

Allergen specific immunotherapy for atopic dermatitis

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Purpose of review

To describe recent developments as well as the pros and cons of allergen specific immunotherapy as a putative therapeutic option for a subgroup of patients with atopic dermatitis.

Recent findings

The question whether specific immunotherapy would impair or improve the severity and course of atopic dermatitis has been a matter of debate for a long time. Double-blind placebo-controlled studies on the safety and efficacy of subcutaneous and sublingual specific immunotherapy in atopic dermatitis are rare; however, a systematic review of the literature on all published studies on specific immunotherapy in atopic dermatitis, together with the results of the most recent controlled studies, provides promising results.

Summary

The review discusses developments and recent advances in the field of specific immunotherapy as a causal therapy of sensitizations in atopic dermatitis. The most promising approaches, outlining putative immunologic as well as clinical changes which might go along with specific immunotherapy in atopic dermatitis patients, are highlighted. Further, we discuss how upcoming clinical studies and research could help to open new avenues for specific immunotherapy as a treatment for atopic dermatitis in the near future.

Keywords

allergen specific tolerance, atopic dermatitis, subcutaneous immunotherapy, sublingual immunotherapy

Introduction

Atopic dermatitis is one of the most frequent chronic inflammatory skin diseases with an increasing prevalence [1], affecting 10–20% of children and 1–3% of adults in industrialized countries [2]. Based on a strong genetic predisposition, complex interactions of deficient innate and adaptive immune responses underlie this multifactorial disease. Skin barrier dysfunction, which has very recently been shown to be genetically determined in a subgroup of atopic dermatitis patients [3–5], contributes to susceptibility to infections, hyperreactivity of distinct immune cells and, most importantly, to the manifestation of a high number of allergic sensitizations, which profoundly direct the severity and course of the disease [6].

The role of allergens in atopic dermatitis

Based on the current disease model, it is believed that allergen uptake by IgE receptor-bearing epidermal dendritic cells, followed by skin homing of cutaneous lymphocyte antigen-bearing T cells, plays a central role in initiating the inflammatory process in the skin [7]. Furthermore, recruitment of inflammatory cell subtypes induced by allergen challenges and directed by chemotactic signals is regarded as a causative factor for the development of the characteristic eczematous skin lesions [8].

About 80% of adult atopic dermatitis patients belong to the subgroup with sensitizations against different aero- and food allergens, reflected by increased total and allergen-specific IgE together with positive skin prick test and atopy patch test results [9]. Allergens may induce both allergic reactions of immediate and delayed type in sensitized patients with atopic dermatitis, and use routes via the respiratory tree as well as cutaneous exposure. House dust mites (HDMs) are top-ranking indoor allergens due to the high rate of sensitization against them, their perennial prevalence and their enzymatic properties [4,10]. Allergen reduction of HDMs is difficult to achieve due to the nearly ubiquitous exposure to HDMs and encasing strategies do not always lead to significant improvement of clinical symptoms. Further, birch and grass pollen and animal dander represent other important airborne allergen trigger factors of atopic dermatitis, which might go along with allergic cross-reactions to food proteins with an additional impact on the disease [11]. As both a diagnostic and experimental tool, application of aeroallergens in the atopy patch test is capable of inducing the characteristic eczematous skin lesions indicating

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Abbreviations

HDM	house dust mite
SCIT	subcutaneous immunotherapy
SCORAD	SCORing Atopic Dermatitis
SIT	specific immunotherapy
SLIT	sublingual immunotherapy

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a sensitization of relevance for atopic dermatitis. In view of all these aspects, without any doubt, sensitizations to allergens play a central role as one of the most common trigger factors leading to repetitive flare-ups of atopic dermatitis. Beyond that, the type and number of allergen sensitizations serve as negative prognostic factors predicting severe chronic and recalcitrant courses of atopic dermatitis. Only symptomatic antiinflammatory and anti-allergic local or systemic therapies exist, however, while no prophylactic or long-term treatment regimen to prevent, attenuate or cure sensitizations in atopic dermatitis patients is available at present [12].

