitis, specific immunotherapy, mechanisms, clinical efficacy.

## Introduction

The assessment of IgE-dependent specific immune response by skin tests and the measurement of serum-specific IgE (sIgE) should be a *sine qua non* condition for the diagnosis of an atopic disease. Atopy is genetically conditioned with a familial predisposition for IgE synthesis in response to some common environmental antigens (allergens). The symptoms of atopic diseases generally involve the skin and mucous membranes, as the primary sites of allergen exposure. The symptoms of atopic diseases can vary between individuals, depending on genetics, sensitization profile and the influence of external factors including infection and the natural environment. They also evolve in a single individual in a manner called the "allergic march". More than 50% of children with atopic dermatitis develop other allergic symptoms, including asthma [1].

The mechanisms underlying the symptoms of atopy include chronic inflammation induced by specific allergen exposure [2]. However, the process is not immunologically uniform. In distinct individuals and at various stages of the disease, marked differences in the effector cell pattern as well as the expression of activation markers are observed. The key regulatory cells in the hypersensitivity reactions are T helper (Th) lymphocytes [2]. The CD4+ Th cells release cytokines involved in initiating and maintaining the inflammatory processes, such as interleukin (IL) IL-4, IL-5 and IL-13 (profile Th2) and interferon γ (IFN-γ) (Th1 profile). Activity of Th1 and Th2 cells is under the control of regulatory T cells (Treg). Currently, other Th subpopulations are under investigation, designated as Th17, Th9, Th22, which along with Th1 cells are involved in inflammatory processes in the local tissues [2].

Aeroallergens and food allergens have been well documented in the pathogenesis of the allergic responses in the course of atopic dermatitis (AD) [3-7]. Early skin changes in AD are characterized by predominant Th2 profile and increased expression of their membrane markers, such as chemokine receptor CCR4. In the chronic phase of the disease, the Th1 profile with IFN-γ and TNF-α production predominates. The mechanisms responsible for the development of this specific inflammatory process involve type IV hypersensitivity reaction by Gell and Coombs and also include keratinocyte death by apoptosis induced by Th1 cells. The dysfunction and decreased numbers of Treg cells have also been reported in AD skin lesions [8].

The heterogeneity of aetiology, pathomechanisms and clinical picture in AD complicate its diagnosis and

**Address for correspondence:** Prof. Marek Jutel MD, PhD, Department of Clinical Immunology, Wroclaw Medical University, Chałubińskiego Str. No 5, 50-368 Wroclaw, Poland, tel. +48 71 784 17 40, e-mail: mjutel@ak.am.wroc.pl

treatment. Thus the management of AD requires a multifaceted approach. The very special role of SIT is provided by its feature as a method restoring normal immunity to specific allergens, which trigger the inflammatory cascade in the skin. Therefore recent data showing efficacy of SIT in AD treatment raise large hopes for clinicians to find a suitable complementary method in the treatment of AD [9, 10].

## Mechanisms of immunotherapy

The processes underlying SIT are complex and include mechanisms which are switched simultaneously or sequentially. They involve modulation of the functions of T and B lymphocytes, changes in immunoglobulin synthesis and in the reactivity of effector cells.

Changes in the number of T cells arising in the course of SIT appear very early and precede the increase in IgG antibody levels [11, 12]. In successfully desensitized allergic patients, suppression of effector responses of Th1 and Th2 is observed. In the process of immune homeostasis, maintenance mechanisms of Treg cell-dependent active suppression are involved. Different populations of Treg cells can actively inhibit immune responses through direct contact or by secreted inhibitory cytokines: IL-10 and transforming growth factor-β (TGF-β) [13]. Cellular mechanisms (at the level of T-lymphocytes) that play a role in successful SIT are probably the same as those responsible for the development of natural immune tolerance, such as anergy, resulting from the absence of co-stimulation, clonal deletion as a result of apoptosis, immune deviation with shift of Th profile from Th2 towards Th0/Th1, with an increase in the synthesis of IFN-γ, induction of Treg cells, or finally a combination of these mechanisms [14-16]. It was shown that allergen-specific proliferation of peripheral blood mononuclear cells (PBMC) [17] and allergen-specific T cells and cytokine production in the course of an effective SIT are inhibited, while the synthesis of IL-10 is increased. But it is not clear whether this is related to clonal deletion, anergy, or induction of suppressor T cells [18].

