

Immunoabsorption for treatment of severe atopic dermatitis

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Abstract

Atopic dermatitis (AD) is a common disease affecting up to 10–20% of the population with the largest disease burden in childhood. Treatment options include basic emollient treatment, topical as well as systemic immunosuppressants. The pathogenesis is complex and among various triggers, genetic predisposition and immunological alterations contribute to development of disease. Atopy is common in patients with AD and many patients have high levels of Immunoglobulin E (IgE), some of which recognizes exogenous or auto/self-allergens. Treatment options targeting IgE such as specific immunotherapy against e.g. house dust mites or using anti-IgE antibodies (omalizumab) showed variable results that were not convincing. We now review recent data on the application of unspecific and IgE-selective immunoabsorption (IA) in AD. All in all, 53 patients have been treated with non-specific pan Ig IA and 28 patients with IgE-selective IA. Side effects were rarely seen. The efficacy of IgE depletion was generally high (<~80%) for each IA cycle, but transient and lasted only a few days/weeks. Of note, disease activity appeared to improve in almost all cases and lasted for several weeks. Although the evidence is still weak, these case studies suggest that IgE depletion in AD is effective and helped control the disease. The mechanism of action is not understood yet. Future controlled trials are needed to validate this observation.

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1. Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease affecting approximately 10–15% of all individuals in industrialized countries [1]. The diagnosis is based on criteria developed by Hanifin and Rajka [2]. AD is characterized by pruritus, a chronic or relapsing dermatitis in predilection sites (e.g. flexural surfaces, face) and a positive family history for allergies. Minor criteria describe trigger factors, typical facial features, complications and the overall skin condition.

The onset of disease is typically within the first year of life (60%) or before the age of 5 (90% of cases). Even

though most patients suffer from AD only during childhood (~80% of cases do not have severe symptoms after beginning of school), the remaining patients often represent severe cases that are hard to control. Disease severity can range from infrequent, localized skin affections at predilection sites to acute exacerbation of the entire skin leading to erythrodermia, or skin infections requiring hospitalization. The patients suffer from a significant reduction in their quality of life due to pruritus, sleeplessness and stigmatization [1].

2. Pathophysiology of atopic dermatitis

The pathogenesis of AD is complex and differs between affected individuals. A genetic predisposition is well documented. As such, mutations in filaggrin are found in 25% of patients leading to immunological and barrier

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dysfunction. Mutations and polymorphisms in various other genes as well as epigenetic mechanisms contribute to onset of disease.

Apart from genetic factors responsible for a predisposition, several alterations of the skin immune system (e.g. differences in the amount of anti-microbial peptides produced by keratinocytes) and stromal cells are important [1,3,4]. Recently, the skin microbiome has been studied extensively. Here, it was shown that the diversity and number of skin commensals is clearly altered in patients with AD compared to healthy controls: fewer species with a higher frequency of *Staphylococcus aureus* colonization are dominating AD skin [3,5,6]. Skin colonization with *S. aureus* seems to be of particular interest since not only exotoxins, but also other *S. aureus* proteins can induce specific B- and T cell-dependent immune responses which partially also correlate with the severity of AD. Acute exacerbation of disease is characterized by a dense infiltrate of the dermis with CD4⁺ T cells showing a Th2-phenotype. Under more chronic conditions, the Th2 predominance is shifted towards a Th1 immune response as shown in atopy patch test experiments [1].

The relevance of the atopic predisposition and IgE as trigger factor for development of AD is unclear. About 1/3 of all AD patients are non-atopic [7,8]. However, Th2-associated cytokines such as IL-4, IL-5 and IL-13 promote B cell activation towards higher IgE synthesis. In some AD patients, epidermal Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) in lesional skin express high affinity IgE receptors, which are functional in IgE-mediated antigen presentation. Interestingly, on the other hand, FcεRI-bearing LCs of the oral mucosa possess anti-inflammatory properties [1,9]. Of note, the expression of FcεRI on IDEC correlated with serum IgE levels suggesting a feedback mechanism.

