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IgE-specific immunoadsorption: New treatment option for severe refractory atopic dermatitis

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Short title: IgE immunoadsorption for atopic dermatitis

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Letter summary

Atopic dermatitis (AD) is an inflammatory skin disease with a complex pathogenesis. Many patients with AD exhibit high levels of immunoglobulin E (IgE). We present a case series of 12 patients (6 males/ 6 females, age range 17-55 years) treated with the newly developed IgE-specific immunoadsorption (IA), after insufficient control of disease by previous guideline treatments, using reusable adsorption columns containing mouse anti-human IgE with a total of 10 IA sessions over a 2-month period divided into 5 cycles of 2 consecutive days every two weeks. No severe adverse events were recorded. Total IgE levels were reduced immediately after each treatment with a mean reduction of 81% (range 67-90%) and increased again quickly in treatment-free periods. Disease activity assessed by determining the EASI decreased within the first 14 days of treatment reaching a mean improvement of >50% by the 5th cycle of IA ($p \leq 0.001$). Despite discontinuation of IA after 8 weeks, most patients benefitted from treatment for up to 4 month. Biweekly IgE-selective IA as used in our cohort seems more effective than less frequent IA and provides relevant clinical benefit for patients without established therapeutic alternatives.

To the Editor:

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease characterized by pruritus, dermatitis at predilection sites and a positive family history for AD and type I allergies¹. The prevalence of AD is ~10-20% of the population with high disease burden during childhood. Currently, therapeutic options run from basic emollients, to external and systemic immunosuppressive drugs, dupilumab as well as light therapy². Unfortunately, for patients with severe forms of disease, treatment options are not always efficacious and harbor side effects.

The pathogenesis of AD is complex. Together with genetic predisposition, epigenetic factors, alterations in skin microbiome and anti-microbial peptide content of keratinocytes are known to contribute to disease manifestation³⁻⁵. Acutely exacerbated lesions are infiltrated with CD4⁺ T cells with a Th2 phenotype, whereas chronic lesions contain Th1 cells. Many AD patients exhibit greatly elevated levels of immunoglobulin E (IgE). The relevance of atopic predisposition and IgE as trigger factor for AD development is unclear. In fact, about 1/3 of all AD patients lack relevant IgE levels directed against common aero- and food allergens^{6, 7}. In addition, treatment with antihistamines is often ineffective as immunotherapy against e.g. house dust mites can be^{4, 8, 9}. Application of anti-IgE treatment with omalizumab in patients with AD showed disappointing results^{10, 11}. It appears that the clinical effectiveness of this therapy is dependent on the initial total IgE levels. Patients with higher IgE levels (>700 kU/ml) benefitted less well compared to patients with lower IgE. It has been proposed that an inadequate neutralization of the IgE antibodies from omalizumab may be the cause of this phenomenon¹². However, Th2-associated cytokines (e.g. IL-4, and IL-13) promote B cell-associated IgE production and recently, dupilumab administration, an inhibitor of IL-4 and IL-13, has shown to be greatly beneficial for AD patients^{13, 14}. IgE elimination as therapeutic option was recently evaluated by several groups (for a relevant review see¹⁵). In the present series, we assessed the effects of IgE-specific immunoadsorption (IA) on disease activity and quality of life in moderate to severe AD using a standardized approach with frequent IAs every other week.

In our case series, a total of 12 patients (6 males/ 6 females, age range 17-55 years) from the Dpt. of Dermatology, University Medical Center Mainz were treated with IgE-specific IA, after previously receiving treatments according to guideline recommendations (avoidance of trigger factors, topical basic therapy, topical steroids and/or calcineurin-inhibitors, UV irradiation, oral antihistamines and systemic cyclosporine A in four cases, the remaining had contraindications or side effects to cyclosporine A) with insufficient control of disease. Fig. 1A shows the characteristics of all 12 patients before treatment initiation regarding total IgE levels, the Eczema Area and Severity Index (EASI), as well as Dermatology Life Quality Index (DLQI) and the WHO questionnaire 'wellbeing five' before therapy, Table S1 shows their concomitant diseases. After discussing all therapeutic options available, the patients have given consent in written form to IA treatment.

IA was performed with reusable adsorption columns containing a matrix coated with mouse anti-human IgE (TheraSorb IgE; Miltenyi Biotec, Germany) and the LIFE 18 Apheresis Unit (Miltenyi Biotec) (Table S2). Since prior case reports have shown that IgE depletion can only be transiently achieved with high efficiency resulting in reduction of IgE into ranges of healthy controls within only 1-3 subsequent IA sessions, we aimed to lower

IgE levels continuously by more frequently applying IA (Fig. 1B). Each patient thus received a total of 10 IA sessions over a 2-month period divided into 5 cycles of 2 consecutive days every two weeks. Adverse events were thrombophlebitis (n=1 treatments), hypotonia during treatment (n=3), nausea/vomiting (n=2) and transient physical weakness after treatment (n=10). Due to the invasiveness of the procedure and a significant burden on the patient from the duration of each individual treatment, a sham treatment group was not included.

