



Allergen-specific immunotherapy for atopic eczema: updated

Ulf Darsow^a

Purpose of review

Aeroallergens are relevant eliciting factors of not only respiratory allergy but also atopic eczema in subgroups of patients. Due to a low number of controlled studies, the use of allergen-specific immunotherapy (ASIT) as potentially curative therapy as in respiratory atopic diseases is controversial in treating atopic eczema. This article summarizes theoretical aspects and recent results of clinical trials associated with ASIT in atopic eczema.

Recent findings

Literature demonstrates variability in study design and results, but ASIT has potential to improve the course of atopic eczema if type I sensitizations are present. Studies suggest the efficacy of ASIT on eczema not only in house dust mite allergy but also in patients with birch or grass pollen sensitization. In several studies, only defined subgroups of patients with atopic eczema showed positive results of ASIT. A generally good tolerability of ASIT was seen.

Summary

Atopic eczema patients with relevant allergies might benefit from ASIT as an additional therapeutic option. Side effects have been overestimated in the past. Hypothetically, the atopy patch test helps to identify an atopic eczema patient subgroup for successful ASIT.

Keywords

allergen immunotherapy, atopic dermatitis, atopic eczema

INTRODUCTION: ROLE OF ALLERGENS AND ALLERGEN-SPECIFIC IMMUNOTHERAPY IN ATOPIC ECZEMA

The chronic inflammatory skin disease – atopic eczema (atopic dermatitis) – affects up to 20% of children and 3% of adults, and is characterized by recurrent intense pruritus and a typically age-related distribution and skin morphology. Atopic eczema shows a genetic predisposition, multiple changes in immune functions, environmental interaction, and a reduced skin barrier function resulting in facilitated contact of allergens with cells of the immune system [1^{*,}2]. It has long been known that environmental substances such as aeroallergens (e.g. house dust mite, pollen) can produce flares in some patients with atopic eczema. In approximately 80% of adults with atopic eczema, sensitizations to allergens are demonstrable. Among the allergens found to be relevant, aeroallergens and food allergens (in children) are most important – often aeroallergens cannot be avoided to the necessary extent [1^{*,}2,3^{*}]. An epicutaneous patch test with allergens

known to elicit IgE-mediated reactions, and the evaluation of eczematous skin lesions [atopy patch test (APT), reviewed in [4]] can be used as a diagnostic tool in further characterizing the reactive subgroup of patients. From APT biopsies, aeroallergen-specific T cells have been cloned. These T cells showed a characteristic T-helper type 2 (Th2) secretion pattern initially, whereas 48 h after allergen provocation, a Th1 pattern was predominant. This same pattern is also found in chronic lesions of atopic eczema. Allergen-specific hyposensitization/immunotherapy (ASIT) is an evidence-based

^aDepartment of Dermatology and Allergy Biederstein, Technische Universität München, ZAUM – Center for Allergy and Environment, Munich, Germany

Correspondence to Ulf Darsow, Department of Dermatology and Allergy Biederstein, Technische Universität München, Biedersteiner Str. 29, D-80802 München, Germany. Tel: +49 89 4140 3463; e-mail: ulf.darsow@lrz.tum.de

Curr Opin Allergy Clin Immunol 2012, 12:000–000

DOI:10.1097/ACI.0b013e3283588cf4

KEY POINTS

- Allergen-specific immunotherapy (ASIT) has potential to improve the course of atopic eczema if type I sensitizations are present.
- Side effects have been overestimated in the past.
- Literature demonstrates variability in study design and results.
- Possibly atopy patch test helps to identify patient subgroup for ASIT.

method of curative treatment of immediate-type allergic diseases that has been in clinical use since 1911 [5]. The immunologic effects of ASIT are not yet completely understood. In short, ASIT induces a shift of immune response from a Th2 to a Th1 pattern, an induction of regulatory T cells, and a reduction of allergen-specific IgE production. Also, simultaneous induction of blocking, allergen-specific IgG antibodies, and a reduction of mediator release by mast cells occur. Release of inhibitory mediators [interleukin (IL)-10] may contribute to the effects [2,3[■],5,6[■]]. 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 [5]. It seemed likely that ASIT could also be effective in patients with atopic eczema and accompanying immediate-type sensitizations. On the contrary, use of ASIT in these patients was controversial due to contradictory clinical observations and theoretical immunologic considerations. We reviewed this topic recently using a comprehensive literature search [3[■]]. This article is therefore focused on the most recent references and study data.

