

Allergen-specific Immunotherapy in Atopic Eczema

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Abstract Aeroallergens are relevant eliciting factors of allergic rhinoconjunctivitis and bronchial asthma but also of atopic eczema. The use of allergen-specific immunotherapy as in respiratory atopic diseases is controversial in patients with atopic eczema, but refined diagnostic methods to characterize subgroups of patients with relevant allergies and the results of smaller controlled studies give rise to new approaches in this field. This article reviews the theoretical problems and practical results associated with allergen-specific immunotherapy in atopic eczema.

Keywords Atopic eczema · Atopic dermatitis · Allergen immunotherapy

Introduction: Allergy and Atopic Eczema

The chronic inflammatory skin disease atopic eczema (atopic dermatitis, atopic eczema/dermatitis syndrome) is characterized by recurrent intense pruritus and a typically age-related distribution and skin morphology [1–4]. Because there is no specific marker for atopic eczema, diagnosis is made by a combination of clinical features. The role of allergy in eliciting and maintaining the eczematous skin lesions was controversial until the past decade, mainly due to a lack of specificity of the classic tests for IgE-mediated hypersensitivity. Among the allergens found to be relevant in atopic eczema, aeroallergens and food allergens (in children) are most important [5]. Therapeutic consequences of the diagnosis of an allergy are based on avoidance strategies,

which can be very difficult for the patient. In many cases, the determination of the clinical relevance of (often multiple) IgE-mediated sensitizations for the skin disease must use time-consuming methods of diagnosis, such as placebo-controlled provocation testing.

It has long been known that environmental substances such as aeroallergens can produce flares in some patients with atopic eczema [5]. An epicutaneous patch test with allergens known to elicit IgE-mediated reactions, and the evaluation of eczematous skin lesions (atopy patch test [APT]) can be used as diagnostic tools in characterizing this subgroup of patients. Patients with atopic eczema often have elevated serum levels of IgE that may correlate with disease severity. Also, aeroallergen avoidance, especially with regard to house dust mites, can result in marked improvement of skin lesions [1, 6–9]. The hypothesis is that Langerhans cells bind and present “immediate-type” allergens [10], which penetrate the impaired epidermal barrier in atopic eczema patients [11]. This concept is derived from studies showing IgE and IgE-binding structures on the surface of epidermal Langerhans cells [12, 13] together with mite allergen [11, 14]. From APT biopsies, allergen-specific T cells have been cloned [15, 16]. These T cells showed a characteristic T-helper type 2 (Th2) secretion pattern initially, whereas 48 hours after allergen provocation, a Th1 pattern was predominant. This same pattern is also found in chronic lesions of atopic eczema.

Several groups demonstrated that eczematous skin lesions can be induced in patients with atopic eczema via patch testing with aeroallergens [11, 14, 16–18]. Patch testing of aeroallergens, especially in patients with atopic eczema, was first documented in 1982 by Mitchell et al. [19]. We performed several studies to standardize the methods of APT on nonabraded skin and subsequently defined the relationship to clinical covariates. With the developed methods [20, 21], significant correlations of

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APT result, and patients' histories were obtained in several studies [22–24]. The results of these studies sustain the concept of atopic (extrinsic/allergic) versus nonatopic (intrinsic) eczema with a heterogeneity of disease subgroups as in bronchial asthma and rhinoconjunctivitis.

Thus, immediate-type sensitizations not only play a role in the elicitation of respiratory atopic diseases in the same patients suffering from eczema, but also in the etiopathophysiology of atopic eczema. Allergen-specific hyposensitization/immunotherapy (ASIT, allergen vaccination) is a method of causal treatment of allergic diseases that has been in clinical use since 1911 [25]. It is defined as “repeated application of increasing doses of the relevant allergen until reaching loss of symptoms or a maintenance dose” [1, 26–29]. The immunologic effects of ASIT are not yet completely understood. The mechanisms have been extensively reviewed elsewhere [26] and are summarized in Table 1 [1]. ASIT is widely used on an evidence-based background for the treatment of allergic rhinoconjunctivitis, insect venom anaphylaxis, and with increasing frequency in allergic bronchial asthma. On the other hand, use of ASIT in patients with atopic eczema is controversial due to contradictory clinical observations and theoretical immunologic considerations.

