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CLINICAL REPORT

Targeting IgE in Severe Atopic Dermatitis with a Combination of Immunoadsorption and Omalizumab

Alexander ZINK[1–3], Anna GENSBAUR[1], Michael ZIRBS[1], Florian SEIFERT[1], Isabel LEON SUAREZ[1], Vagkan MOURANTCHANIAN[1], Stephan WEIDINGER[4], Martin MEMPEL[1,5], Johannes RING[1,2,5] and Markus OLLERT[1,5]

[1]Department of Dermatology and Allergy, [3]Institute of Environmental Medicine, Klinikum rechts der Isar, Technische Universität München (TUM), Munich, Germany, [2]Christine Kühne Center for Allergy Research and Education (CK-CARE), Davos, Switzerland, [4]Department of Dermatology, University of Kiel, Kiel, and [5]Center of Allergy and Environment (ZAUM), Technische Universität München (TUM) and Helmholtz Center Munich, Munich, Germany

Patients with atopic dermatitis (AD) tend to have greatly elevated levels of serum immunoglobulin E (IgE). However, the role of IgE in the pathogenesis of AD is debated. This investigator-initiated open-label pilot study evaluates an anti-IgE-treatment approach by combining extracorporeal immunoadsorption and anti-IgE antibody omalizumab in 10 patients with severe, therapy-refractory AD. IgE levels decreased after immunoadsorption and decreased continuously in all patients during anti-IgE therapy. The reverse trend was observed during 6 months follow-up without treatment. In parallel with these observations, an improvement in AD was observed during the treatment period, with aggravation during follow-up. Further research is needed, based on the principle of reducing IgE levels in order to improve clinical symptoms, using a combination anti-IgE treatment approach, adjusted according to IgE levels. ***Key words: atopic dermatitis; atopic eczema; immunoglobulin E; IgE; immunoadsorption; omalizumab; anti-IgE-treatment.***

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Alexander Zink, Department of Dermatology and Allergy, Technische Universität München (TUM), Biedersteiner Str. 29, DE-80802 Munich, Germany. E-mail: zink@lrz.tum.de

Atopic dermatitis (AD, atopic eczema) affects 20–30% of children and 5–10% of adults in industrialized countries (1, 2). AD is associated with concomitant allergic diseases, reduces health-related quality of life, and leads to considerable economic burden. AD was first noted by Roman historian Suetonius in Emperor Octavian Augustus, but it was not described fully until the 19th century (3). There is no uniformly satisfactory treatment for patients who are severely affected by the disease. Typically, these patients tend to have greatly elevated levels of immunoglobulin E (IgE) (1). However, the role of IgE in the pathogenesis of AD is not completely understood. Studies of treatment with the anti-IgE antibody omalizumab have had ambivalent results (4–10). The IgE levels in many patients with AD are above the level at which an appropriate dose for omalizumab is applicable.

The aim of the current study is to determine whether it is possible to substantially reduce elevated IgE levels in AD patients through immunoadsorption, followed by appropriate use of omalizumab, and whether this sequential treatment has clinically beneficial results. To monitor the clinical development of AD, we used the Scoring Atopic Dermatitis (SCORAD) index (11) and measurement of Thymus and Activation Regulated Chemokine (TARC/Human CCL17) levels, which is established as an objective parameter for disease severity in AD (12, 13).

METHODS

This investigator-initiated, open-label pilot study evaluated 10 patients with severe AD (SCORAD > 50) and greatly elevated IgE levels (> 3,500 kU/l) refractory to at least 2 conventional systemic treatment options, with a wash-out period of at least 3 months prior to inclusion in the study. Importantly, if omalizumab had been used previously, the interval free of omalizumab had to be more than 6 months. All patients were over 18 years of age and provided written informed consent. Patients with systemic infections, bleeding disorders, or allergies to the study material were excluded from the study. The study was approved by the local ethics committee and the national regulatory agencies, and registered with the EU Clinical Trials Register (EudraCT- number 2009-014582-51). Diagnoses were made by an experienced dermatologist based on clinical signs and symptoms, laboratory findings and personal and family history. Informed consent, inclusion and exclusion criteria were assessed carefully at a screening visit, which was followed by the start of treatment (week 1) within a maximum of 7 days.