SIDE EFFECTS AND RISKS 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 unwanted effects of this therapy, which are based on immediate-type reactions. Due to the role of specific IgE in the pathophysiology of atopic eczema, this transient increase may be a reason why atopic eczema flares may be seen after starting ASIT. 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 [3[■]]. 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; in contrast, a generally good tolerability of therapy was shown independent from ASIT success. Several studies have demonstrated improvement of atopic eczema following ASIT with house dust mite and other allergen extracts (see below); only a few reported on transient eczema flares [6[■]]. Noteworthy, such flares were also reported in control groups. Every ASIT bears the risk of unwanted side effects such as increased local reactions, anaphylactic reaction, serum sickness (rare), or transient exacerbation of the underlying atopic disease (not rare) [3[■]]. This holds true for the respiratory atopic diseases as well as for atopic eczema.

A major problem can be seen in the heterogeneity of eczema trigger factors, which can influence the course of the disease simultaneously and may also have effects on the efficacy of other eczema therapies [1[■]]. Actual reactivity to more than one allergen can blur the effects of ASIT to this single allergen. Moreover, eczema-specific relevance of a chosen ASIT allergen is often difficult to prove. This is also the problem of several studies showing no ASIT effect [3[■]].

A strikingly high placebo and/or basic therapy effect in atopic eczema is known from the literature [3[■],4,6[■]] and represents a special risk for smaller and potentially underpowered clinical trials. Remarkable placebo effects were also reported from most of the studies described in more detail below.

RECENT CLINICAL DATA ON ALLERGEN-SPECIFIC IMMUNOTHERAPY IN ATOPIC ECZEMA

Several open, uncontrolled study designs demonstrated promising results of subcutaneous and more rarely sublingual ASIT in patients with atopic eczema; some investigators in the 1970s and 1980s also showed improvement of atopic eczema in controlled trials (all studies reviewed in [3[■]]). Although publication bias cannot be excluded, 10 of 12 placebo-controlled studies published from 1974 to 2007 reported positive results in the active group [3[■]]. Study methods and outcome parameters showed extreme variations.

An early key double-blind, controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with atopic eczema was published in 1992 by Glover and Atherton [7]. 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.

In the past 5 years, only a few studies were published [8–14,15[¶],16[¶]] (Table 1). Werfel *et al.* [8] investigated 89 patients with atopic eczema showing high specific IgE to house dust mite (CAP-FEIA ≥ 4) who were injected weekly with three different doses of house dust mite allergen extract in a multicenter, randomized trial. With higher allergen doses, a beneficial SCORAD (Scoring Atopic Dermatitis) 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 [9] involving 20 patients with house dust mite or grass pollen sensitization also showed objective and subjective symptom relief under ASIT.

Data of a multicenter, double-blind, placebo-controlled study with a depigmented house dust mite extract were presented at the European Academy of Allergy and Clinical Immunology Congress 2011. Novak *et al.* [16[¶]] used an established dosage and injection scheme for allergic rhinoconjunctivitis (18 months) on 164 adult patients with atopic eczema sensitized to house dust mite allergens. Whereas the primary outcome of the study was negative, a post-hoc analysis showed a significant effect in the subgroup of severely affected patients. Further, the good tolerability of ASIT in patients with atopic eczema was confirmed in this larger trial.

Recent placebo-controlled clinical studies on sublingual immunotherapy (SLIT) to house dust mites have also been published [10,11]. Improvement of eczema symptoms and reduced need for concomitant medication during active therapy were seen. However, studies showing no effect of SLIT were previously published [3[¶]] and further research is needed.

Older studies [3[¶],6[¶]] suggest the efficacy of ASIT on eczema not only in house dust mite allergy, but also in patients with birch or grass pollen sensitization. This was recently confirmed in an uncontrolled pilot study [15[¶]] in birch pollen-sensitized eczema patients. Interestingly, another small pilot study in 25 patients [12] proposed that patients with a positive atopy patch test to house dust mite respond particularly well to ASIT, which may be of importance with regard to the problem of appropriate inclusion criteria for eczema subgroups.

