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Monitoring free serum IgE in severe asthma patients treated with omalizumab

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Summary
Background: Benefit of treatment with the monoclonal anti-IgE-antibody omalizumab in severe IgE-dependent asthma requires a significant reduction of serum free IgE concentrations. It is unclear if monitoring free serum IgE is clinically meaningful once omalizumab treatment is initiated.
Methods: Free IgE and omalizumab serum concentrations were quantified in 22 patients with severe asthma (68% female, 47 ± 11 yrs, mean (±SD) pre-bronchodilator FEV_1 62 ± 13%, baseline mean (±SEM) free serum IgE 652 ± 136 ng/ml) treated with omalizumab for 4 months using a Recovery-ELISA.
Results: Omalizumab treatment reduced free serum IgE prior to the second omalizumab injection by 73%, after 16 weeks by 81% to 58 ± 12 ng/ml ($p < 0.001$ vs. baseline). 17 patients responded to anti-IgE therapy as judged by physician-rated global evaluation of treatment effectiveness. There was neither a relation between free serum IgE concentrations and treatment response nor a significant or clinically relevant correlation between free IgE levels and changes in lung function, exhaled NO, asthma control, and quality of life. Serum concentrations of omalizumab were detected in all patients and reached a stable phase within 8 weeks.
Conclusions: Monitoring free IgE and omalizumab serum concentrations in patients treated with omalizumab does not predict clinical response nor does it add to the decision to continue or stop treatment. However, routine measurements of free IgE may be clinically relevant to demonstrate an adequate reduction in free IgE in patients not responding to omalizumab therapy.

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Introduction

Immunoglobulin E (IgE) is central to the pathophysiological cascade that eventually triggers allergic reactions and perpetuates bronchial airway inflammation.[1] Consequently, omalizumab, a recombinant humanized monoclonal anti-IgE antibody, has been approved as add-on treatment for patients with inadequately controlled severe persistent IgE-dependent allergic asthma despite GINA step 4 therapies.[2–4] Omalizumab interrupts the allergic cascade by binding to the Fc region of free serum IgE. Free IgE serum concentrations are rapidly reduced, the expression of the high affinity IgE receptor (FcεRI) on inflammatory cells down regulated, and mast cell and basophil activation and subsequent release of their inflammatory mediators inhibited.[5,6] In patients with allergic asthma and poor disease control despite best available therapy omalizumab as add-on therapy reduced asthma symptoms, clinically significant asthma exacerbations, emergency visits and hospitalizations due to asthma in clinical trials as well as in real-life settings.[5,7,8] The ability of omalizumab to lower free IgE in serum depends on dose, the patients' body weight and baseline total serum IgE level. Clinical trials suggest that benefit with omalizumab is observed when serum free IgE concentrations are reduced to 50 ng/ml (20.8 IU/ml) or less.[9,10] Omalizumab and IgE molecules form small, biologically inactive complexes.[11,12] Commercially available assays to quantify IgE recognize both free IgE and IgE molecules that are part of omalizumab-IgE-complexes, making it impossible to monitor free serum IgE once omalizumab treatment is initiated. Thus, the decision if omalizumab is effective is solely based on the physicians' judgement.[13] Long-term treatment adjustments aimed at the treatment target, free IgE, are not feasible. To overcome this problem a newly available Recovery-ELISA was used to quantify free serum IgE in patients before and during treatment with omalizumab. Serum concentrations of free IgE and omalizumab were measured and correlated with markers of asthma control.

Methods

Patients

22 patients with uncontrolled severe persistent asthma were selected for add-on therapy with omalizumab as recommended by national[14] and international guidelines.[2] All patients had a physician-diagnosed asthma with either documented variable airflow obstruction, increase in FEV_1 of more than 12% and 200 ml after 200 μg of salbutamol and/or a methacholine PC20 of <8 mg/ml. Further inclusion criteria were a reduced lung function ($FEV_1 < 80\%$ pred.), the diagnosis of severe persistent uncontrolled asthma as indicated by frequent daily symptoms or nocturnal awakenings and severe asthma exacerbations despite treatment with high doses of inhaled corticosteroids (>500 μg BDP or equivalent/day) and long-acting β_2-agonists. All except one patient were sensitized to at least one perennial allergen as documented by positive skin prick test or *in vitro* reactivity. One patient neither showed skin prick test reactivity nor specific IgE against common perennial allergens tested as part of our standard allergen panel. However, all clinical entry criteria were fulfilled and total serum IgE was slightly elevated (104 IU/ml) within the dosing range of omalizumab. The patient was included in the trial without further attempts to identify a sensitization to rare perennial allergens. All except one patient had levels of total serum IgE and body weight within the omalizumab dosing table[15] and were treated accordingly. A third patient slightly outside the dosing range (843 IU/ml, 86 kg) was treated with the maximal approved omalizumab dose (750 mg/month).