If IgE has an immediate and direct role for disease activity in AD is a highly controversial issue. As described above, patients with AD often show elevated IgE levels. It appears that the specificity of the IgE is often unknown [5]. In part, these have been shown to recognize exogenous allergens such as house dust mites, pollen etc.. According to Mittermann et al., patients with severe AD exhibited more wide spread IgE reactivity profiles towards several different allergens as compared to patients with moderate AD [10]. The majority of reactivity was found against exogenous allergens, such as cat allergens, birch and grass pollen, yeast, and house dust mites. Interestingly, 28% of all patients with AD also displayed serum IgE auto-reactivity against keratinocyte antigens which was not found in healthy individuals, suggesting that not only exogenous but also autoreactive IgE contribute to disease activity [11]. In addition, in some AD patients, the yeast *Malassezia* induces specific IgE as well as antigen-specific T cell responses. The Mala s 13 allergen, in turn, is characterized by high cross-reactivity to the human corresponding protein (thioredoxin). Induction of a potential autoallergic

mechanism due to molecular mimicry may thus be relevant in some AD patients [6]. In addition to allergen-specific IgE, IgE with self/auto-reactive properties may thus be involved in the pathogenesis of AD.

3. Treatment of atopic dermatitis: basic principles

Therapy of AD is based on a regular treatment with basic emollients supplemented with intermittent immunosuppressive therapy of exacerbated skin disease. Basic emollient application is known to contribute to enhance the impaired barrier function of the skin and control seborrhea. According to prior investigations, usage of basic emollients helps to reduce both the intensity and the frequency of flare-ups [4].

According to (inter)national guidelines, immunosuppression can be achieved either locally by application of corticosteroids or calcineurin inhibitors such as tacrolimus and pimecrolimus [4,12]. In addition, UV irradiation (especially UVA-1) as well as blue light treatment appears to be beneficial in heavily affected patients in whom interval therapy with local immunosuppression does not lead to sufficient disease control [4,13]. However, UV radiation is known to be carcinogenic and, thus, UV phototherapy is usually not recommended as long term treatment, and for young and immunosuppressed patients [4].

Systemic immunosuppression is recommended by administration of cyclosporine A – a treatment reserved for patients with disease activity that cannot be sufficiently controlled by various topical treatments [14]. And finally, as shown recently, several biologicals have also been tested as treatment option against AD. Among these, Dupilumab, a human monoclonal antibody blocking both IL-4 and IL-13, has proven to be very effective in the treatment of moderate-to-severe AD [15,16].

4. Treatments addressing elevated Immunoglobulin E level

Specific immunotherapy (SIT) is well established as treatment of allergic rhinitis, allergic asthma and other, sometimes severe IgE-mediated hypersensitivity reactions e.g. against bee venom [17]. Since many AD patients also suffer from various allergies, several authors have addressed the question if disease activity of AD patients is altered by SIT. All in all, the majority of studies did not report an improvement of AD in patients after SIT (e.g. against house dust mites, or birch pollen). However, some authors reported that patients with severe AD that reportedly exhibited flare-ups upon topical allergen triggering (e.g. during atopy patch testing) did benefit from SIT [4]. In a recently published meta-analysis of the effect of specific allergen immunotherapy for treatment of atopic eczema, the authors identified 12 randomized controlled trials addressing this question [17]. Taken together, the authors

found the information to be very heterogeneous and with weak evidence that SIT may be effective in AD patients.

A few years ago, omalizumab as a recombinant humanized monoclonal antibody targeting the high-affinity Fc receptor of IgE was approved for treatment of patients with allergic asthma and chronic urticaria. Since some of these patients also suffer from AD, several authors have assessed the efficacy of omalizumab against AD. Very recently, Wang et al. published a thorough review of the literature [18]. Most of the existing articles were cases series with small sample sizes. All in all, 83 patients could be analyzed extracted from 12 studies. 43% of the patients showed IgE concentrations >5000 IU/ml. It appeared that only 43% of all patients with AD achieved a therapeutic benefit after omalizumab treatment, especially those patients with lower IgE levels. Since the IgE levels in some AD patients can exceed 1500 IU/ml up to which a dosing regimen is provided by the manufacturer according to results of controlled trials leading to drug approval, the optimal dosage of omalizumab for patients with AD with higher IgE levels will need to be identified.

In summary, the treatment options addressing specific sensitizations of AD patients and their elevated IgE levels, such as specific immunotherapy and anti-IgE treatment, have shown variable to no beneficial effect for disease activity of AD.