Table 1. Recent clinical trials on ASIT in patients with atopic eczema

Study (year)	Design	Patient n; age	ASIT allergen	IT route of administration (treatment duration)	Results	Side effects	Outcome variable
Werfel <i>et al.</i> [8] (2006)	Three doses/ control group	89	ASIT for Dpt	Subcutaneous	Positive	No systemic reactions	Clinical SCORAD, medication
Silny and Czarniecka-Operacz [9] (2006)	DBPC	20	ASIT for Dpt or grass pollen	Subcutaneous	Positive	–	Clinical status, itch, sleep loss
Cadario <i>et al.</i> [10] (2007)	Observ	86; 3–60 years	ASIT for Dpt and Df	Sublingual (at least 1 year)	Positive	No severe reactions	Clinical SCORAD, specific and total IgE
Pajno <i>et al.</i> [11] (2007)	DBPC	56; 5–16 years	ASIT for Dpt	Sublingual (18 months)	Positive	–	Clinical SCORAD, medication
Bussmann <i>et al.</i> [12] (2007)	Observ	25	ASIT for Dpt	Subcutaneous	Positive	–	Clinical SCORAD and immunologic
Nahm <i>et al.</i> [13] (2008)	Observ	20	ASIT for Dpt and histamine–immunoglobulin complex treatment	Subcutaneous (1 year)	Positive	No significant side effects	Clinical SCORAD
Kwon <i>et al.</i> [14] (2010)	Observ	20; 6–33 years	ASIT for Dpt	Subcutaneous (1–5 years)	Positive	No exacerbation	Clinical, no total and specific IgE alteration
Novak <i>et al.</i> [15 [¶]] (2011)	Observ	55; 18–65 years	ASIT for birch pollen	Subcutaneous (1 year)	Positive	Not reported	Clinical, quality of life
Novak <i>et al.</i> [16 [¶]] (2011)	DBPC	164; adult	ASIT for Dpt	Subcutaneous (18 months)	Negative, post-hoc positive in severe eczema	No severe reactions	Clinical

ASIT, allergen-specific immunotherapy; DBPC, double-blind, placebo-controlled; Dpt, Dermatophagoides pteronyssinus; Observ, observational/open trial, uncontrolled; SCORAD, Scoring Atopic Dermatitis (tool).

CONCLUSION

Allergen-specific immunotherapy may be a possibility for improvement of the course of atopic eczema rather than a risk for deterioration of the disease, which is now also recognized in current guidelines [17,18[¶]]. 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 (given below) who give their informed consent. Published studies show a favorable effect of ASIT on disease symptoms of atopic eczema if accompanying relevant type I sensitizations are present. For subcutaneous immunotherapy the data are somewhat better in comparison to sublingual therapy. Particularly patients with house dust mite sensitization have been studied extensively [3[¶],6[¶]]. Better effects may be visible in patients with severe eczema, that is a SCORAD greater than 50 points [2,16[¶]].

Allergen-specific immunotherapy candidate subgroups of patients with atopic eczema:

- 1) house dust mite sensitization [1[¶],3[¶],6[¶]]
- 2) birch and grass pollen sensitization [3[¶],6[¶],15[¶]]
- 3) severe eczema (SCORAD >50) [2,16[¶]]
- 4) positive corresponding atopy patch test [2,3[¶],6[¶],12]

In many patients with respiratory atopy, atopic eczema of early infancy was the first manifestation of atopic disease [19], 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. Ultimately, novel therapies studied in clinical trials should help define the pathogenesis of the diseases and determine the importance of the treatment in large patient populations or in subpopulations of patients based on the concept of distinct phenotypes [20,21].

Especially, patients with a positive APT and corresponding history of eczema flares may be candidates for ASIT with the eliciting allergen [3[¶],6[¶],12]. However, the final judgment on the efficacy of ASIT in atopic eczema is still not possible due to the lack of large controlled and randomized clinical trials with modern allergen vaccines. Several of these trials await publication 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 usually selected for pharmacotherapeutic trials [3[¶]]. Future studies on 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. Longer observation periods and other

appropriate outcome measures for eczema improvement should be considered. With regard to the patient phenotype, differences in atopy patch test reactivity, age groups, and (poly-) sensitization status are of major interest. Regarding the ASIT methods, focus is necessary on efficacy differences between allergen sources, formulations, routes, and schedules of administration.

