

Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course – a randomized, placebo-controlled and double blind pilot study

Peter Maximilian Heil¹, Dieter Maurer¹, Brigitte Klein¹, Thomas Hultsch^{2,3}, Georg Stingl¹

(1) Division of Immunology, Allergy and Infectious Diseases, Department of Dermatology, Medical University of Vienna, Austria

(2) Department of Dermatology, University Mainz, Germany

(3) Novartis Pharmaceuticals, New Jersey, USA

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- IgE depletion

Summary

Background: Our understanding of the pathogenic role of IgE in atopic dermatitis is incomplete. We asked whether blocking free IgE would alter the course of the disease.

Patients and Methods: We administered either omalizumab, a humanized monoclonal mouse antibody against IgE, or placebo subcutaneously for 16 weeks to 20 atopic dermatitis patients and measured immunological and clinical disease parameters.

Results: Omalizumab (I) reduced free serum IgE, (II) lowered surface IgE and FcεRI expression on different peripheral blood mononuclear cells, (III) reduced the saturation of FcεRI with IgE, (IV) increased the number of free FcεRI and (V) lowered the number of IgE+, but not of FcεRI+ cells in skin. The in vivo relevance of these results is evidenced by the increase in the threshold allergen concentration required to give a type I hypersensitivity reaction in the titrated skin test. While not significantly altering the clinical disease parameters, omalizumab treatment led to an improvement of the atopy patch test results in single patients, i.e. an eczematous reaction upon epicutaneous allergen challenge.

Conclusions: The interference with immediate and delayed type skin tests may imply that a therapeutic benefit of omalizumab treatment, if present at all, would be seen in patients with acute rather than chronic forms of the disease.

Introduction

Atopic dermatitis (AD) is an eczematous, genetically predisposed and intensely pruritic skin disease. Despite its high prevalence, our pathogenetic understanding of AD remains incomplete. This is particularly true for the role of IgE in the disease process.

Allergen-induced crosslinking of mast cell/basophil-bound IgE and subsequent release of preformed mediators such as histamine are the causative events of type I allergies such as acute allergic

asthma and allergic rhinoconjunctivitis. If a similar mechanism were operative in the pathogenesis of AD, the clinical picture would be dominated by type I reactions (i.e. urticaria and angioedema) rather than by eczema. Following this reasoning, one could argue that hyperimmunoglobulinemia E, while being a valuable diagnostic tool, may be of little, if any importance in the evolution of AD. On the other hand, evidence that favors an involvement of IgE in disease pathogenesis came from the finding of

sizable numbers of IgE-bearing cells in AD lesions. Interestingly, they not only consist of mast cells and basophils, but also include DCs, and all these cell populations bind IgE via high-affinity receptors (FcεRI) which is the predominant IgE-binding structure in the skin of atopic dermatitis patients [1]. Ex vivo evidence exists [2] that allergen presentation to primed T cells is much more effective when the allergen is being presented via FcεRI-bound allergen-specific IgE rather than in its native form.

Table 1: Baseline characteristics of the two treatment groups.

	omalizumab (n=13)	placebo (n=7)	p-value
Median age (range)	30.0 (18.0-47.0)	26.0 (18.0-43.0)	-
Gender male female	5	1	-
	8	6	-
Baseline serum IgE values (ng/mL; mean; free=total)	372.78	281.86	0.22
Standard Deviation	205.37	116.24	
Investigator's global assessment (mean baseline scores)	2.92	2.71	0.46
Medical history of allergic asthma	2	1	-
Medical history of allergic rhinitis	10	5	-

This explorative study was designed to investigate the in vivo significance of these in vitro data.

For this purpose, we used omalizumab (RhuMab-E25; Xolair®) which is a non complement-fixing, recombinant humanized monoclonal antibody (IgG1) against the Cε3 domain of IgE regardless of its antigen specificity. Due to the fact that Cε3 constitutes part of the FcεR binding site of IgE, only non receptor-bound IgE is recognized by omalizumab. It is well established that omalizumab lowers serum levels of free IgE and subsequently decreases FcεRI expression on basophils [3], mast cells [4] and dendritic cells [5].

Clinically, omalizumab has been shown to express a good safety and efficacy profile in subjects with allergic asthma, rhinitis or food allergy [6–8]. This holds additionally true for its use in specific immunotherapy to minimize the risk of allergic type I reactions [9].

There are also data indicating that omalizumab inhibits late-phase reactions and inflammatory cell infiltration in skin after repeated iatrogenic cutaneous allergen challenge of airway-atopic individuals [10].

We investigated the effects of s.c. administered omalizumab and a vehicle control on the expression of IgE and its receptors on cells and on serum components of AD patients. Additionally, we clinically explored whether omalizumab would revert preexisting lesions in patients with long lasting and ongoing AD. By doing so, we hoped to extend our knowledge of omalizumab-induced immunological and clinical effects in general and to systematically address its impact on AD in particular.

Materials and Methods

This explorative single center, 2:1-randomized, placebo-controlled, double blind mechanistic study enrolling 20 patients

(13 omalizumab, 7 placebo) aged between 18-47 years (Table 1, Figure 1) was performed in accordance with the Declaration of Helsinki. All patients gave their written, informed consent. The study was approved by the ethical committee of the Medical University of Vienna (number 501/2000) and is registered with ClinicalTrials.Gov (NCT 00822783).