After IA, total IgE levels were markedly reduced in all 12 patients. The mean reduction of circulating IgE after all 5 cycles of all 12 patients was 81% (range 67-90%). Tab. S3 describes the total IgE levels before and after each cycle of IA, the percent reduction on day 1 and day 2 as well as per cycle and per patient in all 5 cycles. Interestingly, not only total IgE levels were affected, but antigen-specific IgE directly after IA was significantly reduced as well (Table S4). In line, in the 28 previously published cases, the efficacy of IgE-selective depletion was generally high (>78%)¹⁵. In our hands, the effectivity of IgE-specific IA was independent of initial IgE levels. Within the treatment-free interval, total IgE levels increased again quickly over the entire series of treatments (Fig. 1C). Of interest, 12 days after the previous IA, total IgE levels had reached the individual baseline of each patient again, indicating the existence of feedback mechanisms that tightly control the individual IgE level. Unlike a prior report, we did not observe a decline of the patients' total IgE levels over time⁶. IgM and IgG levels (including subclasses) were only transiently and mildly affected by IgE-specific IA (Fig. S1).

Disease activity was assessed by determining the EASI before each of the 5 cycles (Fig. 2A+B). Moreover, Severity Scoring of Atopic Dermatitis (SCORAD), which includes an evaluation of pruritus and insomnia, was also assessed (Fig. S2). All in all, disease activity decreased within the first 14 days of treatment reaching a mean improvement of >50% by the 5th cycle of IA ($p \leq 0.001$). After 5 cycles, 80% of the patients (10/12) improved by at least 25% (EASI 25), 75% (9/12) by at least 50%, and 25% (3/12) by 75%. By comparing both clinical scores (SCORAD and EASI) and DLQI in the subgroup of patients with high versus those with low IgE levels, we observed a trend towards a better therapy response in patients with IgE levels >5,000 kU (Fig. S3). Therefore, we performed a correlation analysis between baseline IgE levels and SCORAD, EASI and DLQI scores at all time points. We found a statistically significant correlation of IgE levels with SCORAD and EASI, for some time points (cycle 2, cycle 3 and 3-4 weeks after IA for SCORAD; cycle 1-3 for EASI), but no significant correlation with DLQI. Given the small number of patients in the study, we acknowledge that the correlation analysis results should be interpreted with caution. The patients were asked to continue using disease severity adapted, guideline-recommended concomitant treatment: 4 patients used systemic therapy (3 cases with corticosteroids orally, which they

lowered/stopped over time, one patients with occasional antihistamine), and 2 patients used topical therapy with corticosteroids with decreasing amounts needed; 6 patients did not use any concomitant therapy (Table S5).

Previously, non-selective IA only led to a $\geq 50\%$ improvement in 7/43 patients (16%, range 38-88% improvement), and IgE-specific IA achieved a similar effect in 2/28 patients (7%, range 45-65% improvement)¹⁵. Thus, compared to prior reports, it appears that biweekly IgE-selective IA as used in our cohort is more effective than less frequent IA with intervals of 3-6 weeks between treatments, because it may be more effective to reduce IgE with its apparent high turnover. However, due to the variable treatment protocols and assessment time points used in the prior studies, this aspect needs to be evaluated further. Patient-based assessment of their quality of life showed similar effects with a total improvement of $\sim 50\%$ after 5 cycles of treatment. In line, the score evaluating the 'wellbeing five' increased with the number of IA cycles applied.

Interestingly, despite discontinuation of IA after 8 weeks, most patients benefitted from the treatment for a prolonged time reaching an EASI 50 in 7/8 and an EASI 75 in 6/8 patients after 3-4 months, respectively. Similar observations were made by other authors^{6, 7, 16}, which is intriguing considering the rapid re-synthesis of IgE and fast recovery of individual IgE levels in less than 2 weeks.

The mechanism of action remains unclear and may range from depletion of allergen- or pathogen-specific IgE to reduction in tissue-bound IgE¹⁷. In addition, alterations in the level of autoreactive IgE may also be possible¹⁵. In summary, in the present 12 case series, we have observed that repetitive, transient reductions of total IgE in AD leads to long-lasting improvement of AD. In patients previously unresponsive to extensive guideline therapy, both clinical parameters as well as the quality of life were strongly improved. The results suggest that IgE potentially represents an important therapeutic target in AD and controlled trials assessing the efficacy of IgE-selective IA for larger AD patient cohorts are urgently needed.

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Contribution of the authors

Julia Weinmann-Menke, Joachim Saloga, Stephan Grabbe and Esther von Stebut designed the study, Joanna Wegner, Sophia Wilden, Jens Lutz and Julia Weinmann-Menke treated the patients, Nadine Vewinger performed laboratory tests, Joanna Wegner, Julia Weinmann-Menke and Esther von Stebut analysed the data, performed statistics, and wrote the paper.