The humoral response in the course of SIT is also modulated and the profile of synthesized antibodies varies. The level of allergen-specific IgE increases initially after the start of SIT, and then decreases during the maintenance phase of therapy to the pre-treatment level [19]. The concentration analysis of serum IgG and its subclasses indicates a 10-100-fold increase in levels of allergen-specific IgG4 and IgG1 in the course of SIT. A similar phenomenon is observed in the natural course of massive exposure to an allergen in non-allergic individuals, such as beekeepers. The correlation between the level of allergen-specific IgG4 and reduction of clinical symptoms appears to be weak. The IgG4 levels correlate much better with the allergen dose during SIT, so IgG4 antibody levels can be seen as a marker of the administered allergen dose [11]. On the other hand, it is reported that IgG4 antibodies may have the ability to modulate the immune response to the allergen, resulting in clinical symptoms modification. In a study using well-defined mixtures of recombinant allergens there was a strong humoral response with the presence of allergen-specific IgG1 and IgG4 demonstrated in all subjects [11]. Specific IgG4 produced in the course of SIT may block the IgE-mediated immune response [20, 21] through an idiotype (IgE) – anti-idiotype (IgG) network. Furthermore, IgG are potent to inhibit the process of facilitated antigen presentation (FAP) to T cells, mediated by the Fc receptor for IgEε [22]. Specific IgG may also modulate IgE-dependent secretion of cytokines from mast cells. In a study analysing specific antibody affinity it was demonstrated that IgG4 with high allergen affinity is the major factor binding the birch pollen main allergen *Bet v 1* in the sera of patients with birch pollen allergy. In this study, SIT had no effect on allergen-specific IgE, IgG1 or IgG4 affinity. However, in patients with high-affinity IgG1 and IgG4, fewer allergy symptoms were present than in patients with low-affinity antibodies [23]. Endogenous histamine is another factor influencing peripheral tolerance in the course of SIT. The histamine receptor (HR) 2 (H2R) related signal can affect production of IL-10 by dendritic cells [24] and Th2 lymphocyte functions [25]. Furthermore, histamine enhances the inhibitory effect of TGF-β on T cells [26]. All three effects are mediated by HR2, which is relatively highly expressed in Th2 lymphocytes and inhibits the production of IL-4 and IL-13 and T-cell proliferation [27]. It was shown that expression of HR1 on T lymphocytes is significantly reduced in the course of ultra-rush immunotherapy, which may lead to dominant expression and function of HR2, which are crucial in tolerance induction. However, it has not yet been studied whether differences in the prevalence of histamine receptors HR1-HR4 on different subpopulations of |T cells can effectively modulate the immune response. HR4 signalling is of particular interest now, as it has been demonstrated that activation of this receptor potentiates the suppressive function of regulatory T cells [28]. The above-mentioned mechanisms have been generally confirmed in AD, particularly in relation to changes in the synthesis of immunoglobulins and the effect of SIT on the profile of secreted cytokines by T lymphocytes [10, 29]. The effect of SIT on the expression of chemokine receptors on specific T cells and changes in their activity were also investigated [29, 30].

## Specific immunotherapy in atopic dermatitis

Specific immunotherapy has been used in the treatment of AD for several decades [31]. A number of clinical studies have been published which demonstrate favourable outcome and safety of SIT [32]. However, many clinicians and researchers still find it a controversial issue. They indicate patients in the more severe stages of the disease and the possibility of exacerbation due to iatro-

genic high exposure to allergens. In particular, SIT-induced transient increase of sIgE and triggering of Th1-dependent inflammatory mechanisms in the skin could be responsible. However, none of the clinical and mechanistic studies confirmed these claims. For example, better understanding of the mechanisms of tolerance induced by SIT dispel concerns about the possible role of SIT-induced Th1 cell activation in AD exacerbation. These Th1 cells play an important role in tolerance induction in the lymphoid organs and have no significant effect on Th1-dependent inflammation in the skin [33, 34].