Allergen specific immunotherapy – state of the art

Allergen specific immunotherapy (SIT) currently represents the only specific treatment form at our disposal that provides long-lasting amelioration of allergic symptoms, but its application is limited to patients with allergic rhinitis and mild asthma. Administration of the allergens during SIT via the subcutaneous [subcutaneous immunotherapy (SCIT)] and the sublingual [sublingual immunotherapy (SLIT)] route has been well established as long-term treatment, reducing symptoms of the disease as well as the amount of medications required. The main goal of SIT is to induce allergen-specific tolerance. In terms of the key cells targeted by SIT and the immunologic changes which go along with this treatment, an emerging but still fragmented picture arises that SIT mainly modulates responses of T cells, B cells, antigen-presenting cells and effectors cells on different levels [13^{••}]. Despite decreased mediator release by mast cells and basophils, IgE-facilitated antigen presentation by dendritic cells has been shown to be impaired after SIT [14]. Upregulation of the coinhibitory molecule B7-H1 on antigen-presenting cells, which suppresses T cell responses and increases production of antiinflammatory interleukin-10 by monocytes and B cells, together with the counteraction of the increase of CD28⁺CD4⁺ T cells and decrease of cytotoxic T lymphocyte-associated antigen-4⁺CD4⁺ T cells during allergen exposure are other effects of SIT [15]. The generation of allergen-specific T regulatory cells, including CD4⁺CD25⁺ T regulatory cells and inducible type 1 T regulatory cells, which suppress proliferative responses to the specific allergen and T helper 2 cell action is regarded as a crucial event closely related to the development of allergen-specific tolerance. Further, a decrease of IgE but increase of the amount and activity of blocking allergen-specific antibodies of the IgG1 and IgG4 type has been observed as a phenomenon attending SIT [14]. In addition, increase of allergen-specific IgA2 in parallel to the increase of transforming growth factor- β produced locally in the peripheral organs is suspected to contribute to the SIT-related induction of allergen-specific tolerance [16].

Clinical effects of specific immunotherapy in atopic dermatitis

The current approaches for the treatment of atopic dermatitis are mostly limited to the control and reduction of the symptoms and suppression of central and peripheral inflammatory reactions [12]. So far, SIT is not indicated for atopic dermatitis without accompanying allergic rhinitis or asthma with the proviso that it might induce exacerbations of manifest atopic dermatitis or relapses of latent atopic dermatitis. Double-blind placebo-controlled studies including a sufficient and representative numbers of atopic dermatitis patients are missing, and preclude this huge group of patients from causal therapy of their sensitizations so far. One of the most recent and relevant controlled studies on SIT in atopic dermatitis using the subcutaneous route is a multicenter study that included a total of 89 adult patients with atopic dermatitis [17^{••}]. Active placebo as well as two different concentrations of HDM allergen extract were used for a total time period of 12 months. Allergen dosage was increased during a 16-week build-up phase, followed by a maintenance phase with monthly injections. Significant clinical improvement measured by the SCORing Atopic Dermatitis (SCORAD) tool after 4 months of treatment in the active group was achieved without severe side reactions reported in any of the groups. In addition, the use of local corticosteroids decreased during SIT in the active group. The relatively high dropout rate in this study was mostly related to the need for weekly visits during the build-up phase. As a conclusion, adult atopic dermatitis patients with severe forms of atopic dermatitis benefited from SIT in this study.

In another controlled study using the sublingual route for allergen application, 56 children with atopic dermatitis sensitized against HDMs were treated either with SLIT or placebo [18^{••}]. The study included a build-up phase lasting 15 days and was conducted for a total of 18 months. Significant improvement measured by SCORAD in the active group was observable after 9 months of treatment, while lower use of rescue drugs in the active group was observable after 18 months. Subgroup analyses separating atopic dermatitis patients in patients with mild, moderate or severe atopic dermatitis revealed a benefit from SLIT exclusively for children with mild to moderate variants of atopic dermatitis in this study. With regard to side effects, it is worth noting that two patients of the active group had to be excluded from the study due to intense generalized flush reactions occurring within 1 h after sublingual allergen administration.