Inclusion criteria: male and female patients aged between 12 and 60 years; clinical diagnosis of AD (criteria of Hanifin and Rajka [11]); serum IgE between 30 and 1300 IU/ml; at least one significantly positive CAP; a positive skin prick test of the same specificity as the CAP; an Investigator's Global Assessment Score ≥ 2 at randomization; stable AD, as defined as active AD (IGA ≥ 2) for > 9 months per year; signed informed consent. Exclusion criteria: medications or any other circumstances (e.g. poor compliance, concurrent skin disease) that might interfere with the outcome of the study.

All patients fulfilled the inclusion and did not meet the exclusion criteria. All study personnel and patients were blinded to treatment assignment; study drug preparation was provided by a person who was not in contact with the patients.

At the randomization visit, patients were randomized by allocating them to the next blinded treatment kit in the sequences of their inclusion. Patients received either omalizumab (treatment group A) in a dose of 0.016 mg/kg/IgE [IU/ml] per 4 weeks or placebo (treatment group B) subcutaneously.

The study consisted of three periods and was performed regardless of the pollen season:

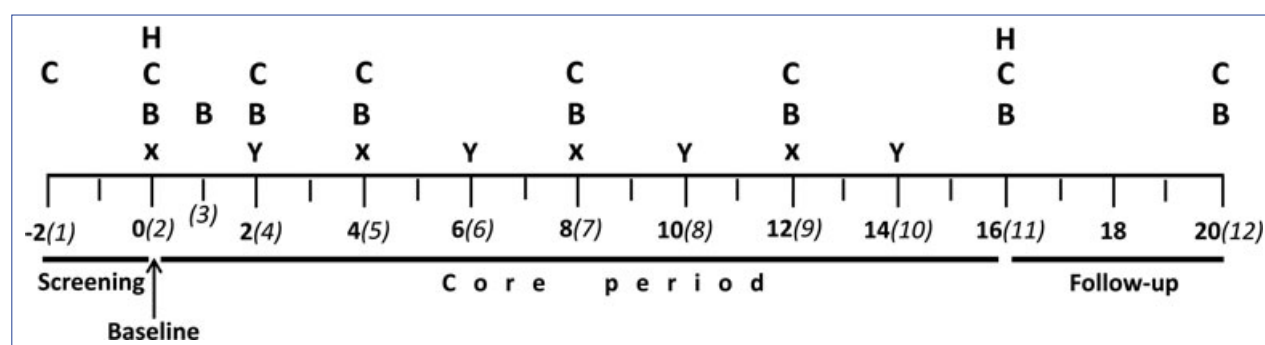


Figure 1: Study flow: upright numbers indicate weeks; cursive numbers indicate visits. Dependent on bodyweight and serum IgE levels dosis per 4 weeks was administered every second (Y) or fourth (X) week. B = blood sampling; C = assessment of clinical parameters; H = Histology (biopsy).

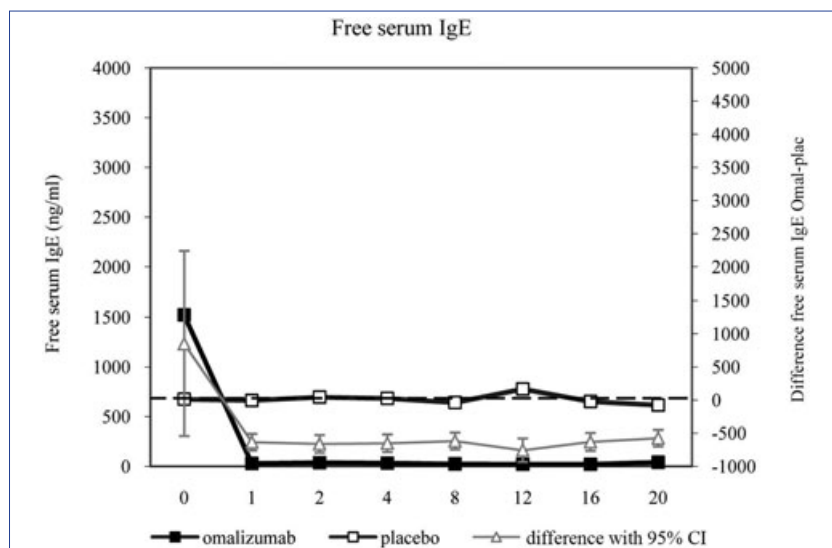


Figure 2: The effect of omalizumab treatment on mean free serum IgE levels (ng/ml). Left y-axis: IgE levels; Right y-axis: differences of the IgE levels between the two treatment groups. The horizontal grey line displays these differences. The vertical grey lines show the 95 % confidence intervals. X-axis: treatment period (weeks).

1) Screening and run-in period (2 weeks).

Patients were allowed to use emollients and hydrocortisone acetate 1 % cream only. At the end of this period, all baseline measurements including the first skin biopsies (lesional and normal appearing skin) were performed and patients were randomized.

2) Core period (16 weeks). Patients were treated with omalizumab or placebo. At the end of this period, patients underwent skin testing and a second double of biopsies. Patients were allowed to use emollients, hydrocortisone acetate 1 % cream and diflucortolon valerate 0.1 % cream. Other therapies that should not have been used included systemic corticosteroids, antihistaminics, antibiotics, immunosuppressants, cytostatics, tranquilizers, hypnotic agents, tricyclic antidepressants and UV-therapy.

3) Follow-up period (4 weeks). Patients were allowed to use emollients and hydrocortisone acetate 1 % cream.