Exclusion criteria were current smoking, a serious coexisting illness, and the possibility of conception. All patients included in the study provided written informed consent. The study was performed according to Good Clinical Practice standards and the declaration of Helsinki and was approved by the local ethics committees and the Paul-Ehrlich Institute, an agency of the German Federal Ministry of Health.

Study design

In this single center clinical trial patients were seen between 2 and 4 weeks prior to start of treatment for a screening visit to confirm eligibility for omalizumab and to assess demographics. Patients were treated with omalizumab subcutaneously according to the dosing table and were followed-up every 2 weeks (total omalizumab doses $>$ 300 mg/month; $n = 13$) or 4 weeks (total dose $\leq$ 300 mg/month) for their omalizumab injections and study visits for a total of 16 weeks. Due to its specific mechanism of action, it is recommended to assess omalizumab effectiveness after 16 weeks of treatment.[15] Serum samples to quantify free IgE and omalizumab concentrations were collected prior to (trough) and 1 h after each omalizumab injection at all visits.

In addition, the following procedures were performed at each study visit: pre- and post-bronchodilator spirometry (according to ATS/ERS criteria Jaeger Masterscreen Body, Hoechberg, Germany), measurements of exhaled NO according to ATS guidelines (Niox Mino, Aerocrine, Solna, Sweden) as well as evaluations of global treatment effectiveness (GETE: complete control, marked improvement in control, discernible but limited control, no appreciable change, worsening in control),[16] asthma control (ACQ-5)[17] and quality of life (Mini-AQLQ).[18] The minimal clinically important difference in ACQ-5 and Mini-AQLQ scores is 0.5. Changes in medication were allowed to adjust treatment based on the patients' asthma control. During the trial the patients and investigators were blinded to results of the free IgE and omalizumab assays.

Quantification of free serum IgE and omalizumab concentrations

Free serum IgE and omalizumab concentrations were quantified with a commercially available Recovery-ELISA kit by the manufacturer (Patent EP1957980, BioTeZ Berlin-Buch, Germany) according to ISO9001 and the rules of Good Laboratory Practice.[19,20] The Recovery-ELISA is

a modification of the traditional sandwich immunoassay. Using standard serum samples spiked with IgE and omalizumab in a defined concentration range standard curves and reference functions were created for samples with or without omalizumab, respectively. This multi-dimensional calibration procedure enables the simultaneous measurement of free IgE and omalizumab in serum samples of patients treated with omalizumab. In undiluted serum the Recovery-ELISA is able to assay for free IgE in a concentration range of 1–2000 IU/ml in samples without omalizumab and of 1–500 IU/ml in samples containing omalizumab as well as for omalizumab in a range of 0.4–80 μg/ml. Inter- and intra-variability of the assay were between 3.2 and 12.1% (coefficient of variation) for free IgE and between 6.9 and 14.4% for omalizumab. All serum samples were frozen immediately and kept in a −80 °C freezer until assayed for free IgE.

Statistical analysis

The primary outcome parameter was the correlation of free IgE with treatment effectiveness rated by the physician based on the GETE scale.[16] Patients with complete or marked improvement in asthma control were considered responders. Secondary outcome measures were change in lung function, exhaled NO, asthma control and quality of life after 16 weeks of treatment as well as the relation of free serum IgE to these parameters.

Sample size was calculated based on the primary outcome parameter. In clinical trials free IgE was reduced below the therapeutic target of 50 ng/ml in approximately 90–95% of patients treated with omalizumab, and the responder rate was 60–75%.[8–10,21–23] With p-values < 0.05 indicating statistical significance of 22 patients were calculated as appropriate for the study.

Data description was primarily based on means and standard deviation or standard error of mean or medians and quartiles (interquartile ranges) for continuous endpoints (e.g., free IgE), and on frequencies for categorical endpoints (e.g., responder vs. non-responder). Comparisons between patient subpopulations were based on Wilcoxon or t-test for continuous endpoints and on Fishers exact test for categorical endpoints. Intraindividual comparisons were based on sign or paired t-test. A logistic regression model was used for multivariate analyses. Data analysis was performed using SPSS® 11.5 software for Windows.