None of the authors declare a conflict of interest.

References

1. Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; 361:151-60.
2. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol* 2018; 32:657-82.
3. Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358:1483-94.
4. Werfel T, Heratizadeh A, Aberer W, Ahrens F, Augustin M, Biedermann T, et al. S2k guideline on diagnosis and treatment of atopic dermatitis--short version. *J Dtsch Dermatol Ges* 2016; 14:92-106.
5. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; 22:850-9.
6. Daeschlein G, Scholz S, Lutze S, Eming R, Arnold A, Haase H, et al. Repetitive immunoadsorption cycles for treatment of severe atopic dermatitis. *Ther Apher Dial* 2015; 19:279-87.
7. Reich K, Deinzer J, Fiege AK, von Gruben V, Sack AL, Thraen A, et al. Panimmunoglobulin and IgE-selective extracorporeal immunoadsorption in patients with severe atopic dermatitis. *J Allergy Clin Immunol* 2016; 137:1882-4 e6.
8. Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of

atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016; 30:729-47.

9. De Benedetto A, Yoshida T, Fridy S, Park JE, Kuo IH, Beck LA. Histamine and Skin Barrier: Are Histamine Antagonists Useful for the Prevention or Treatment of Atopic Dermatitis? *J Clin Med* 2015; 4:741-55.
10. Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. *J Am Acad Dermatol* 2005; 53:338-40.
11. Wang HH, Li YC, Huang YC. Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis. *J Allergy Clin Immunol* 2016.
12. Sheinkopf LE, Rafi AW, Do LT, Katz RM, Klaustermeyer WB. Efficacy of omalizumab in the treatment of atopic dermatitis: a pilot study. *Allergy Asthma Proc* 2008; 29:530-7.
13. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; 387:40-52.
14. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; 371:130-9.
15. Wegner J, Weinmann-Menke J, von Stebut E. Immunoabsorption for treatment of severe atopic dermatitis. *Atheroscler Suppl* 2017; 30:264-70.
16. Kasperkiewicz M, Sufke S, Schmidt E, Zillikens D. IgE-specific immunoabsorption for treatment of recalcitrant atopic dermatitis. *JAMA Dermatol* 2014; 150:1350-1.
17. Kasperkiewicz M, Schmidt E, Frambach Y, Rose C, Meier M, Nitschke M, et al. Improvement of treatment-refractory atopic dermatitis by immunoabsorption: a pilot study. *J Allergy Clin Immunol* 2011; 127:267-70, 70 e1-6.

Figure legends

Figure 1: IgE-specific immunoadsorption: treatment plan and efficacy

A, Patient characteristics before treatment regarding age, individual baseline IgE, baseline disease activity as determined by Eczema Area and Severity Index (EASI) and patient-based assessment of disease burden (DLQI, wellbeing five). **B**, Treatment plan with biweekly application of IA (2 IA on 2 consecutive days) and schematic drawing of the IA procedure. **C**, Individual total IgE levels before and after each IA treatment as well as after ~1 and 3 months treatment.

Figure 2: Results of IgE-specific immunoadsorption in atopic dermatitis

A, Before each IA cycle and after ~1 and 3 months treatment, the Eczema Area and Severity Index (EASI) was determined and the patient-assessed disease burden by DLQI and wellbeing five was monitored. Data are shown as absolute values and as relative change compared to baseline (week 0). Statistical differences compared to baseline were calculated using the Bonferroni test (*= $p \leq 0.05$, ***= $p \leq 0.001$). **B**, The percentage of patients with an at least 25%, 50%, or 75% EASI improvement compared to baseline (week 0) was calculated. **C**, Photos of treatment results in 3 patients.