Theoretical Problems of Allergen-specific Immunotherapy in Atopic Eczema

A transient increase in serum IgE levels often occurs in ASIT and may be related to some of the known side effects of this therapy, which are based on immediate-type reactions.

Table 1 Allergen-specific immunotherapy mechanisms

Induction of specific “protecting” IgG antibodies
•Blocking antigen
•Reducing IgE synthesis
•Blocking the IgE receptor of basophils and mast cells
Anti-idiotypic antibodies
Mucosal secretion of IgG and IgA antibodies
Induction of suppressor cells
Hapten inhibition
Reduction of inflammatory cells due to the following:
•Reduced recruitment
•Reduced activation
•Reduced releasability (mediators)
Tachyphylaxis
Induction of immunologic tolerance
Interleukin-10–induced anergy in peripheral T cells
T-helper type 2 to T-helper type 1 switch in reaction pattern
Induction of allergen-specific regulatory T cells

(Adapted from Ring [1])

However, as specific IgE also has been shown to play a role in the pathophysiology of atopic eczema (see above), this transient increase may be a reason why atopic eczema flares may be seen after starting ASIT. Another problem may be seen in the principal mechanism of ASIT, which leads to a switch from Th2 to Th1 cytokine patterns and is followed by immunotolerance [27]. As described, serial biopsies in atopic eczema showed a time course of inflammatory responses in the skin, starting with a Th2 response, which was followed by a Th1 pattern after 48 hours. A very similar Th1 cytokine pattern is also found in chronic lesions of atopic eczema. Even if the time course of cytokine pattern changes in ASIT and the pathophysiology of atopic eczema are not directly comparable, this similarity could be seen as a theoretical risk leading to chronicity of skin inflammation. Increased releasability of other involved effector cells during ASIT may also add to the known altered reactivity in atopic eczema patients, leading to acute symptoms [1].

Clinical Experience

In clinical discussions of the problems associated with ASIT and atopic eczema, the deterioration of atopic eczema course is often mentioned as a reason for the reluctance of clinicians to treat patients with this disease with ASIT. However, this point of view can hardly be proven from the literature. According to the 1993 European Academy of Allergy and Clinical Immunology position paper on immunotherapy, severe atopic eczema is a relative contraindication for ASIT [30], but the reasons for this remain unclear, and the recommendation is not found in more recent guidelines. Taken together, not much evidence is available to suggest a special risk of ASIT in patients with atopic eczema. In contrast, several studies have demonstrated improvements of different degrees in patients with atopic eczema following ASIT with house dust mite and other allergen extracts (see below). In an animal ASIT model of atopic eczema in dogs, Willemse et al. [31] also demonstrated marked improvement of eczematous skin lesions in 59% of verum-treated, but only 20% of placebo-treated dogs. Principally, every ASIT bears the risk of unwanted side effects such as increased local reactions, anaphylactic reaction, serum sickness (rare), or exacerbation of the atopic underlying disease (not rare) [29]. This holds true for the respiratory atopic diseases as well as for atopic eczema.

If ASIT is acknowledged as an effective mode of therapy in atopic eczema, at least three criteria should be fulfilled apart from the safety considerations [32]:

- Aeroallergens (with which ASIT is usually performed in respiratory allergies) should be considered as significant factors in atopic eczema.

- Individual relevance of the allergen should be proven by accurate diagnostic methods.
- A mode of ASIT should be available that has proven efficacy and induces significant improvement in the course of atopic eczema.

From Case Reports to Controlled Trials

Our own experience in a pair of monozygotic twins with atopic eczema (with spring and summer exacerbations) treated with grass pollen ASIT or placebo in a double-blind fashion showed significant improvement and a decrease in serum IgE in the twin treated with ASIT [33]. Several open, uncontrolled study designs also demonstrated advantages of ASIT in patients with atopic eczema; these data were often published in national or non-Anglo-Saxon journals. Some investigators in the 1970s and 1980s also showed improvement of atopic eczema in controlled trials (Table 2). A double-blind, controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with atopic eczema was published in 1992 by Glover and Atherton [34]. This study failed to demonstrate superiority over placebo after a standard 8-month course of treatment with tyrosin-adsorbed house dust mite extracts in 24 children with atopic eczema and immediate hypersensitivity to this allergen. However, in a second study phase, children were randomly allocated to continue with active treatment or placebo for an additional 6 months. The numbers were too small to permit confident conclusions, but the clinical scores suggested that prolonged hyposensitization may be more effective than placebo with regard to several objective parameters of eczema severity. The authors noted that a high placebo effect led to problems in comparing the active treatment. In the placebo-controlled study conducted by Kaufman and Roth [35], the skin condition of 13 of 16 treated patients improved, whereas this effect was only noted in 4 of 10 placebo-treated patients. Similar results were reported by Warner et al. [36] and Zachariae et al. [37], showing improvement of eczematous skin lesions under ASIT with house dust mite extracts. The results of the studies available are presented in Table 2.