Difficulties in assessing the efficacy and safety of SIT may result from a possible impact of non-specific factors, such as the heating season in autumn or winter, which can significantly deteriorate SCORAD. Also natural UV light, from sunshine exposure, can cause improvement of AD. Other factors include natural course of the disease (resolution of symptoms in children) and, last but not least, the beneficial effect of placebo in the course of AD [35, 36].

The main issue in SIT is the proper selection of patients and demonstration of the atopic background of their clinical symptoms. A number of patients demonstrate symptoms from the airways – both upper and lower due to sensitization to aeroallergens [37]. This can ease the decision on treatment with SIT. Some researchers suggest that atopy patch tests (APT) are more specific but less sensitive than skin prick tests and serological tests for the diagnosis of clinically significant airborne allergies [38]. In the vast majority of patients with AD there can be serum-specific IgE against the aeroallergens found and their role in the induction of exacerbations of the disease has been indicated [39].

In the published studies there were mild, moderate and severe AD patients enrolled [30, 40-48]. Populations were diverse in terms of gender and age. In the studies only children [35, 43, 46, 49-53] or only adults [40-42, 45, 47, 48, 54-58], or combined age populations [10, 29, 30, 36, 44, 59-62] were included.

Study design included double-blind placebo-controlled (DBPC) [10, 35, 43, 48, 50, 56], placebo-controlled [36, 52, 57], observational group-controlled or comparator-controlled studies [49, 52, 60, 62] and also open-label or observational studies [29, 40-42, 44, 45, 47, 51, 53-55, 61, 63]. However, in most studies rather small groups of patients are investigated, especially in studies including a placebo control group. Observational study groups range from 1 to 86 subjects [29, 30, 40-42, 44, 47, 51, 53-55, 59, 61, 63]. In studies with a control group the patient numbers were as follows (active group – placebo group): 26 (16-10) [36], 2 (1-1) (compared the effects of SIT in 10-year-old identical twins in which one child received the drug and the other did not) [52], 60 (42-18) [49] and 99 (28-39, with additional no-intervention group – 32) [57]. In the study by Noh and Lee, which also evaluated the role of IFN-γ in disease remission in AD, 58 patients were divided into groups: active, receiving SIT (6 persons), active receiving IFN-γ (22 persons), active, receiving IFN-γ and SIT (10 persons) and the control group (20 persons) [60]. In the Werfel *et al.* study, which evaluated the safety and efficacy of SIT in 89 patients receiving in 3 groups different doses and schedules of the vaccine, the numbers were respectively 26, 26 and 27 individuals, respectively [64]. In the Juji *et al.* study of 22 patients, the active group was 10 individuals and the control group 12 [62].

In the DBPC studies the number of patients was as follows (active group – placebo group): 51 (27-24) [50], 24 [35], 24 [56], 20 (10-10) [10], 56 (28-28) [43], 164 [48].

The preparations used in the studies were allergen extracts. One study used a vaccine designed as allergen immune complexes with autologous antibody [40, 56]. In some others concomitant agents were simultaneously used including histamine-immunoglobulin complexes [61], IFN-α [42] or IFN-γ [60], as factors modifying the immune response. In an open-label study of Bussmann *et al.*, house dust mites (HDM) allergoids were administered [29]. Novak *et al.* used a depigmented polymerized birch pollen allergoid preparation [45].

Most of the studies were performed with perennial allergens, such as HDM [10, 29, 30, 35, 36, 40, 41, 43, 44, 46-57, 59-61, 63, 64]. In one observational study, desensitization with dog allergens was performed [42]. Several studies used pollen extracts including grass [10, 36, 52, 53, 59, 63], weed [59, 63], olives [63], cedar [62] and birch [45].