Immunoadsorption and omalizumab

All patients first underwent immunoglobulin apheresis (immunoadsorption) depending on their respective baseline IgE levels, before starting treatment on 2 (IgE level < 6,000 kU/l), 3 (IgE level 6,000–20,000 kU/l) or 4 (IgE level > 20,000 kU/l) consecutive days, in order to reduce IgE levels as much as possible, followed by regular administration of the anti-IgE-antibody omalizumab every 2 weeks for 24 weeks. After this treatment period, the patients were followed up bi-weekly for another 24 weeks (Fig. 1). For immunoadsorption, the LIFE 18 Ig-flex TheraSorb apheresis system (Miltenyi Biotec, Germany) was used, which has adsorption columns containing polyclonal sheep antihuman immunoglobulin antibodies and binds the different human immunoglobulins, including IgE, with similar affinity. Within 20–60 min of completing the immunoadsorption setting, omalizumab was administered every 2

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weeks by subcutaneous injections at a dose of 450 mg (Fig. 1). Omalizumab is a recombinant DNA-derived IgG1 humanized (from mouse) monoclonal antibody selectively binding to human IgE and approved by the FDA and international regulatory agencies for patients with severe allergic asthma and, recently, for chronic spontaneous urticaria (14–16). Besides therapy with immunoadsorption and omalizumab, the patients were not allowed to receive any other systemic medications for their AD. Topical treatments, such as skin care emollients or mild topical glucocorticoids (potency class I defined for European countries), had to be documented if used.

Clinical and laboratory assessment

Clinical presentation was evaluated with the SCORAD index (11) by an experienced dermatologist and with a visual analogue scale (VAS) ranging from 0 ("free of symptoms") to 100 ("worst case") for the subjective severity of AD by the patients themselves. IgE and TARC levels were measured for further evaluation. On every visit, biologically active IgE (free IgE) and TARC were quantified according to standardized protocols (R&D Systems, Abingdon, UK) (17, 18), the severity of AD was documented with the SCORAD index, and the patient's personal evaluation on the VAS and standardized photographs were taken. According to the manufacturer of the system used, normal TARC levels in apparently healthy adults range from 71 to 848 pg/ml. Total IgE was determined using the ImmunoCAP system (ThermoFischer/Phadia, Freiburg, Germany). Free IgE levels were determined in a lateral flow system (Milenia Biotech, Giessen, Germany) using a chimeric molecule based on the fusion of the human FcεR1a and avian immunoglobulin IgY (17). All statistical analysis was performed using SPSS Statistics v.19.0 (IBM Corp., Armonk, NY, USA).

The primary end-point of the study was a free IgE level below 150 kU/l, i.e. within the normal range for healthy adults without allergic diseases. Secondary end-points were a free IgE level below 1,000 kU/l, a reduction in TARC levels, and a clinical benefit for the patients measured with SCORAD and VAS.

RESULTS

Characteristics of the patients

From April 2010 to December 2011, 10 patients who had previously unsuccessfully undergone 2–4 different continuous systemic treatments were enrolled in the study. Their baseline characteristics are shown in Table I. There were 2 females and 8 males, age range 26–65 years (mean ± standard deviation (SD) 43.7 ± 11.2 years). Nine of 10 patients had allergic rhinitis, 7 of 10 patients had asthma. Serum levels of total IgE were in the range 3,728–69,872 kU/l (mean ± SD 18,094 ± 19,573 kU/l). At the time of enrollment, all patients had a SCORAD value above 50, internationally recognized as "severe" disease. In detail, SCORAD values ranged from 50.2 to 74.6 (mean ± SD 59.9 ± 8.4). Baseline VAS ranged from 20 to 90 (56 ± 26.6) (Table I).

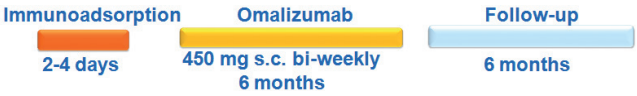

Fig. 1. General study design.

IgE during immunoadsorption

During immunoadsorption IgE levels were found to be reduced in all patients. Depending on their baseline total IgE levels, 3 patients underwent immunoadsorption on 2 consecutive days, 5 patients on 3 consecutive days and 2 patients on 4 consecutive days. Mean ± SD IgE levels after the first day of immunoadsorption were 10,567 ± 9,393 kU/l, and 7,537 ± 5,716 kU/l after the second day. Where applicable, IgE levels were 6,933 ± 3,821 kU/l (mean ± SD) after 3 days of immunoadsorption and 2,606 ± 1,728 kU/l after 4 days. After completion of the respective last day of immunoadsorption, IgE levels were in the range 1,384–14,380 kU/l (4,927 ± 4,243 kU/l), and had thus reduced by 25.1–94.5%. Mean total IgE levels after immunoadsorption were 36 ± 23% of the respective values before immunoadsorption.