5. Efficacy of immunoadsorption in atopic dermatitis

Recently, several investigators have studied the effect of non-selective Ig depletion as well as the recently established selective IgE depletion in patients with atopic dermatitis. The results of these studies and case reports will be described below. For each study, we report the size of the treatment cohort, inclusion criteria (serum IgE level, SCORAD = SCORing Atopic Dermatitis or EASI = Eczema Area and Severity Index) and the results. To allow a comparison and overview, Table 1 highlights the most important findings of each report.

In Kasperkiewicz et al. [19], the treatment group involved 12 patients with severe AD who did not respond to guideline recommended therapy administered before. These patients were treated with 10 non-selective IA on days 1–5 (week 1) and days 29–33 (week 5). For each of these patients, the individual medication was, depending on specific disease activity, continued, reduced or discontinued. From the 12 patients that initially started the treatment, 10 received full treatment. The baseline mean SCORAD was 78.6 ± 3.9 was significantly lowered to 41% of baseline by the end of week 13 (32.4 ± 3.5). The mean reduction in the circulating IgE levels for each IA cycle was >90%. IgE levels were increased approximately 12 h after each IA and 3 weeks after IA levels of IgE had returned to their baseline levels.

Two years later, the same group followed up by treating 2 patients with IgE-specific IA [20]. This is the first report

on IgE-specific IA. The 2 patients (2 males) exhibited total serum IgE levels of 40,848 and 111,696 $\mu\text{g/L}$, and baseline SCORADs of 66 and 77. On top of their current therapy, these patients received 2 cycles of 5 IA sessions on days 1–5 (week 1) and days 29–33 (week 5). In patient 1, the SCORAD decreased by 48% in week 17. The other patient exhibited a good response with an improvement of 65% at week 25. The mean reduction in circulating IgE for each IA cycle was 92%. Relative to that, there was less reduction in IgM, IgG, and IgA. This study indicates that IA treatment may be efficient in the long-run, up to 6 months after therapy.

Daeschlein and co-authors [21] treated a group of 7 patients (5 males and 2 females, mean age 35.3 ± 15.1) who exhibited total serum IgE levels >700 IU/ml with non-selective IA. The entire treatment consisted of up to five series of five consecutive treatments (day 1–5, 1 week = 1 series) performed every four weeks. In particular, whereas one patient received just one cycle of IA, two other patients received two of such cycles, one patient three, two patients four and one patient five. The mean SCORAD before treatment was 52.0 ± 21.0 , the mean total serum IgE levels were $11,015 \pm 10,081$ IU/ml. Total serum IgE and SCORAD were determined every 1st and 5th treatment day of every series of IA. IgE reductions were significant in each series and for each patient. These reductions were not monotone, but IgE levels decreased and increased in a sawtooth-like manner over the entire series of treatments and returned to initial levels at the end, except for three patients, who exhibited decreasing IgE levels before each cycle throughout their treatment series and one patient, who did not develop an increase in IgE levels (no sawtooth manner). The reduction of circulating IgE in a single series reached about 75–85% and was associated with the improvement of SCORAD. The total reduction of SCORAD from all patients over all series was from 100% to 34.4%. The authors concluded that patients with severe AD benefit from repetitive IA with long-term effects over 12 months after at least five series of therapy.

Reich et al. [22] administered pan-Ig and IgE selective IA to a group of 50 (24 vs 26) patients to compare the clinical effects of these two therapies. Patients received a total of 10 IA sessions over a 2-month period divided into 3 cycles of 4 consecutive days in week 1, 3 days in week 4, and 3 days in week 8. The mean EASI was 21.3 and the total serum level was between 5000 and 10,000 kU/l. Each of the two IA types successfully reduced total serum IgE level by 85–90% per IA cycle. In addition, pan-Ig IA also had a significant effect on circulating IgG levels. 6 months after IA the median EASI reduction in the IgE-selective IA group was still at about 60% of the initial level. The reduction in the pan-Ig IA group showed similar values.

Finally, Zink and co-workers [23], the treatment cohort consisted of 10 (8 males and 2 females, mean age 43.7 ± 11.2) patients with severe AD (SCORAD >50) and

Table 1
Summary of reports about atopic dermatitis patients who received immunoadsorption.