In comparison to the two studies mentioned above, a relatively rapid clinical effect was observed in a recent open-label study performed with a HDM allergoid applied via the subcutaneous route in 25 adult atopic dermatitis patients sensitized to HDM [19[•]]. Improvement of SCORAD already occurred during the 4-week

Table 1 Placebo-controlled studies of specific immunotherapy in atopic dermatitis: summary of the results of randomized, controlled studies

Reference	Year published	Total number of patients	Age (years)	Type of immunotherapy	Type of allergens used	Total duration (months)	Result
[20] ^a	1974	26	2–47	SIT	Animal dander; HDM, moulds; pollen	24	(+) improvement in the active group
[21] ^a	1978	20	5–14	SIT	HDM	12	(+) improvement in the active group
[22]	1982	2	10	SIT	Grass pollen	24	(+) improvement in the active group
[23] ^a	1992	24	5–16	SIT	HDM	13.5	(–) placebo effect higher
[24]	1993	24	5–50	Allergen–antibody complexes	HDM	16	(+) improvement in the active group
[25]	1994	60	0.5–12	Oral hyposensitization	HDM	mean duration 18.7	(–) improvement in all three groups, no difference between the groups
[26]	1998	58	Not mentioned	IFN- γ immunotherapy; IFN- γ -induced hyposensitization; SIT	HDM	2.5	(–) SIT not beneficial
[27]	2005	56	5–40	SIT	HDM; grass pollen	36	(+) improvement in the active group
[28 [•]] ^a	2006	20	5–40	SIT	HDM; grass pollen	12	(+) improvement in the active group
[29]	2001	99	15–62	SLIT	HDM	not mentioned	(+) improvement in the active group
[17 ^{••}] ^a	2006	89	18–55	SIT	HDM	12	(+) improvement in the active group
[28 [•]]	2006	56	5–16	SLIT	HDM	18	(+) improvement in the active group

^a Studies comparable for statistical analysis. HDM, house dust mite; IFN, interferon; SIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy. Adapted from [30[•]].

build-up phase and advanced further with a reduction of up to 60% compared to SCORAD at baseline during the maintenance phase.

A systematic analysis of all controlled and uncontrolled studies on SIT in atopic dermatitis published until the end of 2006 identified a total of 23 studies (11 controlled studies, 10 uncontrolled studies and two case reports) which showed a high heterogeneity (Table 1) [17^{••}, 18^{••}, 20–27, 28[•], 29, 30[•]]. This diversity originated mainly from the different types of allergens applied, the treatment schedules and duration of the treatment, as well as the readout criteria used to assess the safety and efficacy of SIT and lack of environmental control and standardized baseline medications recommended. Biostatistical analysis of four comparable controlled studies conducted since 1974 indicated significant improvement of atopic dermatitis after SIT (Table 1). Additionally, the comparison of seven observational studies provided evidence for 70% improvement of atopic dermatitis under SIT [30[•]]. In summary, most of the studies, regardless of whether controlled, uncontrolled or single reports, showed a trend for amelioration of atopic dermatitis under SIT. In terms of lack of efficacy, one study reported no change or worsening of eczema in 22% patients of the treatment group, but also in 72% of the patients of the placebo group [30[•]]. This implies that a careful selection of patients with atopic dermatitis for such studies is warranted in order to obtain valuable data. One of the most striking results was a significantly higher improvement in the placebo than in the verum group observed in one study, indicating that a quite high placebo effect (up to 30–40%) has to be expected in such interventional studies [30[•]]; however,

over 50% of the past studies were performed without a placebo group and are therefore only of limited value. With regard to side effects, severe exacerbation of atopic dermatitis in about 20% of the cases has been reported in some studies [30[•]]. With regard to the lower frequency of severe adverse reactions going along with the sublingual route of allergen application in patients with allergic rhinitis and mild asthma, it would be interesting to evaluate whether this trend would hold true for atopic dermatitis. So far, only one study has included a group of atopic dermatitis patients treated via the subcutaneous and in parallel a group treated via the sublingual route, and reported adverse reactions in 19.5% of atopic dermatitis patient in the subcutaneous as opposed to 14.6% in the sublingual group [30[•]].