IgE during omalizumab and follow-up

During the bi-weekly administration of omalizumab, levels of biologically active IgE fell continuously,

Table I. *Baseline characteristics of patients enrolled in the study*

Patient	Age, years/sex	Diagnosis			Prior systemic treatments	Total IgE (kU/l)	SCORAD (screening)	VAS severity (0–100)	TARC (pg/ml)
		Atopic dermatitis	Allergic rhinitis	Asthma					
1	65/M	Yes	Yes	No	GCs, UVA	13,989	54.3	20	1,035
2	50/F	Yes	Yes	Yes	GCs, UVA, CyA, OMZ	24,494	74.6	90	3,730
3	31/M	Yes	Yes	Yes	GCs, UVA, CyA	19,413	73.9	45	410
4	35/M	Yes	No	No	GCs, UVA	3,728	62.0	70	355
5	40/M	Yes	Yes	No	GCs, UVA, CyA	3,894	54.3	55	2,278
6	49/M	Yes	Yes	Yes	GCs, UVA, CyA	6,802	61.0	30	1,955
7	26/M	Yes	Yes	Yes	GCs, UVA, CyA, MTX	15,059	55.5	90	2,146
8	48/F	Yes	Yes	Yes	GCs, UVA, CyA, OMZ	69,872	50.2	20	3,279
9	45/M	Yes	Yes	Yes	GCs, UVA, CyA, OMZ	5,337	53.0	90	3,800
10	48/M	Yes	Yes	Yes	GCs, UVA, CyA	18,354	60.1	50	2,379

GCs: glucocorticoids; UVA: phototherapy with ultraviolet UVA-1; CyA: cyclosporin A; OMZ: omalizumab; MTX: methotrexate; SCORAD: clinical index SCORing atopic dermatitis (0–103: <25=mild AD, 25–50=moderate AD, >50=severe AD); TARC: Thymus and Activation Regulated Chemokine (TARC/Human CCL17); VAS severity: severity of atopic dermatitis marked by patients on a visual analogue scale ranging from 0 ("free of symptoms") to 100 ("worst case"). Last systemic treatment had to be completed at least 3 months (GCs, UVA, CyA, MTX) or at least 6 months (OMZ) prior to study inclusion.

reaching free IgE-levels < 150 kU/l in 5/10 and < 1,000 kU/l in 9/10 patients in the 24 weeks of treatment. After stopping the regular application of omalizumab, free IgE levels increased again during follow-up, starting in week 25, reaching individual levels in week 49 similar to pre-study values (Fig. 2). In parallel with the free IgE levels, a clinical improvement in AD was observed during the treatment period and an aggravation of AD during follow-up.

SCORAD and VAS

Just before initiating sequential anti-IgE therapy, the SCORAD was 62.0 ± 11.6 (mean ± SD). Two weeks after immunoadsorption, a first reduction in SCORAD was observed in all 10 patients, with a mean ± SD SCORAD of 43.7 ± 9.9 in week 3. Throughout the treatment period, the mean ± SD SCORAD continued to decrease, with a value of 35.6 ± 13.2 in week 13 ($p < 0.01$) and 27.2 ± 12.0 in week 25. A reverse trend occurred during follow-up, and on the last visit of our study (week 49) mean ± SD SCORAD was 48.7 ± 15.9 (Fig. 2). Individual SCORAD is shown in Table II. In parallel with SCORAD a continuous decline in the subjective severity of AD measured with VAS was seen throughout the treatment period (40.5 ± 14.8 in week 13 and 37.9 ± 18.9 in week 25) ($p < 0.05$). Interestingly, VAS values reached almost identical levels during follow-up without treatment in week 49 (56.7 ± 24.6) compared with baseline VAS before starting treatment (56.0 ± 26.6).

Two patients dropped out due to acute exacerbation despite anti-IgE therapy in weeks 15 and 17, but were included in the follow-up. Despite an initial clinical improvement under sequential anti-IgE treatment until week 13, 1 patient was excluded due to lack of compliance in week 15 and absence from follow-up examinations.