Oral ASIT for *D. pteronyssinus* was not effective in a controlled study enrolling a total of 60 children with atopic eczema, who were observed for 3 years [38]. In contrast, Mosca et al. [39] was able to show the effect of subcutaneous conventional ASIT ($n=41$; 76% improved) and sublingual route immunotherapy (SLIT; $n=48$; 64% improved). This study also reported on medication used and adverse drug reactions. The latter occurred in 15% to 20% (both groups). Efficacy of both methods of ASIT was also demonstrated in the multicenter trial by Zwacka et al. [40]. Mastrandrea et al. [41, 42] reported on a 6-year-study in 35 selected atopic

eczema cases undergoing SLIT, with an average of 72% remission of atopic eczema after 2 years. However, this observational study also lacked a control group.

Later, Noh and Lee [43] reported in a pilot study on the improvement of atopic eczema together with changes in T-cell subpopulations induced by interferon- γ pretreatment before ASIT with house dust mite allergens. Patients receiving placebo, interferon- γ , or only ASIT showed no treatment effect.

The attempt to achieve ASIT efficacy in atopic eczema via some kind of additional immunomodulation is not new. In an open study, Leroy et al. [44] showed impressive improvement within 3 to 4 months in 10 patients with atopic eczema who were injected with a mixture of allergen (*D. pteronyssinus*) and allergen-antibody complexes. The rationale for this approach was the efficacy of such complexes in suppressing IgE antibody production through anti-idiotypic antibodies, a process called *idiotypic suppression*. The authors corroborated their results in a controlled trial published in 1993 showing significantly reduced symptoms after 4 months in the actively treated group only [45]. A total of 82% of the treated patients had lasting substantial improvement (mean, 83%) in atopic eczema over 1 year.

Werfel et al. [46] investigated 89 patients with atopic eczema showing a sensitization to house dust mite (CAP-FEIA ≥ 4) who were injected weekly with three different doses of house dust mite allergen extract. With higher allergen doses, a beneficial SCORAD (Scoring Atopic Dermatitis [tool]) decrease occurred after 8 weeks compared with a control group receiving a very low allergen dose. The effect was maintained over 1 year and accompanied by lower glucocorticosteroid use. A smaller double-blind, placebo-controlled study involving 20 patients with house dust mite or grass pollen sensitization also showed objective and subjective symptom relief under ASIT [47].

Even if the results of the studies are interpreted very carefully with regard to the therapeutic effects of ASIT, it is remarkable that exacerbations of the skin disease during this specific treatment were rare. In contrast, the treatment was well-tolerated in most patients. The same was true for studies in patients with coexistent atopic eczema who were treated with ASIT for respiratory atopic diseases and experienced not any more often flares of eczematous skin lesions. One also has to keep in mind that eczema flares were seen in the control or placebo groups as well.

Conclusions

The role of allergens in the pathophysiology of atopic eczema has been proven in controlled studies of allergen avoidance and APT [7, 9, 22, 24]. In respiratory atopic diseases, ASIT plays an important role not only for

Table 2 Observational and controlled clinical trials on ASIT in patients with atopic eczema