The primary endpoints were defined as changes of immunological disease parameters assessed throughout the study: flow-cytometry, immunohistology and the measurement of serum IgE levels. The secondary endpoints were changes of skin tests (skin prick test, titrated skin prick test, atopy patch test) and the clinical course of the disease assessed by the Investigator's Global Assessment (IGA), the eczema and severity index (EASI) score and the investigator's pruritus severity assessment (IPSA).

Statistical methods

All data analysis was carried out according to a pre-established analysis plan and performed by Biometrical Practice BIOP AG, Basel; Version 8.2 of SAS was used. The sample size was small (20 patients), allowing for intensive monitoring. Beyond the specific mechanistic aspects of the study design, this trial was built on proven elements of a large number of omalizumab studies in related indications (allergic asthma, allergic rhinitis) where safety and efficacy of omalizumab had been demonstrated. All randomly assigned participants (omalizumab: placebo ratio 2:1) were included in the analysis of all parameters (intention-to-treat analysis): there were no drop-outs. For continuous variables the following summary statistics were calculated: mean, standard deviation, median, interquartile range, range. For discrete variables the following summary statistics were calculated: number of values in each category, percentage in each category given the total number of non-missing values for that variable.

All confidence intervals in this report are two sided and use a Type I error rate of $\alpha = 5\%$. Skin prick test, titrated skin prick test, EASI, immunohistochemistry: in order to identify any differences between the treatment groups, 95 % confidence intervals were also constructed for each treatment group on the absolute change to baseline values. Similarly, confidence intervals were constructed on the

geometric mean differences between the treatment groups.

Total/free IgE. Total IgE levels (including IgE-omalizumab complexes) were measured in both treatment groups at all visits. After starting omalizumab therapy or placebo (= at visits 3, 4, 5, 7, 9, 11 and follow-up) also free IgE levels were determined.

Flow-cytometry analysis

Immunophenotyping of peripheral blood mononuclear cells was performed shortly after venipuncture at baseline (week 0) as well as at weeks 1, 2, 4, 8, 12, 16 and 20.

Heparinized blood samples (40 ml) were collected by venipuncture and subjected to Ficoll-Hypaque (Pharmacia) density gradient centrifugation. Thus isolated, mononuclear cells were washed in phosphate buffered saline and subjected to immunostaining. Half of each mononuclear cells sample was subjected to lactate-buffer treatment ("stripping", [12]) prior to the mAb staining protocol in order to elute surface-bound IgE.

Used antibodies: BDCA-1 (=CD1c, Miltenyi Biotec); CD19/CD123 (=anti IL-3 α receptor)/HLA-DR (BD Biosciences); anti-Fc ϵ RI α mAb 15-1 ([13]; our own laboratory); chimeric human IgE (Serotec); anti-IgE mAb (Southern Biotechnologies); anti-Fc ϵ RII mAb (BD Biosciences). Control staining (anti-TCR mAb, BD Biosciences).

Surface-bound IgE: results were obtained from staining of non-stripped cells with anti-IgE. Total Fc ϵ RI/total IgE-binding capacity: staining of lactate-buffer treated cells with anti-Fc ϵ RI and cIgE antibodies, respectively. Free Fc ϵ RI/free IgE-binding capacity: staining of non lactate buffer-treated cells with anti-Fc ϵ RI and cIgE antibodies, respectively. Fc ϵ RI saturation/IgE saturation: calculated using results of free and total Fc ϵ RI/free and total IgE-binding capacity, respectively; formula: $100 - (\text{MFI}_{\text{non-stripped cells}} / \text{MFI}_{\text{stripped cells}}) \times 100$.

Immunohistochemistry of lesional skin biopsies. Frozen tissue sections obtained from lesional skin before (visit 2) and after (visit 11) therapy with omalizumab or placebo were stained with anti-CD1a/anti-CD32/anti-CD54(=ICAM1)/anti-CD207(=DC-Langerin)/anti-CD208(=DC-lamp): all Beckmann Coulter Immunotec; anti-CD4/anti-CD23/anti-CD80/anti-CD86: (all Dako); anti-CD40 (Serotec), anti-HLA DR (BD