Table II. *Clinical symptoms of atopic dermatitis (AD) (SCORAD; SCORing Atopic Dermatitis Index) over the study period*

	Before IA	Administration of omalizumab (bi-weekly)			Follow up (bi-weekly)
Pat. No.	Week 1	Week 3	Week 13	Week 25	Week 49
1	54.3	35.0	28.9	Drop out	45.2
2	74.6	49.1	48.2	Lost	Lost
3	73.9	47.5	36.0	Drop out	68.3
4	62.0	52.5	22.3	15.4	30.4
5	54.3	32.0	48.5	39.6	29.0
6	61.0	39.7	16.1	12.3	41.4
7	55.5	52.6	52.8	45.8	74.7
8	50.2	29.6	44.8	28.6	37.7
9	53.0	61.6	42.8	32.7	70.8
10	60.1	37.5	16.0	16.3	40.7
Mean ± SD	59.9 ± 8.4	43.7 ± 9.9	35.6 ± 13.2	27.2 ± 12.0	48.7 ± 15.9

IA: immunoadsorption, SD: standard deviation.

TARC

Consistent with the development of the SCORAD index, TARC levels decreased during anti-IgE treatment, from mean ± SD 2,136 ± 1,187 pg/ml in week 1 before immunoadsorption to 1,410 ± 691 pg/ml in week 25 ($p < 0.01$), and increased again during follow-up, with a mean ± SD value of 1,748 ± 1,131 pg/ml in week 49 (Fig. 3). It is notable that an initial slight increase in TARC values was seen in the first weeks after immunoadsorption.

Adverse events

During the study temporary dizziness was observed during immunoadsorption in 1 patient and 2 of 10 patients reported fatigue on the days following immunoadsorption. Further adverse events were registered in 4/10 patients during treatment with omalizumab: 1 patient reported headaches, 1 reported a slight pain in the upper right abdomen, axillary lymph node swellings

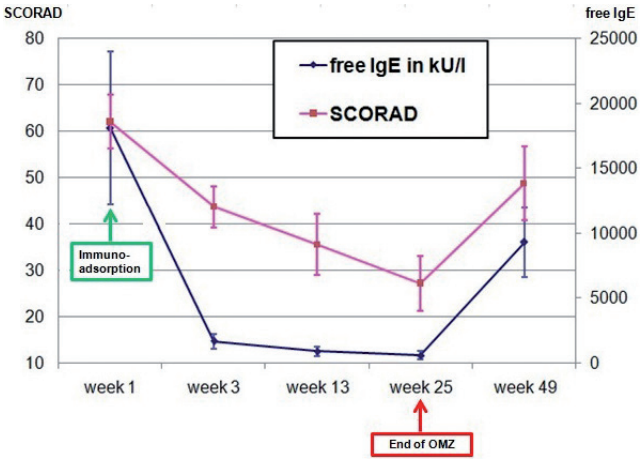

Fig. 2. Mean SCORAD (SCORing Atopic Dermatitis Index) and free immunoglobulin E (IgE) levels in the course of study with standard deviations before immunoadsorption (week 1), during (weeks 3 and 13), and at the end of treatment with omalizumab (OMZ) (week 25) as well as after follow-up; $n = 10$ patients.

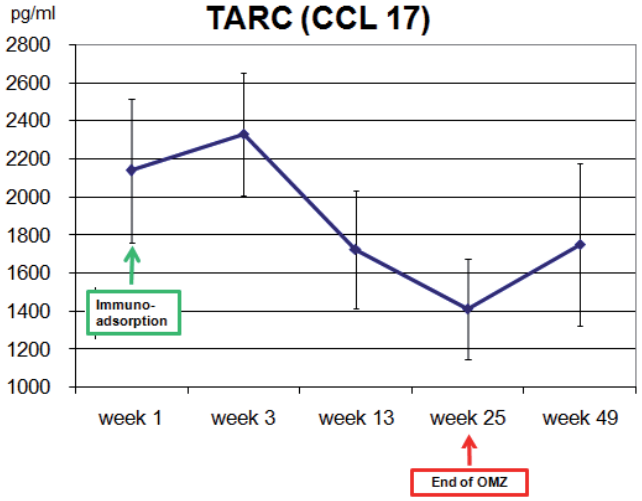

Fig. 3. Mean Thymus and Activation Regulated Chemokine (TARC/Human CCL17) levels with standard deviations before immunoadsorption (week 1), during (weeks 3 and 13) and at the end of treatment with omalizumab (OMZ) (week 25) as well as after follow-up; $n = 10$ patients.