The side effects of SIT appeared mainly in the induction phase and they were generally transient, mild or moderate in severity, and did not require dose adjustments, or additional systemic treatment. Vaccines were usually administered subcutaneously [10, 45, 47, 48, 51, 59, 61, 63, 64]. In the studies of Leroy *et al.*, intradermal [40, 56] SIT injections caused mainly local skin reactions. Mainly local skin reactions have been observed in other studies: 39.3% in the verum group and 35.7% in the placebo group [48]. Also systemic reactions were reported. They included exacerbation of inflammation, generalized itching or urticaria (Werfel *et al.* – < 1% [64], Novak *et al.* – 9% [45], Silny *et al.* – mild or moderate transient exacerbation in 8 of 10 patients in the active group and 6 of 10 in the placebo group). Orally administered vaccines induced symptoms mainly from the digestive system mucosa: swelling of the face and lips, mouth itching (Pajno *et al.* – 14.2% [43]), diarrhoea, but also generalized skin symptoms (Pajno *et al.* – 7.1%, Kwon – 2 of 20 patients) [30, 43, 63]. Moreover, in some cases, symptoms of rhinitis and conjunctivitis were observed, for example, Novak *et al.* – 1 patient (1.8%) [42, 45]. In several studies nonspecific symptoms have been reported. They included fatigue, headache, and dizziness [42, 43, 45]. Novak *et al.* reported mild systemic reactions (flare up of eczema/urticaria, rhinitis, pruritus, transient headache, asthma (placebo group) in 8% of *verum* group and 10.7% of placebo group [48]. In the Pajno *et al.* study of sublingual immunotherapy (SLIT) in children allergic to house dust mites, 2 of 28

patients developed systemic symptoms (generalized pruritus and urticaria) requiring pharmacological intervention, and these patients were excluded from the study [43]. In the study by Bussmann *et al*., 1 of 25 treated patients had symptoms of mild bronchoconstriction (a vague relation to the treatment), and another had generalized flares after injection; the 2 patients were excluded from the study [29]. In some studies there were no adverse events of SIT reported, with good clinical effect of the therapy [44, 47]. Generally, the AD exacerbations during SIT were usually occasional, transient, mild or moderate, not requiring changes in the treatment and were reported in 4% (1 patient, excluded from the study) [29], 5.7% [63], 6.3% [59], 7.1% ( 2 patients, excluded from the study) [43], 8% [45], 10% [30] to 80% of the SIT-treated patients in the Silny *et al*. study; however, in this study AD was exacerbated also in 60% of the placebo group [10].

The efficacy of SIT was assessed by subjective and objective clinical observations (quality of life questionnaires, dermatology assessment); in some studies also the immune profile of the desensitized patients was investigated (sIgE, chemokines, T cell activation and function markers, skin tests). A beneficial effect was observed both in observational studies [29, 30, 40-42, 44, 45, 47, 51, 53-55, 59, 61, 63] and controlled studies [36, 52, 57, 62, 64], as well as in DBPC studies [10, 43, 48, 56]. The total period of the patient observation varied from 12 weeks [45] to 6 years [63]. The clinical improvement during SIT was reported after several weeks [29, 45, 64] to several months, up to a year [10, 43, 63].

## Controlled studies

In the Kaufman *et al*. placebo-controlled trial [36] (effectiveness of subcutaneous (s.c.) SIT in HDM allergy in children, 2 years) there was an 81% improvement in the active group and 40% improvement in the placebo group observed (after [32]). The positive effect of SIT is reported by Ring [52] (s.c. desensitization in twins with eczema and allergies to grass pollen, for 2 years), Juji *et al*. (cedar pollen allergy desensitization) [62] and Petrova (oral HDM allergy immunotherapy in adolescents and adults) [57]. In the Werfel *et al*. study (adults intradermal HDM allergy desensitization, 1 year) SCORAD was observed after 2, 4, 6, 9 and 12 months of treatment. A dose-dependent effect (reduction of symptoms) was observed. A statistically significant effect using medium and high doses of vaccine was demonstrated after 2 months of therapy. Significant reduction in the use of local glucocorticoids (GCS) in the high SIT dose group was also demonstrated [64].