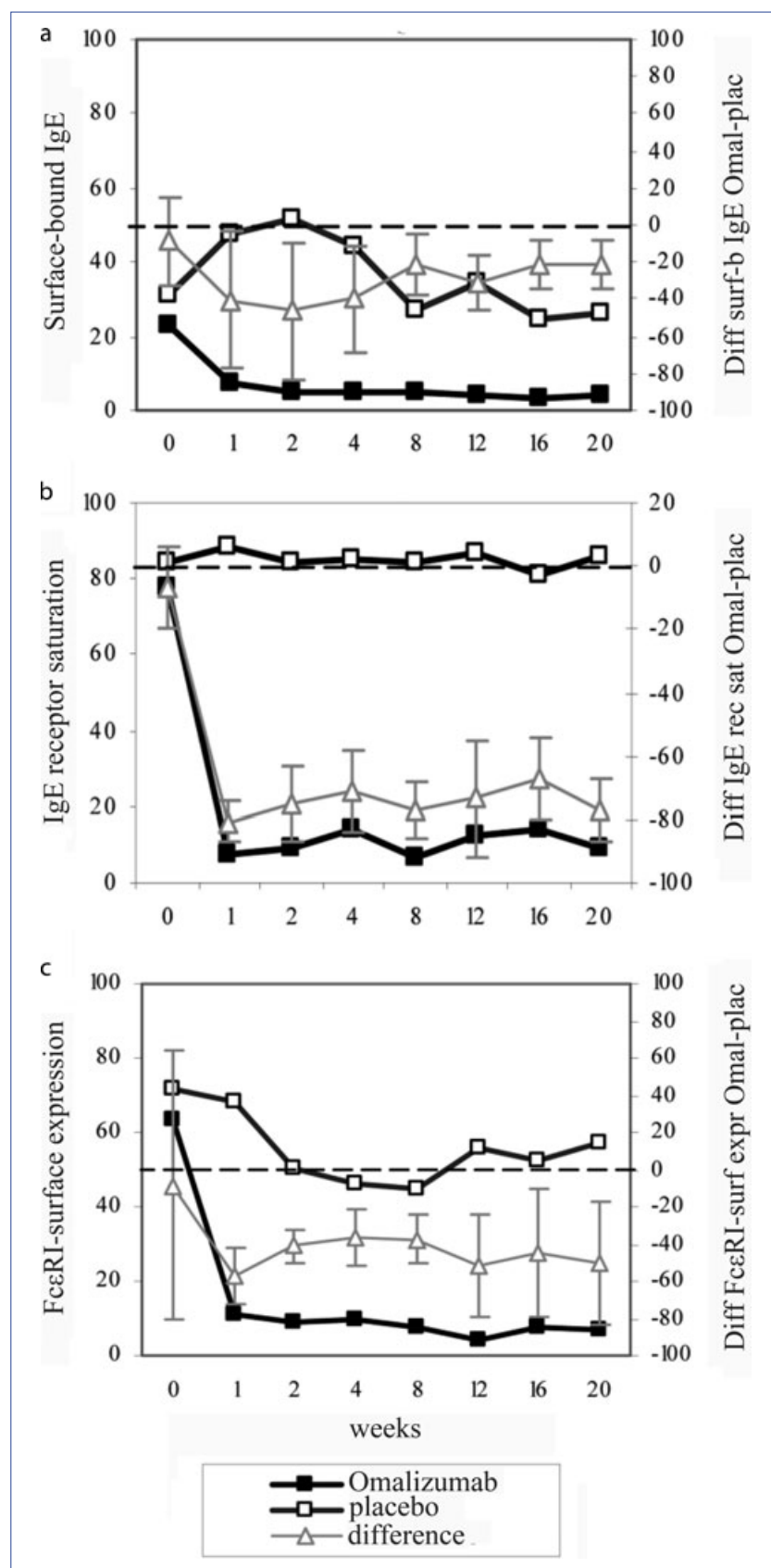


Figure 3: Flow-cytometry analysis pDC: effect of omalizumab treatment on mean fluorescence intensity. Left y-axes: (a) surface-bound IgE, (b) IgE receptor saturation (cIgE staining) and (c) total FcεRI expression; right y-axes: (a) difference surface-bound IgE omalizumab-placebo (Δ MFI), (b) difference IgE receptor saturation omalizumab-placebo and (c) difference total FcεRI expression omalizumab-placebo; x-axes: treatment period (weeks); — = 0.

Biosciences), anti-IgE (Southern Biotechnologies) and anti-FcεRI ([13]; our own laboratory). The number of positive cells per mm epidermis and mm² dermis was determined.

Lead allergen: Lead allergens were defined as those allergens to which patients showed positive reactions in skin prick test and immunoCAP.

Skin prick test: At screening and the end of study, skin prick tests were performed. Wheal sizes were recorded after 20 minutes.

Titrated skin prick test: The lead allergen was tested in serial dilutions (1:1 – 1:128). Wheal sizes were recorded after 20 minutes.

Atopy patch test (scale: no-or-doubtful/weak+/strong+/extremely+reaction): Lead allergens were applied occlusively on the upper arm. Redness and infiltration of the skin were documented after 48 hours.

IGA Scale: clear (1)-almost clear (2)-mild (3)-moderate (4)-severe (5)-very severe (6): The IGA provides an overall impression of the subject's disease state.

EASI-score: Head and neck, trunk, upper limbs and lower limbs were assessed separately for erythema (E), infiltration (I), excoriation (Ex) and lichenification (L). The average degree of severity of each sign in each of the four body parts was assigned a score of 0-3 indicating none (0), mild (1), moderate (2) and severe (3). **IPSA:** Pruritus within 24 hours prior to each assessment was assessed using a 4-point score (0-3): absent (0), mild (1), moderate (2) and severe (3).

Adverse events (AEs)

There were no deaths and no serious AEs. All patients completed the study, there were no AE-related discontinuations. 14 out of 20 patients reported 19 AEs in 16 categories; 10 patients in the omalizumab group (injection site reaction, vertigo, headache, migraine, pruritus, blepharitis, tonsillitis, herpes simplex labialis, pharyngolaryngeal pain, nasopharyngitis, muscle strain, hematoma) and 4 in the placebo group (headache, pruritus, food allergy, hematoma). 3 of these AEs were considered to be related to the study drug, i.e. injection site reaction, vertigo and migraine.