were noticed in 1 patient and 3 patients had elevated liver enzymes (aspartate aminotransferase in 3/3, maximum 114 U/l; alanine aminotransferase in 2/3, maximum 83 U/l; gamma-glutamyl transaminase in 3/3, maximum 274 U/l). All adverse events ceased and normalized spontaneously without medical interference. No other adverse events, e.g. infections, were seen.

DISCUSSION

These findings suggest that free IgE can be reduced through immunoadsorption prior to treatment with omalizumab, and that a therapeutically lowered free IgE-level has a clinical benefit in severe AD. These findings shed light on the role of IgE in the pathogenesis of some forms of AD.

Despite some variability in the reduction in IgE between individual patients, total IgE could be reduced via immunoadsorption in all patients, as seen previously (19). After the initial reduction in total IgE levels by immunoadsorption, free IgE levels continued to fall during regular administration of omalizumab and began to increase again during follow-up after anti-IgE therapy was stopped. These results were paralleled by TARC levels, which have previously been shown to correlate with disease severity in AD (12, 13). In parallel with free IgE levels, a clinical improvement in AD was observed during treatment and an aggravation of the skin disease during follow-up (Fig. 2, Fig. S1[1]), which suggests that IgE plays a role in the pathogenesis and disease "activity" of AD.

A few studies have used omalizumab and one study has used immunoadsorption alone in AD. Whereas the latter resulted in a temporary clinical benefit after significant reduction in IgE levels in AD (19), studies with omalizumab typically had very ambivalent results: some showed a benefit for patients with AD (4, 5), some rejected this treatment approach (6, 7) and others discussed the high IgE level in AD as a possible limitation for a promising use of this anti-IgE antibody (8–10). Bearing in mind that omalizumab "inactivates" IgE by building immune complexes based on a molecular ratio (20), it cannot be excluded that the dose of omalizumab used in the studies mentioned above was insufficient to lower biologically active IgE enough to have a clinical benefit.

By initially reducing IgE with immunoadsorption, we assume that we reached a condition with a more appropriate stoichiometric molar ratio between IgE and omalizumab. This enabled the drug to release its known anti-IgE effect, seen in the continuous fall in biologically active IgE in our pilot study during the administration of omalizumab, associated with the observed clinical benefit. After stopping the anti-IgE treatment, biologically active IgE increased again within weeks, as did the SCORAD and VAS with worsening eczema. This further suggests an association between IgE and AD severity in at least some patients. It is believed that there are different types (21) or phases (1) of AD with differing elevations of IgE; some might be even influenced by IgE autoantibodies (22, 23). Our results suggest that some of these AD forms, e.g. patients with severe AD and grossly elevated IgE levels, may be treated successfully with an IgE-targeted approach. In the context of up to 40% of placebo-induced clinical improvement in patients with AD enrolled in clinical trials (3, 4), the findings of our pilot study with only a limited number of patients merit further evaluation. In addition, the high cost of immunoadsorption (24) and omalizumab (25) therapy limit their widespread use and currently justify a respective treatment only in patients with severe recalcitrant AD.

The adverse events experienced in our study were all expected, except the elevation of liver enzymes during omalizumab therapy in 3 out of our 10 patients, which is not a typical side-effect of omalizumab. Several previous publications have described a possible transfer of the donor's IgE-mediated allergies to the recipient of liver transplants (26–28) and, although this phenomenon cannot yet be explained clearly, an involvement of the liver in IgE-mediated allergies is suggested (29, 30). However, the lowering effect of our study treatment on IgE could also affect several aspects of cellular immunology, including the liver.

In conclusion, sequential anti-IgE treatment, combining immunoadsorption and omalizumab in severe refractory AD with highly elevated levels of IgE, appears to have an effect on IgE levels and a clinical benefit for the patients. To the best of our knowledge, this is the first study to combine immunoadsorption and omalizumab in treatment of AD. Due to the limited number of patients and the open-label design, further studies are needed to strengthen the results of this pilot study, and our hypothesis that IgE might play an important role in the pathogenesis of patients who are severely affected by AD.

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