## Observational studies

In the observational study of Di Prisco *et al*. (s.c. SIT in children with airborne allergies), improvement was observed in 60% of patients [51], in the Zachariae *et al*. study (s.c. SIT in HDM allergic adults) in 50% of the patients [55] (after [32]). A positive result was also reported by Chait (1 year s.c. SIT of allergy to HDM in an adult) [54], Pacor (3 years of SIT in adult, s.c., allergy to HDM) [41], Michils (observation of a dog-allergic patient, receiving 7 months of oral SIT with 6 weeks of IFN-$\alpha$ injections) [42], Trofimowicz (3 years of SIT in children allergic to grass pollen and HDM) [53], Vidal (2 years of s.c. SIT in HDM allergy in a patient) [47], Kwon (12-60 months of s.c. SIT in children and adults with allergies to HDM; improvement in 50% assessed on the basis of the Eczema Area and Severity Index [EASI] before and after the treatment) [30]. Seidenari observed significant improvement in 65% of children and adults, occurring after 4-5 months of therapy (SIT s.c. 6-24 months with HDM and pollen allergens). Additionally, in the group of 4-15 year-old children a significantly better effect of SIT was observed. The effect of the natural course of disease cannot however be excluded [59]. A positive effect was shown in sublingual SIT by Mastrandrea *et al*. treatment lasted 3 years. The patients (adults and children) were subjected to dermatological clinical assessment, in terms of lesion regression, after 6, 12 and 24 months, and overall clinical assessment every 2 months during the SIT and in the next 3 years at least once a year. Significant improvement was observed after 6 months of SIT in patients with AD without concomitant respiratory allergies (12.6%) vs. 0% in patients with such symptoms, and after 12 months – both in the group without (31.2%) and with symptoms of rhinitis and conjunctivitis, and/or asthma (36.8%). After 24 months these values were respectively 68.8% and 73.7% [63]. Bussmann (observation of adult patients treated for 32 weeks s.c. for HDM allergy) reported a significant decrease in the SCORAD index already within the first 4 weeks of therapy, although this result might also be influenced by the fact that vaccination had been started in February-May – outside the "HDM season". Nahm *et al*. reported a similar result (observation of adult patients 1 year desensitized s.c. with additional histamine-immunoglobulin complexes) – SCORAD assessed at 6 and 12 months was significantly lower compared to baseline [61]. A beneficial effect of desensitization of allergy to HDM in patients with AD was also observed by Leroy *et al*. (intradermal SIT for one year in adolescents and adults allergic to HDM; in addition, immune complexes containing HDM allergens were administered) [40], and confirmed in a double-blind placebo-controlled study (intradermal SIT as before, for 4-8 months) [56]. The Cadario *et al*. study (children and adults sublingual HDM allergy desensitization for a year) evaluated SCORAD at baseline and after therapy. It showed a reduction in the index scoring by 46% on average, yielding a significant improvement in 59% of patients (SCORAD reduction of > 30%), while in patients with baseline severe AD (SCORAD index > 40) the index scoring reduction was

50% [44]. In the study of Novak *et al*. (open-label s.c. birch pollen allergy SIT in adults and children, 12 weeks) the SCORAD index as well as the Dermatology Life Quality Index (DLQI) at time-points of 1, 2, 3, 9, 15 and 17 weeks of treatment was assessed and a significant reduction in both indices already after 1 week of treatment was observed. Importantly, each patient was desensitized for an average of 19.2 days during the birch pollen season (at that time, 60% of the patients were already on a maintenance dose) [45].