Acknowledgements

Dedicated to Professor Johannes Ring ('and the allergy goes on!').

Conflicts of interest

U.D. is project-related consultant for Bencard-Allergy Therapeutics (UK).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Ring J, Alomar A, Bieber T, *et al.* Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venerol* 2012; 26:1045–1060.
2. Novak N, Werfel T. Specific immunotherapy and atopic dermatitis: what is new? *Hautarzt* 2011; 62:650–656.
3. Darsow U, Forer I, Ring J. Allergen-specific immunotherapy in atopic eczema. *Curr Allergy Asthma Rep* 2011; 11:277–283.
- Recent comprehensive literature review on the topic – ends with clinical studies published 2008.
4. Darsow U, Ring J. IgE-mediated allergy plays a role in atopic eczema as shown in the atopy patch test. *WAO J* 2008; 1:51–56.
5. Ring J, Guterthum J. 100 years of hyposensitization: history of allergen-specific immunotherapy (ASIT). *Allergy* 2011; 66:713–724.
6. Weller K, Soost S, Worm M, *et al.* Atopic dermatitis and allergic rhinitis: do co-effects in therapy exist? *J Dtsch Dermatol Ges* 2012; 10:221–236.
- Recent review on therapeutic synergy in eczema and respiratory allergy.
7. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin Exp Allergy* 1992; 22:440–446.
8. Werfel T, Breuer K, Rueff F, *et al.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multicentre, randomized, dose-response study. *Allergy* 2006; 61:202–205.
9. Silny W, Czarnecka-Operacz M. Specific immunotherapy in the treatment of patients with atopic dermatitis. Results of a placebo-controlled double-blind study [in German]. *Allergologie* 2006; 29:171–183.
10. Cadario G, Galluccio AG, Pezza M, *et al.* Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study. *Curr Med Res Opin* 2007; 23:2503–2506.
11. Pajno GB, Caminiti L, Vita D, *et al.* Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007; 120:164–170.
12. Bussmann C, Maintz L, Hart J, *et al.* Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin Exp Allergy* 2007; 37:1277–1285.
13. Nahm DH, Lee ES, Park HJ, *et al.* Treatment of atopic dermatitis with a combination of allergen-specific immunotherapy and a histamine-immunoglobulin complex. *Int Arch Allergy Immunol* 2008; 146:235–240.
14. Kwon YS, Oh SH, Wu WH, *et al.* CC chemokines as potential immunologic markers correlated with clinical improvement of atopic dermatitis patients by immunotherapy. *Exp Dermatol* 2010; 19:246–251.
15. Novak N, Thaci D, Hoffmann M, *et al.* Subcutaneous immunotherapy with a depigmented polymerized birch pollen extract: a new therapeutic option for patients with atopic dermatitis. *Int Arch Allergy Immunol* 2011; 155:252–256.

Recent study using birch pollen ASIT with positive outcome.

16. Novak N, Zuberbier T, Sager A. Efficacy and safety of a depigmented polymerised mite extract in patients suffering from atopic eczema with clinically relevant IgE-mediated sensitisation against house dust mites. *Allergy* 2011; 66 (Suppl 94):103.

Largest recent study with modern blinded design showing positive effect of house dust mite ASIT only in the high severity subgroup of eczema patients.

17. Darsow U, Wollenberg A, Simon D, *et al.*, for the European Task Force on Atopic Dermatitis /EADV Eczema Task Force. ETFAD /EADV Eczema Task Force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2010; 24:317–328.

18. Ring J, Alomar A, Bieber T, *et al.* Guidelines for treatment of atopic eczema (atopic dermatitis) part II. *J Eur Acad Dermatol Venereol* 2012; 26:7776–7777. New European guideline for eczema treatment (part II).
19. Olze H, Zuberbier T. Comorbidities between nose and skin allergy. *Curr Opin Allergy Clin Immunol* 2011; 11:457–463.
20. WHO Collaborating Center for Asthma and Rhinitis. Severe chronic allergic (and related) diseases: a uniform approach—A MeDALL–GA(2)LEN–ARIA Position Paper. *Int Arch Allergy Immunol* 2012; 158:216–231.
21. Ring J, Akdis C, Behrendt H, *et al.* Davos Declaration. Allergy as a global problem. *Allergy* 2012; 67:141–142.