Study (year)	Design	Patients, <i>n</i> ; age	ASIT allergen	IT route of administration (treatment duration)	Results	Side effects	Outcome variable
Kaufman and Roth [35] (1974)	PC	16 (active group), 10 (placebo group); 2–47 y (active group), 7–25 y (placebo group), 24 (placebo group); mean age: 10, 25 y (active group), 10 y (placebo group)	Alum-precipitated pyridine extract	Subcutaneous (2 y)	Improved in treated group 81%, in placebo group 40%	–	Clinical status
Warner et al. [36] (1978)	DBPC ASIT for asthma	27 (active group), 24 (placebo group); mean age: 10, 25 y (active group), 10 y (placebo group)	ASIT for Dpt	Subcutaneous (1 y)	Positive	–	Clinical status
Di Prisco de Fuenmayor and Champion [51] (1979)	Observ	15; 6–14 y	ASIT for aeroallergens	Subcutaneous	Improved in 60% of patients	Occasional exacerbation of dermatitis	Clinical status
Ring [33] (1982)	PC	Twins; 10 y	ASIT for grass pollen	Subcutaneous (2 y)	Positive	Occasional flare of eczema in active treated patient	Clinical status, grass pollen-specific and total IgE antibodies
Chait and Allkins [52] (1985)	Observ ASIT for asthma	1	Tyrosine-adsorbed vaccine for Dpt	Subcutaneous (1 y)	Positive	–	Clinical status
Zachariae et al. [37] (1985)	Observ	12; 24–48 y	ASIT for Dpt	Subcutaneous	Improved in 50% of patients	–	Clinical status, Dpt-specific and total IgE antibodies, consumption of topical steroid
Seidenari et al. [53] (1986)	Open study	63; 4–45 y	Alum hydroxide-adsorbed extract	Subcutaneous (6–24 mo)	Improved in 65% of patients	Occasional slight exacerbation of dermatitis	Clinical status
Leroy et al. [44] (1991)	Open trial	10; 17–61 y	Allergen-antibody complexes: Dpt allergen and autologous-specific anti-Dpt antibodies	Intradermal (1 y)	Positive	No systemic reactions	Clinical status, Dpt-specific and total IgE antibodies
Glover and Atherton [34] (1992)	DBPC	24; 5–16 y	Tyrosine-adsorbed glycerinated extract of Dpt	Subcutaneous (8+6 mo)	Uncertain	No systemic reactions	Clinical status, specific and total IgE antibody, skin prick test
Leroy et al. [45] (1993)	DBPC	24; 17–56 y (active group), 15–64 y (placebo group)	Allergen-antibody complexes: glycerinated extract of Dpt and autologous-specific anti-Dpt antibodies	Intradermal (4+8 mo)	Positive	Occasional pruritus, flare of dermatitis, erythema, inflammatory reaction at the injection site	Clinical status, Dpt-specific IgE and IgG antibodies
Mosca et al. [39] (1993)	Observ	41 and 48	–	Subcutaneous vs sublingual (3 y)	Positive	15%–20%	Clinical status, drug consumption
Heijer [54] (1993)	Observ	93; 6–66 y	ASIT for aeroallergens; alum-precipitated, pyridine-extracted depot extracts	Subcutaneous (mean duration, 3.3 y)	Positive	Occasional asthma, rhinitis, conjunctivitis, fever, chills, tiredness, hoarseness, sweating, headache, vertigo, pruritus, urticaria	Clinical status, total IgE antibodies
Pacor et al. [55] (1994)	Observ	32	Sodium alginated, dialyzed allergenic extract of Dpt	Subcutaneous (3 y)	Positive	–	Clinical status, Dpt-specific and total IgE antibodies, skin prick test
Galli et al. [38] (1994)	Control group	42 (active group), 18 (control group); 0.5–12 y	ASIT for Dpt	Oral (3 y)	Negative	–	Clinical status