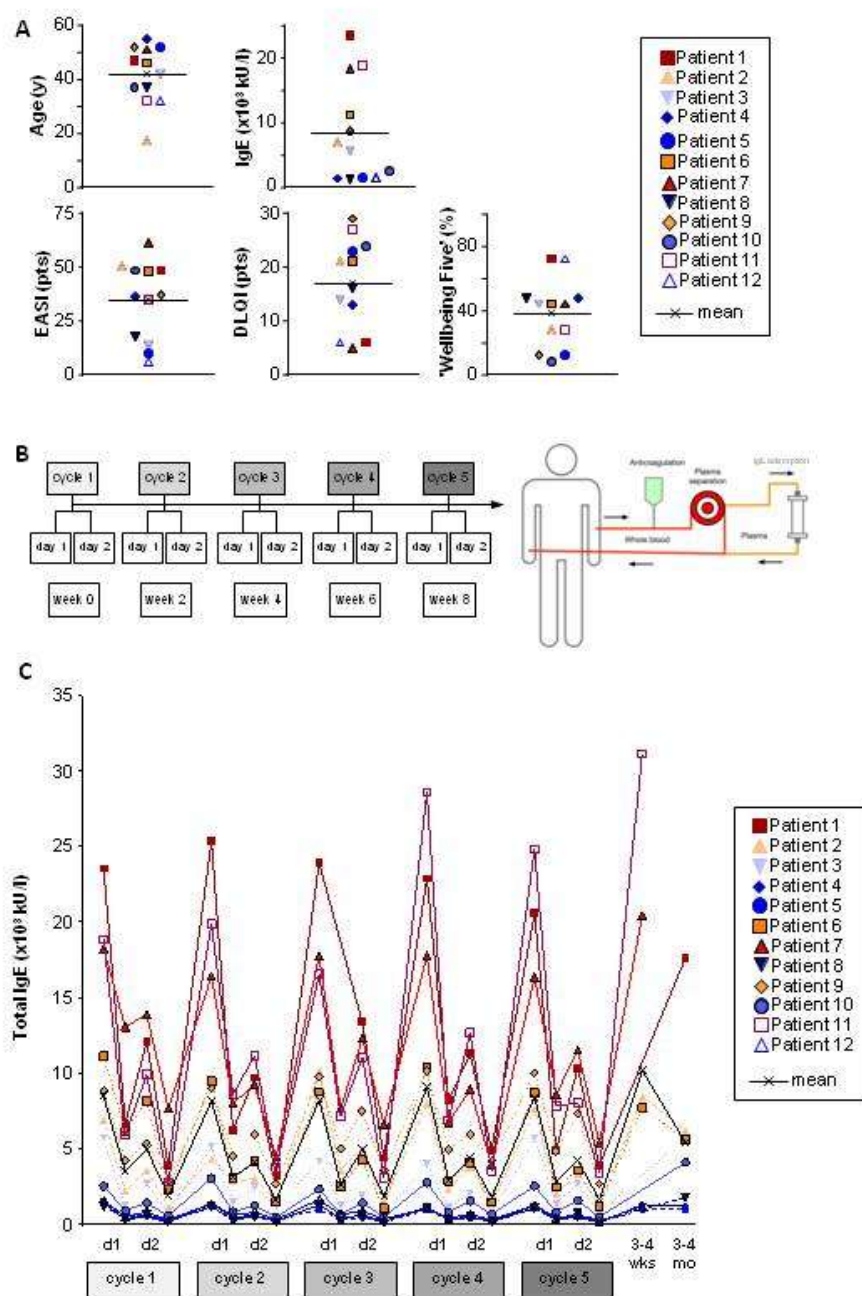


Figure 1

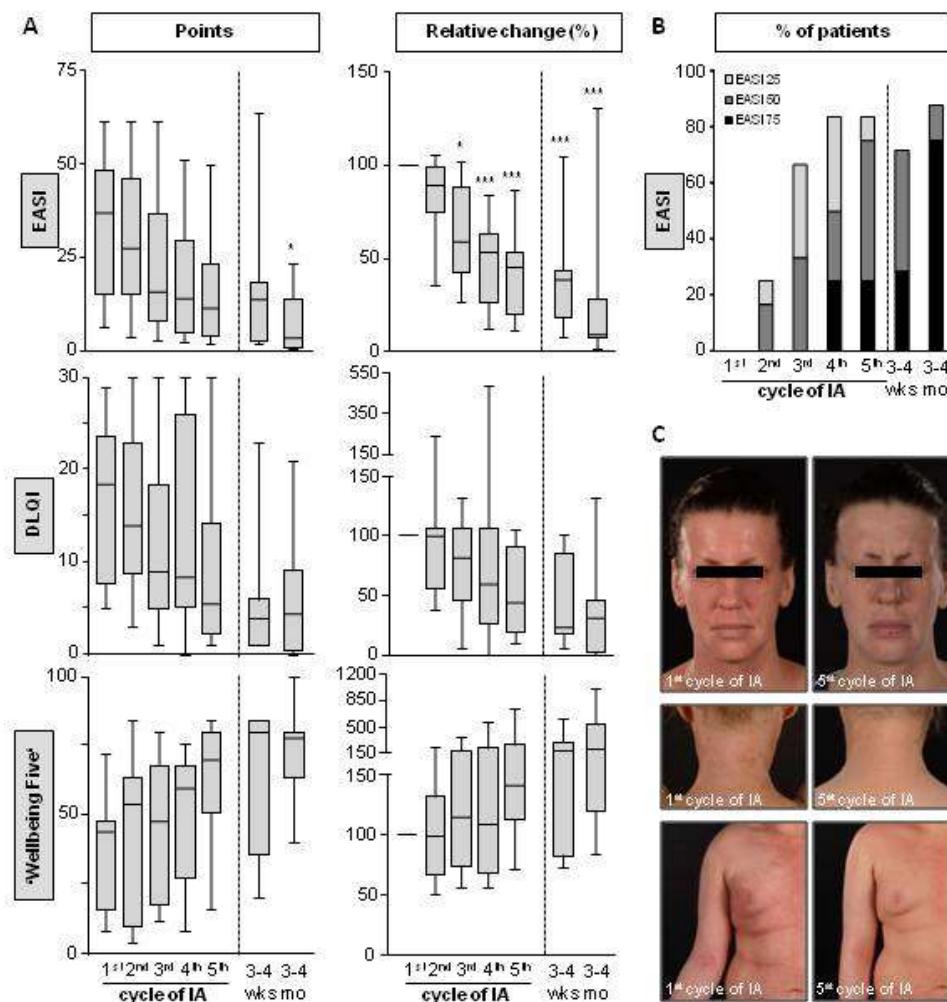


Figure 2

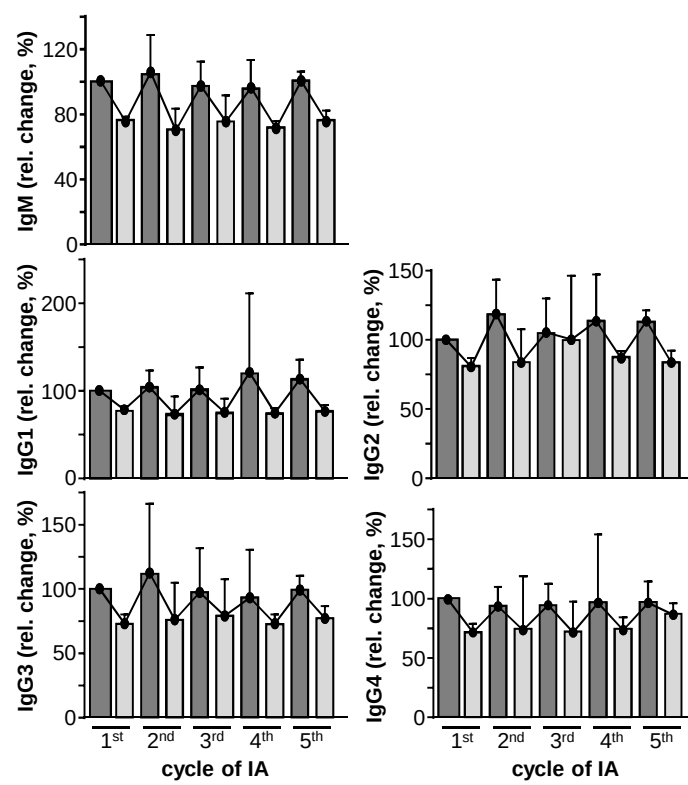


Figure S1

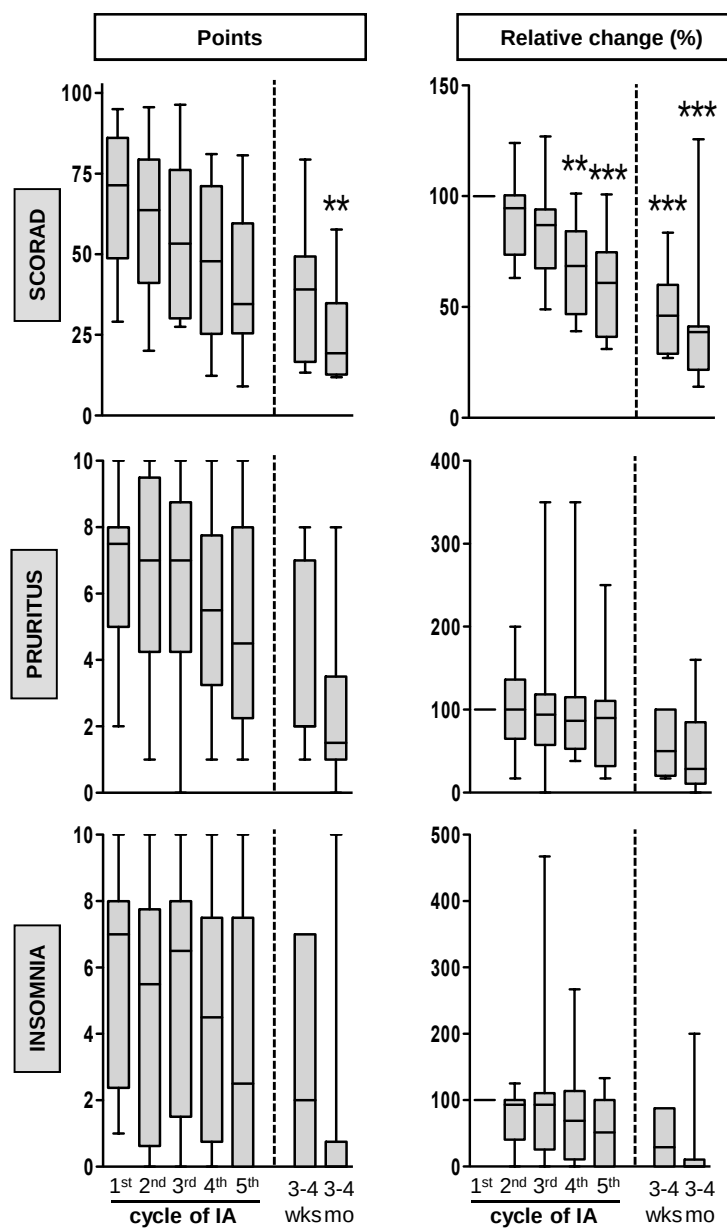


Figure S2

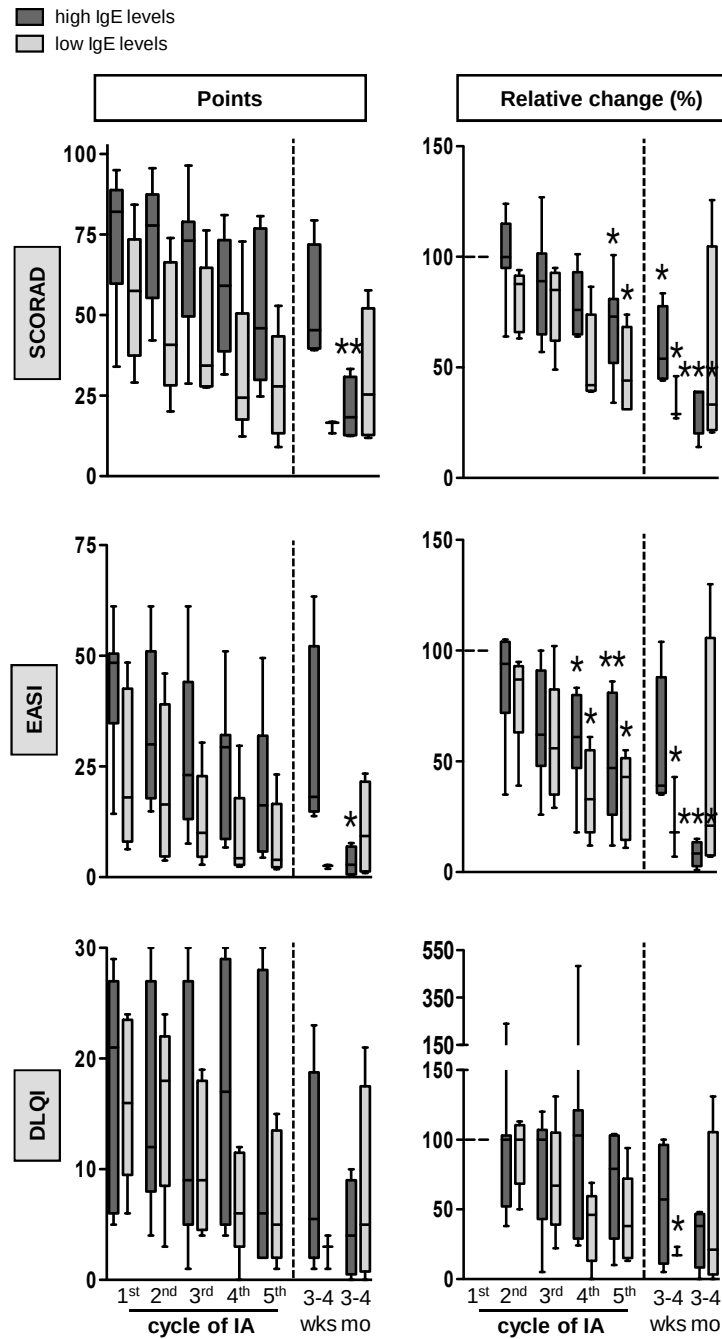


Figure S3

Supplemental Figure legends

Figure S1: Change in IgM and IgG levels in patients after IgE-selective immunoadsorption

Relative changes in IgM, IgG1, IgG2, IgG3, and IgG4 levels as determined by ELISA (mean±SD) before and after each cycle of IgE-specific IA.

Figure S2: Severity Scoring of Atopic Dermatitis

Before each IA cycle and after ~1 and 3 months treatment, the SCORAD (Severity Scoring of Atopic Dermatitis) was determined. SCORAD total score as well as pruritus and insomnia results are shown. Data are shown as absolute values and as relative change compared to baseline (week 0). Statistical differences compared to baseline were calculated using the Bonferroni test (**=p≤0.01, ***=p≤0.001).

Figure S3: IgE-specific immunoadsorption: comparison of treatment efficacy between patients with high and low IgE levels

The clinical response scores (SCORAD and EASI) and quality of life (DLQI) of 7 patients with high IgE levels (>5,000 kU/l, first 7 patients in Table S2) in comparison to 5 patients with lower IgE levels (<2,500 and >1,000 kU/l, last 5 patients in Table S2) are presented. Data are shown as absolute values and as relative change compared to baseline (week 0). Statistical differences compared to baseline were calculated using the Bonferroni test (*=p≤0.05, **=p≤0.01, ***=p≤0.001).