Protocol deviations

Three deviations from the protocol occurred: one patient received 0.009 mg

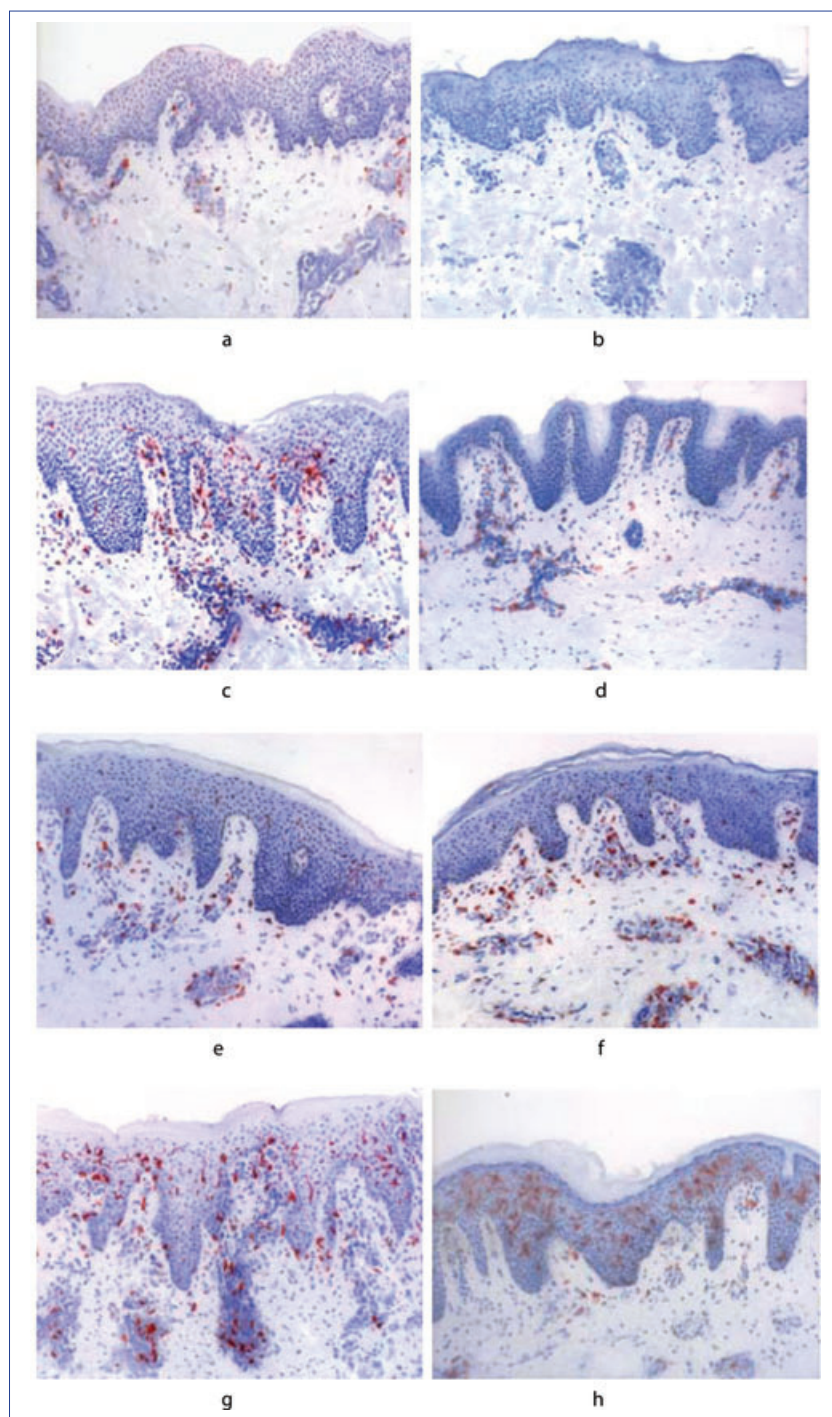


Figure 4: Immunohistochemistry, stainings: (a) anti-IgE: baseline (BL) Omalizumab; (b) anti-IgE: end of study (EOS) Omalizumab; (c) anti-IgE: BL placebo; (d) anti-IgE: EOS placebo; (e) anti-FcεRI: BL Omalizumab; (f) anti-FcεRI: EOS Omalizumab; (g) anti-CD1a: BL Omalizumab; (h) anti-CD1a: EOS Omalizumab.

omalizumab/kg/IgE(IU/ml) at visit 10 (reason: extension of visit schedule); another patient received 0.009 mg omalizumab/kg/IgE(IU/ml) at visit 6 (reason: study medication split) and 0.011 mg omalizumab/kg/IgE(IU/ml) at visit 10 (reason: extension of visit schedule).

Results

Studies of the peripheral blood

Effect of omalizumab treatment on serum IgE levels: In our study, omalizumab but not placebo treatment resulted in a dramatic reduction of free serum IgE levels at the end of week 1 which was persistent

throughout the entire treatment period (Figure 2). These results confirm previous data [3, 4].

Effect of omalizumab treatment on leukocyte numbers and phenotypes: Basophils (CD123⁺/HLA-DR⁻) and, to a lesser extent, mDC (BDCA-1⁺/CD19⁻), monocytes (CD123⁻/HLA-DR⁺) and pDC (CD123⁺/HLA-DR⁺) of untreated AD patients exhibited pronounced anti-IgE surface reactivity. Already one week after beginning omalizumab treatment, we observed a significant decrease of surface IgE on all these cell populations, and this effect was maintained until the end of the treatment period (Figure 3a for pDC; exemplary for the other populations). We also noticed a slight decrease of IgE surface staining in the placebo group but this effect was far less pronounced.