Reference	Patients (n)	Baseline SCORAD (or EASI)	Treatment modalities		Change in SCORAD/EASI	IgE elimination	IgG elimination	AEs
			Type	Schedule				
Kasperkiewicz et al. (2011)	12	78.6 ± 3.9 (mean ± SEM)	Non-selective IA	d1-5 (wk1)	–38% wk3	>90%	++	2 AEs (catheter infection)
				d1-5 (wk5)	–46% wk5			
					–56% wk9			
					–59% wk13			
Daeschlein et al. (2015)	7	72		d1-5 every 4 weeks (5×)	–88% wk21	75-85%	++	2 AEs (transient blood pressure drop)
		60		d1-5 every 4 weeks (4×)	–67% wk17			
		21.3			–62% wk17			
		62		d1-5 every 4 weeks (3×)	–61% wk13			
		77		d1-5 every 4 weeks (2×)	–66% wk9			
Reich et al. (2016)	24	34			–71% wk9	85-90%	++	8 AEs in 7 patients (infections)
		43		d1-5 (1×)	–51% wk2			
		46.3 ± 13.6 (mean ± SD)		d1-4 (wk1)	–39% wk7			
		24.1 ± 15.2 (mean ± SD)		d1-3 (wk4)	–52% wk13			
				d1-3 (wk8)	–61% wk37			
Zink et al. (2016)	10	59.9 ± 8.4 (mean ± SD)	Non-selective IA + anti-IgE	d1-2, d1-3 or d1-4 depending on IgE level	–27% wk3 (after IA, before anti-IgE)	64%	++	3 AEs (transient dizziness, fatigue)
				+ Omalizumab every 2 weeks for 24 weeks	–41% wk13			
					–55% wk25			
Total	n = 53							15
Kasperkiewicz et al. (2014)	2	66	IgE-specific	d1-5 (wk1)	–48% wk17	92%	(+)	–
		77		d1-5 (wk5)	–65% wk25			
Reich et al. (2016)	26	35.1 ± 12.7 (mean ± SD)		d1-4 (wk1)	–47% wk7			
		18.7 ± 15.6 (mean ± SD)		d1-3 (wk4)	–45% wk13			
				d1-3 (wk8)	–60% wk37			
Total	n = 28							2

increased IgE levels (>3500 kU/l, mean $18,094 \pm 19,573$ kU/l) and refractory to at least 2 conventional systemic therapy. The exact procedure of the treatment was as follows: First, patients were treated with non-selective IA depending on their baseline IgE levels - 2 IA (IgE Level <6000 kU/l), 3 IA (IgE level $6000-20,000$ kU/l) or 4 IA (IgE level $> 20,000$ kU/l), followed by anti-IgE-antibody omalizumab every 2 weeks subcutaneously at a dose 450 mg for 24 weeks and then completed by a follow up bi-weekly for another 24 weeks. Mean total IgE levels after IA were $36 \pm 23\%$ of the respective values before IA.

6. Immunoglobulin depletion efficacy of immunoadsorption in patients with atopic dermatitis

In all reports about IA treatment of patients with high levels of IgE and AD, the efficiency of IgE deletion was closely monitored. The efficiency ranged from 64% to 92% for each treatment cycle and appeared to be independent of the baseline IgE (Table 1). Interestingly, Immunoglobulin G (IgG) levels were also mildly reduced in patients receiving selective IgE depletion only ($\sim$ to 80% of baseline), which appeared to be transient. In all patients receiving pan-Ig IA, both IgE as well as IgG levels were dramatically reduced as expected.

Several of the authors were also able to monitor IgE levels for several days/weeks after IgE depletion. Kasperkiewicz et al., who performed IA for 5 days in week 1 and another time in week 5, observed that the IgE levels were back to normal baseline levels comparable to before therapy as early as 3 weeks [19]. In between time points were not determined. All in all, a long lasting reduction of IgE was not achieved by the two cycles of IA performed. Daeschlein et al. observed three IgE response patterns: one in which IgE levels were reduced in a sawtooth pattern from day to day of IA, rising back again to baseline levels within 3–4 weeks ($n = 2$), and another one with a similar response to IA with the IgE remaining below baseline as determined before the next cycle ($n = 4$) [21].

7. Treatment outcome of immunoadsorption

Treatment efficacy was reported in all studies using both life quality measurements as well as clinical scores indicating the severity of disease. The most commonly clinical scoring system, the SCORAD, was used to assess the extent and severity of eczema. Within the score, both the extent as well as severity of the eczema are documented by the physician and combined with an assessment of itching and sleeplessness of the patient on a visual scale from 1 to 10. As indicated in Table 1, the baseline SCORAD of all patients treated with IA in the reports was high indicating that the majority of patients investigated suffered from severe AD. Reich et al. also reported responses using the EASI score.