Michilis et al. [56] (1994)	Observ	1; 21 y	1. IFN- α 2. ASIT for dog dander	1. Subcutaneous (6 wk) 2. Oral (7 mo)	Positive	1. Fatigue 2. Moderate rhinoconjunctivitis	Clinical status, dog-specific and total IgE antibodies
Trofimowicz et al. [57] (1995)	Observ	22; children	ASIT for Dpt or grass pollen	Subcutaneous (3 y)	Positive	–	Clinical status
Zwacke et al. [40] (1996)	Control group	212; 6–15 y	ASIT for aeroallergens	Subcutaneous vs sublingual (2 y)	Positive	–	Clinical status, total IgE antibodies
Mastrandrea et al. [42] (2000)	Observ	35	–	Sublingual (3 y)	Positive	Occasional diarrhea, eczema, urticaria	Clinical status
Grewe [58] (2000)	Observ	13	ASIT for Dpt and Df	Subcutaneous (1 y)	Improved in 69% of patients	No systemic reactions	Clinical status, total IgE antibodies
Noh and Lee [43] (2000)	Control group	58; mean age as follows: 1. 14, 7 y 2. 15, 6 y 3. 12, 8 y 4. 10, 9 y	1. IFN- γ -induced hyposensitization for Dpt 2. IFN- γ 3. ASIT for Dpt 4. Negative control group	Subcutaneous	Improved only in group 1	–	Clinical status, disappearance of aggravation episodes
Petrova et al. [59] (2001)	PC	28 (active group), 39 (placebo group), 32 (control group); 17–52 y (active group), 17–40 y (placebo group), 16–27 y (control group)	ASIT for Dpt	Oral	Positive	–	Clinical and immunologic status
Silny and Czamecka-Operacz [47] (2006)	DBPC	20	ASIT for Dpt or grass pollen	Subcutaneous	Positive	–	Clinical status, itch, sleep loss
Werfel et al. [46] (2006)	3 doses/control group	89	ASIT for Dpt	Subcutaneous	Positive	No systemic reactions	Clinical SCORAD, medication
Pajno et al. [60] (2007)	DBPC	56; 5–16 y	ASIT for Dpt	Sublingual (18 mo)	Positive	–	Clinical SCORAD, medication
Bussmann et al. [61] (2007)	Observ	25	ASIT for Dpt	Subcutaneous	Positive	–	Clinical SCORAD and immunologic
Cadario et al. [62] (2007)	Observ	86; 3–60 y	ASIT for Dpt and Df	Sublingual (at least 1 y)	Positive	No severe reactions	Clinical SCORAD, specific and total IgE
Nahm et al. [63] (2008)	Observ	20	ASIT for Dpt and histamine-immunoglobulin complex treatment	Subcutaneous (1 y)	Positive	No significant side effects	Clinical SCORAD

ASIT allergen-specific immunotherapy, DBPC double-blind, placebo-controlled, Df Dermatophagoides pteronyssinus, IFN interferon, IT immunotherapy, Observ observational/open trial, uncontrolled, PC placebo-controlled, SCORAD Scoring Atopic Dermatitis (tool)

treatment, but also in preventing further sensitizations and progression to more severe respiratory disease (change from rhinitis to bronchial asthma). Due to the well-established specific immunologic and clinical effect, ASIT has been recognized by the World Health Organization as the only therapy that can affect the natural course of allergic diseases [48]. In many patients with respiratory atopy, atopic eczema of early infancy was the first manifestation of atopic disease, often accompanied by sensitizations to food or aeroallergens. One may speculate that ASIT in these patients could be of preventive value, but this remains to be proven in controlled trials.

In addition, patients with a positive APT and corresponding history of eczema flares may be candidates for ASIT with the eliciting allergen. The performed studies point to the safety of ASIT also in atopic eczema if the treatment is performed according to the guidelines. However, the final judgment on the efficacy of ASIT in this diagnosis is still not possible due to the lack of large controlled and randomized clinical trials with modern allergen vaccines. Several of these trials are currently being conducted in Europe. As ASIT works in the sense of a biological response modifier, it may require a longer time to exert all its effects on inflammatory reactions as usual selected for pharmacotherapeutic trials [41]. The issue of combining ASIT with immunomodulating (pre-)treatment may also deserve further investigation in atopic eczema patients. Thus, the addition of anti-IgE treatment (with a monoclonal, commercially available antibody) to ASIT has been shown to result in increased improvement in patients with respiratory atopy [49]. New routes of administration of ASIT have been investigated [42], and SLIT showed encouraging results with a favorable profile of side effects.

In conclusion, ASIT may be a possibility for improvement of the course of atopic eczema rather than a risk for deterioration of the disease [50]. To date, it may be too early to recommend ASIT as a general treatment option for atopic eczema, but it may prove valuable for individually selected patients who give their informed consent. Clinical studies designed to investigate the efficacy of ASIT in these patients should also record the quantities of rescue medication needed in the investigated patients compared with the placebo group, and longer observation periods and other appropriate outcome measures for eczema improvement should be considered.

Disclosure No potential conflicts of interest relevant to this article were reported.

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