## DBPC studies

The efficacy of SIT in achieving AD symptom control has been demonstrated in the Leroy *et al*. [56], Silny and Czarnecka-Operacz [10], Pajno *et al*. [43], Novak *et al*. [48] studies. All the studies were performed in HDM allergic people. The SIT was administered intradermally (Leroy; allergen in the form of immune complexes), subcutaneously (Silny and Czarnecka-Operacz, Novak) or sublingually (Pajno). In the Leroy *et al*. study (SIT of adolescents and adults), the DBPC SIT treatment lasted for 4 months and afterwards both the *verum* and the placebo group patients were administered the active agent for the next 8 months. A significant clinical improvement was observed after 4 months in the *verum* group and after a year in 82% of patients (83% improvement) [56]. In the Silny and Czarnecka-Operacz study (12 months SIT in children and adults) the therapy effectiveness was assessed, among others, with a clinical score of the severity and skin inflammation extent index before and after 12 months of SIT. They found a significant indexed score decrease of 55.7% in the treated group, and an increase of 29.7% in the placebo group, the difference between the two groups was statistically significant [10]. In the study of Pajno *et al*. (18 months of SIT in children) SCORAD evaluation was performed before and after 3, 6, 9, 12, 15 and 18 months of therapy. A significant difference between the value of this index in the *verum* and placebo group starting from the 9$^{th}$ month of therapy was observed, but not in children with severe AD. Similarly, in the assessment of subjective well-being of patients with the visual analogue scale (VAS), VAS values showed a decrease after 9 months of treatment by 39.2%, but only in the group of mild to moderate AD [43]. In the study of Novak and Zuberbier (18 months s.c. with allergoid – depigmented polymerized mite extract), the overall results showed no significant differences between the *verum* and placebo groups; however, there was a significant clinical improvement in moderate to severe AD *verum* vs. placebo patients [48].

On the other hand, some studies did not confirm the efficacy or showed a questionable impact of SIT in the course of AD. Glover and Atherton in a DBPC study (s.c. SIT in children with allergy to HDM), in which the patients were divided into groups of *verum* and placebo for 6 months after 8 months of active treatment, reported that although there was some improvement in the *verum* group, this difference was not significant to draw some conclusions about the effectiveness of SIT. They also highlighted the importance of the placebo effect for improvement of the disease [35]. In a study with a control group of Galli *et al*. (3 years of oral SIT in children with allergy to HDM) SIT, although safe (no side effects), had no effect on the course of AD in any of the observed clinical groups (with or without accompanying allergic respiratory disease), compared to the control group [49]. Also Noh and Lee (1-year study with a control group of s.c. SIT and/or IFN-γ in 56 adults and children, mean age in the groups was 12.8 ±10.4, 14.7 ±5.3, 15.6 ±10.3 and 10.9 ±8.0 years, allergic to HDM) reported no statistically significant clinical improvement in patients desensitized traditionally but only in a group with additional interferon administration [60].

The Joint Task Force on Practice Parameter recommendation ("Allergen immunotherapy: a practice parameter third update", published in January 2011) "There are some data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity" received indication strength B, that is, “directly based on category II evidence (evidence from at least 1 controlled study without randomization or evidence from at least 1 other type of quasi-experimental study) or extrapolated from category I evidence (evidence from meta-analysis of randomized controlled trials or evidence from at least 1 randomized controlled trial) [65].

## Summary

Specific immunotherapy is an important and accepted tool for treatment of patients with properly diagnosed allergic airway disease. Currently available studies on SIT effectiveness in AD show its high clinical efficacy in the treatment of patients sensitized to aeroallergens. Decreases in clinical symptoms scoring in different routes of administration, in children and adults, in age, gender, severity of skin symptoms as well as in allergic profile of different populations were observed.

## Current recommendations

It was shown that SIT is safe also in severe AD. The side effects of SIT, primarily occurring in the skin, are usually mild and transient. Systemic symptoms are rare; however, patients with confirmed food allergy or more severe bronchial asthma were generally excluded from the clinical trials. Although many studies show the benefits of SIT in AD, DBPC studies in large patient groups are lacking. Furthermore, long-term follow-up studies are necessary to identify suitable patients showing the best prognosis.

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