Our results also demonstrate that omalizumab treatment reduces the saturation of FcεRI with IgE on basophils, mDC, pDC and monocytes significantly, reduces the expression of (total) FcεRI on these populations significantly (Figure 3b, c for pDC, exemplary for the other populations) and shows a non significant trend towards an increment of the number of unoccupied (i.e. free) FcεRI (data not shown). Similar changes, although less pronounced, occurred in the placebo group, but there were no changes of the IgE receptor saturation.

In both treatment groups, we observed no relevant changes of total leukocytes, of the percentages of mDC and pDC within the entire leukocyte population and of eosinophils. Due to high background fluorescence results of anti-CD23 staining were not conclusive.

Studies of the skin

Immunohistology: The major omalizumab-specific effect was a dramatic decrease of IgE-positive, but not of FcεRI-positive cells in both the epidermis and dermis (Figure 4). The majority of these cells represented DC as could be judged from their configuration, others qualified as mast cells. We also found a significant decrease of accessory DC molecules in both the omalizumab (dermal CD86) and the placebo (dermal CD86/CD40/FcεRI/HLA-DR) group (data not shown); all the other molecules showed no significant changes.

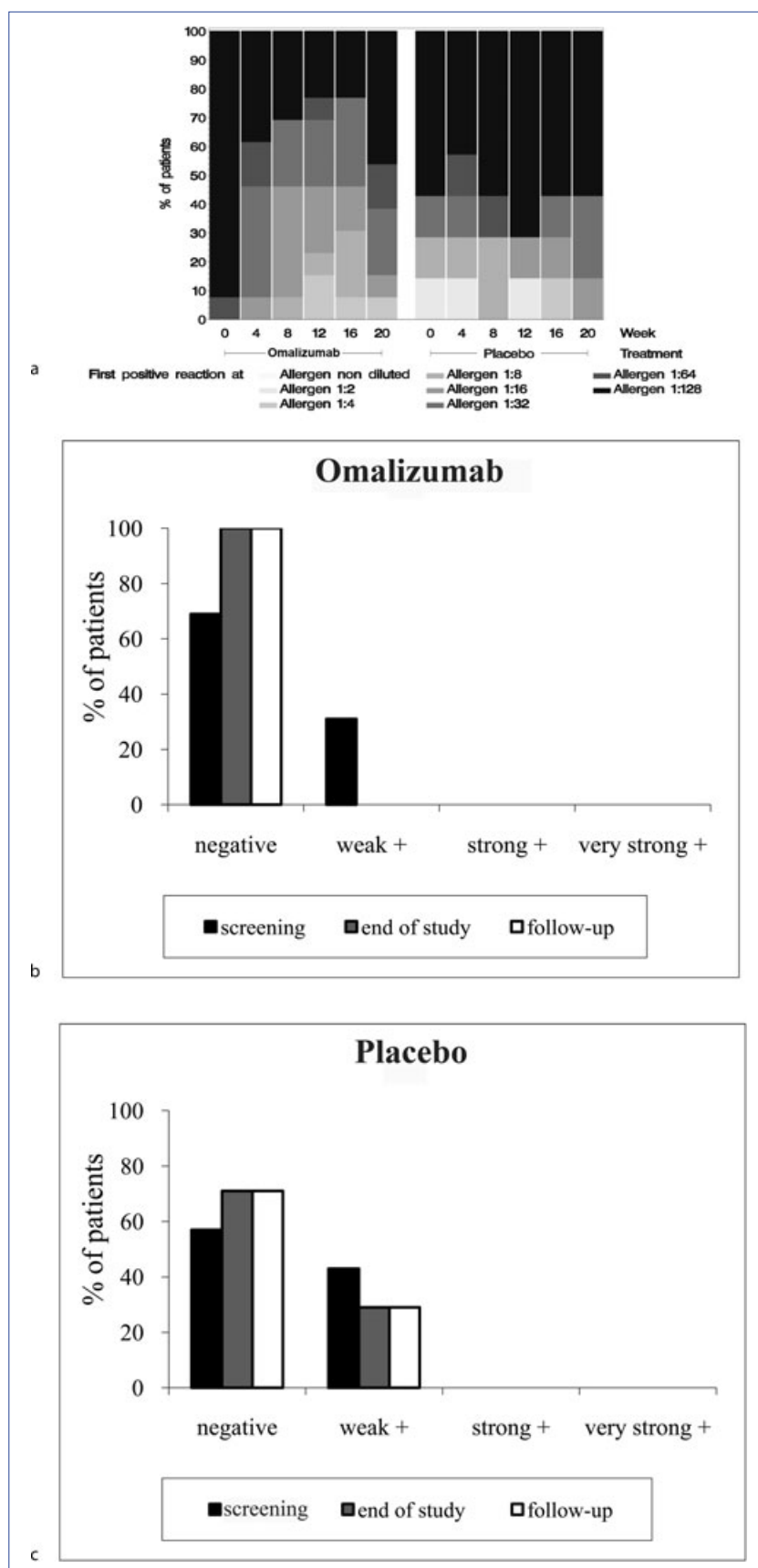


Figure 5: (a) Titrated skin prick test: dilutions at which first positive reaction occurred for both treatment groups (treatment period: weeks). (b) Results of the atopy patch test at screening, end of study (week 16) and follow-up (week 20) for the omalizumab group. (c) Results of the atopy patch test at screening, end of study (week 16) and follow-up (week 20) for the placebo group.