Treatment efficacy was determined as percent change of the SCORAD compared to baseline SCORAD before IA. Most patients showed a moderate to good response to IA ranging from 27 to 88% improvement. In the non-selective IA patient cohort ($n = 43$, not considering co-treatment with IA and omalizumab), treatment efficacy ranged from very good improvement with a reduction by 88% to moderate responses (reduction by 38%). In the largest cohort by Reich et al. ($n = 24$), the overall improvement was 39–61% reduction of baseline SCORAD. Even though a detailed analysis is not possible since not all patients were reported separately, it appears that a SCORAD 50 (50% reduction of baseline score) was achieved in 7/43 patients within the non-selective IA treatment group.

A total of 28 patients were treated with IgE specific IA. Treatment efficacy ranged from 45 to 60% (largest cohort, $n = 26$ [22]) to 65% improvement, a SCORAD 50 was achieved in $\sim 2/28$ patients.

As indicated in Table 1, the duration of the clinical response was monitored in several of the patients [19–22]. Even though a comparative assessment is hard to perform due to the different treatment modalities used by the different centers, in each case it seemed that the clinical response remained stable for several additional weeks/months post IA suggesting that the transient depletion of circulating IgE from AD patients has a long-lasting effect on disease activity.

8. Adverse events

As indicated in Table 1, several adverse events (AEs) have been reported during/after IA. AEs have only been observed in non-selective IA with concomitant IgG depletion, leading to severe catheter infections (in 2 patients) resulting in discontinuation of the IA [19]. In 8 additional patients [22], other types of infections were reported such as Herpes simplex reactivation, bacterial sinusitis and *S. aureus* conjunctivitis. These findings are somewhat expected, since IgG depletion is associated with an increased risk to acquire infections. All these patients received IA as add-on therapy to systemic (immunosuppressive) treatment, which was continued or modified. In addition to IgG reduction, the concomitant immunosuppressive therapy cannot be excluded as a further risk factor for these infections.

Three other serious AEs, i.e. air embolism during central venous catheter placement, cubital vein thrombophlebitis and generalized cutaneous allergic reaction (by prophylactic antibiotic therapy), have been also reported. Transient, IA-associated AEs such as blood pressure changes, dizziness and transient fatigue have been observed in a total of 5 patients receiving non-selective IA [21,23]. However, all of these were of transient nature, did not impact the quality of life beyond the treatment and did not affect further treatments.

Interestingly, even though a mild decrease of IgG levels was also reported in patients with selective IgE depletion by Reich et al., AEs related to infections were not reported in this group of patients [22].

9. Mechanism of action

The mechanisms that may explain the clinical response of patients with AD to selective (or non-selective) IgE depletion are completely unknown so far. Kasperkiewicz et al. performed some analyses of potential underlying mechanisms. The authors performed a comparison of skin-bound to serum IgE levels and found that decreases in skin-bound IgE corresponded with immunological and clinical improvement, whereas IgE serum levels were only transiently reduced [19]. These findings suggest a redistribution of circulating and bound IgE upon IgE depletion from AD. However, other potential mechanisms such as an alteration of the levels of specific/autoreactive IgE may also contribute to the effect observed.

10. Summary and outlook

Atopic dermatitis is a common disease in western countries and the treatment options, especially for severe forms of disease, are limited and not without side effects. The role of IgE for disease pathogenesis is still not fully understood. Several treatment attempts with specific immunotherapy addressing sensitization against relevant allergens and treatment with anti-IgE have shown unreliable results with benefit for only a minority of AD patients.

IgE-selective IA may represent an interesting option for the treatment of AD as indicated by the reports discussed in this review. The IgE deletion efficacy by IA was excellent, but only transient. However, in most reports, improvement of disease activity and severity was seen even after several weeks post IA suggesting that IgE is indeed involved in the pathogenesis of AD. This conclusion is justified since during IA, no potential unknown or unwanted effects of drug administration can be used as explanation of an effect; only the removal of IgE may be responsible for the effect observed. Several IA protocols have been shown in the reports discussed; which one of these leads to the best improvement of disease activity and/or IgE reduction is still unclear. Future studies and controlled trials will be important to prove the efficacy of IA for patients with AD.

Conflict of interest

The authors declare no conflict of interest.

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