Supplemental Tables

Table S1: Comorbidities of patients with AD treated with IgE IA

Patient #	Gender	Age (years)	Comorbidities
1	f	47	allergic bronchial asthma multiple allergies arterial hypertension
2	m	17	multiple allergies obesity
3	f	42	allergic bronchial asthma multiple allergies osteopenia ex-nicotine abuse
4	m	55	multiple allergies arterial hypertension hyperuricemia coronary heart disease
5	f	52	hypothyroidism nicotine abuse
6	m	46	allergic bronchial asthma multiple allergies arterial hypertension hyperthyroidism IgA-nephritis
7	m	51	multiple allergies arterial hypertension ex-nicotine abuse
8	f	37	multiple allergies
9	f	52	allergic bronchial asthma multiple allergies cataract Raynaud's syndrome steatosis hepatis
10	f	37	multiple allergies glaucoma chronicum simplex
11	m	32	allergic bronchial asthma multiple allergies chronic conjunctivitis pectus excavatum with scoliosis depression
12	m	33	multiple allergies depression

f= female, m= male

Table S2: Plasma volume, duration of IA and blood flow*

Patient #	Plasma volume (ml)	Duration of IA (hrs)	Blood flow (ml/min)
1	5,306±163	3.37±0.13	69±4.57
2	6,014±33	3.63±0.42	65.25±24.81
3	5,910±914	3.66±1.42	62.57±8.24
4	3,992±903	3.06±0.67	56.25±3.34
5	6,349±790	4.69±0.45	57.78±20.02
6	2,550±134	2.65±0.51	46.78±8.41
7	6,550±1080	4.63±0.53	71.56±6.06
8	6,710±247	5.01±1.19	63.10±6.37
9	544±396	3.97±0.33	61.89±5.85
10	4,895±172	3,71±0.51	58.50±7.28
11	4,563±1057	3.05±0.73	62.87±3.95
12	5,722±1775	3.11±1.98	53.80±22.91

*Two adsorption columns were used per patient, allowing for adsorber regeneration during IA. Anticoagulation was achieved by a bolus injection of 2500 IU of sodium heparin and anticoagulant citrate dextrose, formula A (ACD-A; Baxter, Munich, Germany). In all patients, the median cubital or cephalic veins of both arms were used for venous access, generating a blood flow between 40-90 mL/min. During each IA session, at least the 2-fold plasma volume was processed. In 6 of a total of 120 IA sessions (5%), the procedure was stopped before the 2-fold of the plasma volume was processed because of problems with creating an adequate blood flow/vein access. All values are given as mean±SD.

42 **Table S3: Efficacy of IgE IA with patients sorted by baseline IgE levels**

Patient #	Treatment cycle	Total serum IgE (kU/l)				IgE Reduction (%)				Follow-up Total serum IgE (kU/l)	
		d1 (before)	d1 (after)	d2 (before)	d2 (after)	d1	d2	Per cycle	Per patient in 5 cycles	3-4 weeks	3-4 months
1	1	23,553	6,649	12,083	3,829	72	68	84	83	-	17,612
	2	25,396	6,226	9,686	3,146	75	68	88			
	3	23,911	n.d.	13,366	4,355	n.d.	67	82			
	4	22,872	8,189	11,250	4,903	64	56	79			
	5	20,582	4,843	10,340	3,842	76	63	81			
11	1	18,840	5,858	9,880	2,745	69	72	85	84	31,159	-
	2	19,855	8,564	11,137	3,707	57	67	81			
	3	16,517	7,147	11,052	3,051	57	72	82			
	4	28,594	6,855	12,665	3,492	76	72	88			
	5	24,842	7,811	7,997	3,368	69	58	86			
7	1	18,234	13,058	13,879	7,650	28	45	58	68	20,429	-
	2	16,420	7,998	9,201	4,435	51	52	73			
	3	17,741	7,621	12,283	6,584	57	46	63			
	4	17,779	6,721	8,911	3,899	62	56	78			
	5	16,353	8,570	11,515	5,353	48	54	67			
6	1	11,106	6,095	8,108	2,297	45	72	79	85	7,683	5,555
	2	9,431	2,991	4,173	1,450	68	65	85			
	3	8,737	2,473	4,231	1,011	72	76	88			
	4	10,384	2,15	4,032	1,424	73	65	86			
	5	8,710	2,417	3,524	1,189	72	66	86			
9	1	8,831	4,172	5,350	2,874	53	46	67	67	-	-
	2	8,981	4,458	5,910	2,638	50	55	71			
	3	9,749	4,950	7,469	3,530	49	53	64			
	4	10,144	4,954	5,937	4,158	51	30	59			
	5	10,003	4,805	7,275	2,639	52	64	74			
2	1	6,877	2,159	3,517	1,118	69	68	84	81	8,427	6,199
	2	4,304	2,839	2,985	1,506	34	50	65			
	3	10,138	3,532	4,990	1,452	65	71	86			
	4	7,999	2,247	3,771	1,248	72	67	84			
	5	7,580	2,005	3,344	1,181	74	65	84			
3	1	5,694	1,204	2,630	701	79	73	88	84	-	5,759
	2	5,122	1,458	2,438	1,183	72	51	77			
	3	4,115	1,190	1,884	590	71	69	86			
	4	3,943	1,067	1,981	654	73	67	83			
	5	5,696	1,297	2,702	694	77	74	88			
10	1	2,489	889	1,352	538	64	60	78	81	-	4,065
	2	3,023	788	1,204	430	74	64	86			
	3	2,289	619	1,377	445	73	68	81			
	4	2,726	771	1,505	615	72	59	77			
	5	2,502	783	1,544	436	69	72	83			
12	1	1,524	481	762	255	68	67	83	81	1,158	-
	2	1,335	546	761	271	59	64	80			
	3	1,602	604	841	301	62	64	81			
	4	1,012	385	603	246	62	59	76			
	5	1,233	387	560	179	69	68	85			
5	1	1,509	406	635	171	73	73	89	87	923	934
	2	1,132	310	466	198	73	58	83			
	3	936	250	420	105	73	75	89			
	4	924	246	412	125	73	70	86			
	5	1,010	241	468	138	76	71	86			
4	1	1,352	289	478	86	79	82	94	90	1,261	1,194
	2	1,346	404	564	178	70	68	87			
	3	1,251	326	571	153	74	73	88			
	4	1,050	266	483	134	75	72	87			
	5	1,206	285	450	56	76	88	95			
8	1	1,149	365	591	180	68	70	84	84	-	1,747
	2	1,106	263	475	152	76	68	86			
	3	1,238	269	548	159	78	71	87			
	4	1,075	257	456	139	76	70	87			
	5	1,046	341	660	210	67	68	80			