Immunologic effects of specific immunotherapy in atopic dermatitis

Most of the studies on SIT in atopic dermatitis have focused primarily on safety aspects and clinical parameters such as improvement of atopic dermatitis measured by different scoring systems or changes in medication scores. Data on changes in IgE and IgG4 serum levels, cytokines, and chemokines or immunologic outcomes of SIT in atopic dermatitis patients at the cellular level in the blood and skin of atopic dermatitis patients is rare. Looking at the complex pathophysiology and important role of allergens as potent trigger factors of the disease, however, immunologic data showing the effectiveness of SIT in inducing allergen-specific tolerance, on the one hand, and evaluating the general impact on the complex pathophysiological network of atopic dermatitis, on the other hand, would be indispensable. With regard to the high activity of B cells

and deregulation of IgE synthesis in atopic dermatitis patients, one key question which needs to be addressed is in which way IgE serum levels change in response to frequent allergen challenges during SIT in this subgroup of atopic patients. Only three recent studies monitored the level of total and allergen-specific serum IgE [17^{••},19[•],28[•]] under SIT. While in two studies using allergen extracts, total and allergen-specific IgE levels remained unchanged [17^{••},28[•]], a reduction of allergen-specific IgE after 3 months of SIT and unchanged total serum IgE has been reported in one open-label study using a HDM allergoid as treatment [19[•]]. In parallel, blocking IgG antibodies have been evaluated only in one open-label pilot study with HDM allergoid so far, showing increasing levels of allergen-specific IgG4 already after 3 months in atopic dermatitis patients treated with SIT and a further increase after 6 months of treatment [19[•]]. There was no significant amplification of the characteristic T helper 2 overbalance in atopic dermatitis patients mirrored by T helper 2 cytokines in the sera of atopic dermatitis patients despite repetitive allergen challenge in SIT-treated atopic dermatitis patients in the two studies which evaluated this aspect [19[•],28[•]]. Further, in parallel to clinical improvement of the severity of the skin lesions, serum levels of chemokines which go along with the disease activity such as interleukin-16 or thymus and activation regulated chemokine (CCL17) were shown to drop during SIT in a recent pilot study [19[•]]. In view of these data, it might be speculated that a SIT-related decrease of chemokine levels of the treated patients could generally reduce the disposition of these patients to initiate inflammatory recruitment processes even after challenge with other allergens or trigger factors of the diseases. This might explain, in part, why even the treatment of a single sensitization in multisensitized atopic dermatitis patients would make sense, and putatively lead to profound improvement of the total clinical picture and disease-related immune state of these patients. In contrast, changes on the level of T cells might be related to rather specific mechanisms induced by SIT leading to activation of pathways which result in the induction of tolerance towards a single allergen. The issue of which way SIT would impact on the short- and long-term changes of the complex immunologic mechanisms underlying the disease and whether allergen-specific tolerance mirrored by the induction of T regulatory cells would be inducible even in the subgroup of atopic dermatitis patients, in which deregulation on the level of T regulatory cells has been reported in some recent studies [31,32], requires further evaluation in studies which take these aspects into account.

Future directions of specific immunotherapy in atopic dermatitis

Double-blind placebo-controlled studies conducted in adults and children with atopic dermatitis using different types of allergens are indispensable to improve our knowl-

edge on the issue of SIT in atopic dermatitis and to finally answer the important question of whether patients with atopic dermatitis would benefit from SIT or not. To minimize the risk of flare-ups, environmental control as well as standardized local and systemic therapy should be recommended, in particular during the build-up phase of SIT as well as during the allergen season. Since most of the adult atopic dermatitis patients are already multisensitized, it would be a challenge to develop valuable readout criteria to select the most relevant allergens impacting on the course of atopic dermatitis in each individual patient in the clinical practice. Further, the putative value of SIT not only as causal therapy for already manifest sensitizations, but also as a preventive measure to avoid the development of further sensitizations and to counteract the continuation of the atopic march (if conducted early enough in life) would be a key question worth addressing in this context. This is of particular importance in view of recent developments which provide clear evidence that a genetically determined skin barrier dysfunction predisposes a subgroup of patients with atopic dermatitis to the manifestation of a high number of sensitizations and concomitant asthma. For such individuals at risk for severe courses of atopic dermatitis, SIT would represent a promising strategy to attenuate this risk besides specific measures to restore their skin barrier dysfunction.

Conclusion

Continuous improvement of our knowledge about optimal routes of allergen application and treatment schedules [33], advances in allergen preparation, such as introduction of highly purified allergoids [34] or recombinant allergens [35], as well as increasing insights in the concomitant use of adjuvants [36] together with double-blind placebo-controlled studies conducted to sufficiently answer all open questions on SIT in atopic dermatitis, will hopefully break new ground for atopic dermatitis treatment in the near future.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 593).

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