Skin tests

Immediate type reactivity: The skin prick test with the lead allergen resulted in wheal diameters of 0.9 cm (omalizumab) and 0.8 cm (placebo) at screening and 0.6 cm (omalizumab) and 0.7 cm (placebo) at the end of study. These differences between the treatment groups were consistent, but not statistically significant. Evaluation of the titrated skin prick test showed an omalizumab-induced increment of the threshold allergen concentration required to give a positive reaction (Figure 5a). No such shift occurred in the placebo group.

Delayed type hypersensitivity: At screening, 4/13 patients in the omalizumab group and 3/7 patients in the placebo group had weakly positive atopy patch tests to the individual lead allergen; at the end of study, no patient in the omalizumab group but 2/7 patients in the placebo group were still weakly positive (Figure 5b, c). This observation between the two treatment groups was statistically not significant.

Clinical parameters

IPSA: The number of omalizumab patients reporting moderate or severe pruritus increased from 9 (baseline) to 11 (end of treatment) (Figure 6a). In the placebo group the respective numbers decreased from 6 to 1.

IGA (Figure 6b) and EASI total score (data not shown): Both parameters slightly improved in both treatment groups; the differences between the treatment groups were not statistically significant.

Corticosteroids as concomitant and rescue medication: None of the study patients took oral corticosteroids. 12/13 patients in the omalizumab group (median: 24.0 g) and 5/7 patients in the placebo group (median: 31.5 g) used hydrocortisone acetate 1 % cream as concomitant medication. 10/13 patients in the omalizumab group (median: 36.0 g) and 5/7 in the placebo group (median: 22.5 g) applied diflucortolon valerate 0.1 % cream as rescue medication.

Discussion

In order to clarify the role of IgE in the pathogenesis of AD, we asked in this explorative study [14] whether omalizumab treatment can deplete free IgE from blood and skin of AD patients, and, if so, whether this would have an

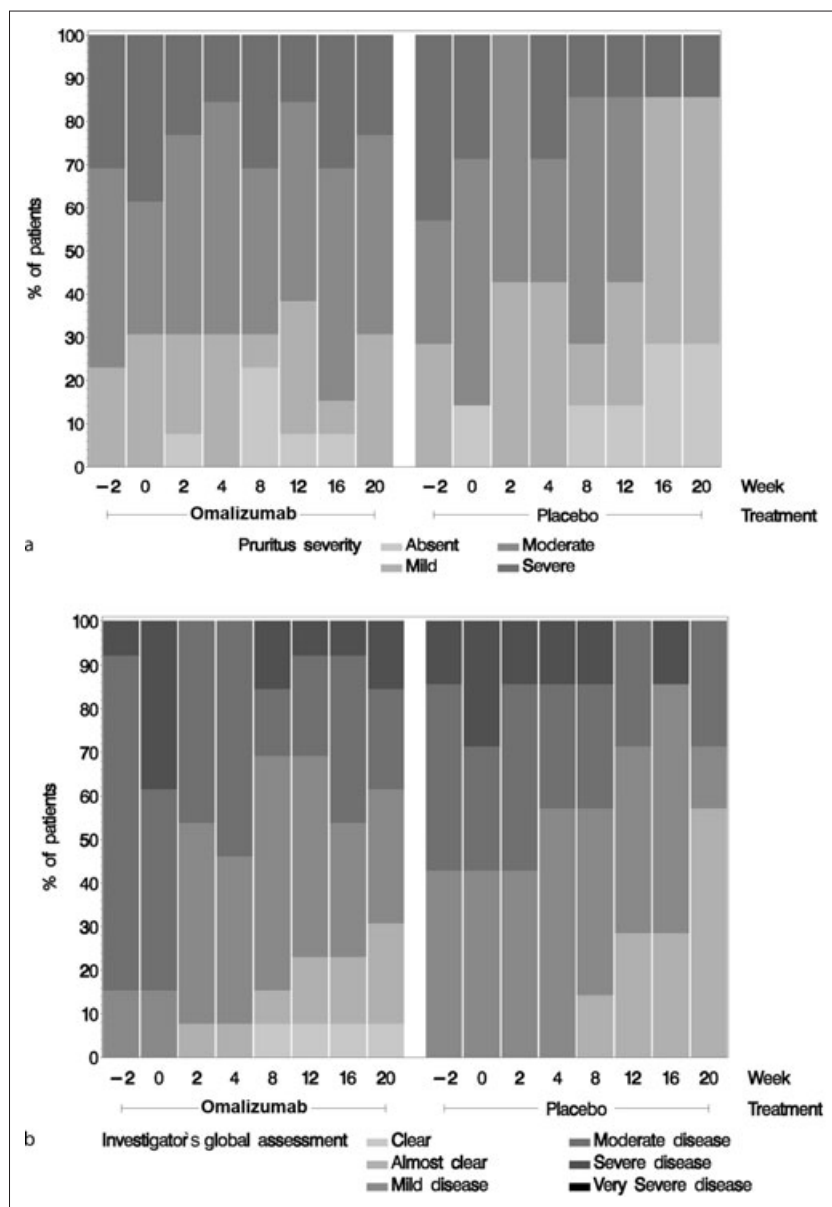


Figure 6: (a) Pruritus severity assessment for both treatment groups (treatment period: weeks). (b) Investigator's global assessment for both treatment groups (treatment period: weeks).

impact on the immunological and clinical course of the disease. This is the first randomized, double blind and placebo-controlled trial investigating effects of omalizumab therapy in AD.