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45 **Table S4: Efficacy of IgE IA in patients with house dust mite-specific IgE**

Patient #	Treatment cycle	Total serum IgE Reduction (%)		House dust mite-specific IgE Reduction (%)	
		Per cycle	Per patient in 5 cycles	Per cycle	Per patient in 5 cycles
1	1	84	83	49	78
	2	88		90	
	3	82		85	
	4	79		83	
	5	81		81	
2	1	84	81	77	86
	2	65		77	
	3	86		90	
	4	84		90	
	5	84		94	
6	1	79	85	78	88
	2	85		91	
	3	88		95	
	4	86		91	
	5	86		87	
7	1	58	68	56	41
	2	73		30	
	3	63		15	
	4	78		20	
	5	67		83	
10	1	78	81	76	82
	2	86		86	
	3	81		82	
	4	77		78	
	5	83		88	
11	1	85	84	94	87
	2	81		82	
	3	82		84	
	4	88		84	
	5	86		89	

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47 **Table S5: Change in concomitant treatment**

Patient #			Concomitant treatment
1	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None None None Accidental food allergy anaphylaxis, bolus of corticosteroid/antihistamine i.v. None
	Observation	3-4 wks 3-4 mo	- None
2	Treatment	1-5	None
	Observation	3-4 wks 3-4 mo	None None
3	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	Prednisone 10 mg po Prednisone 5 mg po + antihistamine po Topical class II corticosteroid (10 g/wk) None None
	Observation	3-4 wks 3-4 mo	- Prednisone 2.5 mg po
4	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None Dexamethasone for 8 days (total of 48 mg) po Dexamethasone for 10 d (total of 40 mg) po Dexamethasone for 7 d (total of 22 mg) po Dexamethasone for 3 d (total of 6 mg) po
	Observation	3-4 wks 3-4 mo	None None
5	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None Topical class II corticosteroid (5 g/wk) + class III corticosteroid (5 g/wk) Topical class II corticosteroid (5 g/wk) + class III corticosteroid (5 g/wk) Topical class II corticosteroid (5 g/wk) Topical class II corticosteroid (5 g/wk)
	Observation	3-4 wks 3-4 mo	None Topical class II corticosteroid (5 g/wk) + pimecrolimus (5 g/wk)
6	Treatment	1 st - 5 th cycle	None
	Observation	3-4 wks 3-4 mo	None None
7	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None None Topical class III corticosteroid (100 g/wk) None None
	Observation	3-4 wks 3-4 mo	None -
8	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None None None None Desloratadin 5 mg po
	Observation	3-4 wks 3-4 mo	- Desloratadin 5 mg po + Dimetindenmaleat 4 mg po
9	Treatment	1 st cycle 2 nd cycle 3 rd cycle 4 th cycle 5 th cycle	None Prednisone 5 mg po for 3 days None None None
	Observation	3-4 wks 3-4 mo	- -
10	Treatment	1 st - 5 th cycle	None
	Observation	3-4 wks 3-4 mo	- None
11	Treatment	1 st - 5 th cycle	None
	Observation	3-4 wks 3-4 mo	None -
12	Treatment	1 st - 5 th cycle	None
	Observation	3-4 wks 3-4 mo	None -

48 -= not recorded, po= per os, iv= intravenous

49 Baseline therapy with emollient was recommended for all patients at all times.