Our finding that omalizumab treatment dramatically reduces serum levels of free IgE and decreases surface-bound IgE confirms and extends previous observations [15, 16]. We further show for the first time that omalizumab lowers the FcεRI saturation with IgE on peripheral blood and skin leukocytes. We also found that omalizumab-treated patients exhibit decreased levels of total FcεRI expression [3–5]. This finding might

support the concept of *in vivo* regulation of FcεRI by IgE [17]. The fact that placebo induced similar effects in some parameters, although to a much lesser extent, did not come by surprise, given the high placebo effects in trials with patients suffering from AD [18, 19] and allergic rhinitis [20].

At the same time and somewhat surprisingly, skin reactivity with anti-FcεRI antibodies persisted. One may argue that, as opposed to the blood, the outer parts of the skin had only limited access to omalizumab, thus retaining residual amounts of IgE still sufficient to sustain FcεRI expression; alternatively, remain-

ing anti-FcεRI reactivity despite anti-IgE therapy might reflect higher constitutive FcεRI expression on cellular structures in skin than in blood.

Given the caveat that the efficacy data of a pilot clinical investigation with only 20 patients can only be interpreted with great caution, our study did not reveal a superior effect of omalizumab over placebo in reverting pre-existing chronic atopic lesions in adults.

At the first glance, the lack of a significant therapeutic effect speaks against a major role of IgE in AD pathogenesis and seemingly confirms previous observations documenting the failure of omalizumab-treatment in patients with chronic severe AD [21]. One may argue that an effect of an anti-IgE therapy was not to be expected in this eczematous rather than urticarial disease that occasionally occurs in the absence of elevated IgE levels in the blood. Additionally, to date, no anti-IgE therapy has the power to result in a total depletion of IgE on leukocytes in blood and skin; minimal amounts of residual IgE might sustain functional responses influenced by inter-individual variations in the cellular sensitivity towards IgE.

On the other hand, we should not forget that, apart from intrinsic AD, no other form of the atopic triad has similarly high IgE levels and that allergen-specific IgE, when bound to the surface of dendritic cells, can greatly facilitate presentation of the respective allergen to T cells [2].

A closer look at our data reveals that omalizumab treatment also induced certain *in vivo* effects, i.e. omalizumab led to an improvement of the atopy patch test results in single patients and elevated the threshold in the titrated skin prick test required to give a positive reaction. This is in keeping with data from other investigators showing (I) a decrease of immediate-type skin prick reaction and of FcεRI⁺ cells in intradermally challenged omalizumab-treated patients with allergic rhinitis [4] and (II) a preventive effect of omalizumab on late-phase reactions and inflammatory cells in skin after repeated iatrogenic cutaneous allergen challenge of airway-atopic individuals [10, 22].

In the case of AD, favourable responses to omalizumab have been reported mainly [23–26], but not exclusively [27], in patients suffering also from

asthma. One explanation for the obvious discrepancy between these findings and our results could be the difference in the patient cohorts treated. Whereas others treated children with mostly acute AD of short duration [28, 29] or AD patients with asthma [23–26; 30–32] which - in the case of impairment - might act as a source of triggering acute skin deterioration that is responsive to omalizumab treatment, we were dealing with adults exhibiting a chronic and long lasting course of the disease, many of them without asthma. In this context, one should also not forget that acute and chronic AD lesions exhibit different cytokine milieus [33]; acute AD is dominated by a Th2/Th17-reaction pattern [34] that can be sustained by IgE and allergen exposure. Chronic AD, in contrast, is characterized by a Th-1 signature.

It was shown that a dominant Th2 cytokine pattern impairs both, the expression of filaggrin and of antimicrobial peptides [35, 36]. In view of recent findings [16, 37] demonstrating an omalizumab-induced decrease of Th2-defining cytokines, i.e. IL-4, IL-5 and IL-13, it is tempting to speculate that an anti-IgE induced interruption of the Th2 loop would at least partly restore the skin barrier defect and the impaired host defense against microbes. Whether such a therapeutic strategy could even prevent or stop the atopic march of children remains to be seen.

The lack of clinical efficacy despite profound changes of IgE related immune reactions points to the complexity of the disease, which is probably not solely IgE dependent.

The use of reagents with a higher affinity than currently available and, thus, an even better IgE-depleting capacity in well designed studies with longer treatment periods and clearly defined larger patient populations is needed to find the correct answers.

Acknowledgement

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Conflict of interest

Thomas Hultsch: former full time employee of Novartis, co-promoter of Xolair® (omalizumab). The study was sponsored by Novartis.

Abbreviations

AD = atopic dermatitis
AE = adverse events
BL = baseline
cIgE = chimeric IgE
EOS = end of study
IGA = Investigator's Global Assessment
IPSA = investigator's pruritus severity assessment
IHC = immunohistochemistry
mAb = monoclonal antibody
mDC = myeloid dendritic cell
MFI = mean fluorescence intensity
pDC = plasmacytoid dendritic cell

Correspondence to



Peter Maximilian Heil, M.D.
Division of Immunology, Allergy and Infectious Diseases
Department of Dermatology
Medical University of Vienna
Währinger Gürtel 18-20
A-1090 Vienna
Austria
Tel.: +43-1-40-400-7704/7705
Fax: +43-1-40-400-7574
E-mail: peter.heil@meduniwien.ac.at

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