Results

Clinical response to omalizumab

22 patients with a physician-diagnosed severe persistent asthma (Table 1) were treated prospectively with omalizumab for 16 weeks. At the end of the study period efficacy of omalizumab was rated by GETE as complete or marked improvement in control in 17 patients (77%, responders). In the remaining 5 patients the treatment offered no clinical benefit.

At the end of the study period lung function had improved in 12 of 17 patients who responded to omalizumab treatment. The exhaled NO had decreased in 10 of the 17 patients, and oral corticosteroids could be reduced or withdrawn in 5 of the 7 responders who had been on oral corticosteroids prior to study. ICS doses were unchanged in 10, could be reduced in 3 and had to be increased in 4 patients (median change 0 μg/day). Asthma control and/or quality of life had improved significantly (ACQ-5 $p < 0.001$, AQLQ $p = 0.001$) in all responders (Table 2). In contrast, no clinically relevant changes were seen in the 5 non-responders, including doses of inhaled and/or oral corticosteroids. Further, in a logistic regression model among all covariables treatment response to omalizumab was significantly associated only with an ACQ improvement of more than 0.5 points ($p = 0.010$), not surprising given that ACQ and GETE questionnaires both probe for subjective symptomatic improvements. The variables recorded as part of the present trial cannot predict response to omalizumab treatment. Doses of inhaled corticosteroids were unchanged in non-responders (median change 0 μg/day, range −500–0 μg/day BDP or equivalent).

Table 1 Demographic and baseline clinical characteristics of study participants.

Age (years)	47.3 ± 11.4 (21.5–65.1)
Female sex (n, %)	15, 68%
Total serum IgE[a] (IU/ml)	263 (139–418; 42–843)
Body weight (kg)	79.6 ± 12.3 (50.0–93.0)
Omalizumab dose (mg/month)	600 (300–600; 150–750)
Pre bronchodilator FEV_1[a] (L)	1.96 ± 0.55 (0.93–2.95)
% of predicted normal	61.8 ± 13.1 (33.0–79.7)
Post bronchodilator FEV_1[a] (L)	2.09 ± 0.50 (1.17–2.91)
% of predicted normal	64.8 ± 11.4 (40.0–78.7)
Exhaled NO (ppb)	40 ± 29 (8–108)
Asthma control (ACQ-5)	3.0 ± 1.2 (0.2–4.8)
Quality of Life (Mini-AQLQ)	3.6 ± 1.3 (1.8–6.5)
Inhaled corticosteroids[b] (μg/day)	1000 (1000–2000; 500–4000)
Use of oral corticosteroids (n, %)	9, 21%
Dose of oral prednisolone (mg/day)	12.5 (10–17.5; 8–40)

Plus-minus values are means ± SD (range), all other values are medians, interquartile ranges and minimum–maximum. Values are those recorded at baseline (week 0). FEV_1 denotes forced expiratory volume in 1 s. NO denotes nitric oxide in exhaled air.
[a] Total serum IgE and FEV_1 values were obtained prior to baseline (screening visit).
[b] The doses of inhaled corticosteroid were converted to the equivalent dose of beclomethasone dipropionate.

Free IgE and omalizumab serum concentrations

One hour after the first omalizumab injection free serum IgE was slightly reduced (Table 3). Prior to the second injection trough free serum IgE was reduced in all patients by 73% (Fig. 1). After 4 weeks of treatment, independent of baseline IgE and omalizumab dose, trough free IgE was below 100 ng/ml in all but three patients (102, 102, and 270 ng/ml). Concentrations remained low for the rest of

Table 2 Responder status and clinical parameters.

Change: week 16 vs. baseline	Responder	Non-responder	*p*-value
Free serum IgE (% reduction)	79 ± 6 (−4–98)	70 ± 13 (29–98)	0.537
FEV_1 (L)	0.1 ± 0.1 (−1.4–1.1)	−0.1 ± 0.1 (−0.3–0.2)	0.212
FEV_1 (% of. pred.)	3.8 ± 3.8 (−36.8–26.3)	−2.1 ± 3.2 (−9.7–5.7)	0.249
Exhaled NO (ppb)	−5 ± 8 (−53–70)	6 ± 7 (−14–24)	0.305
ACQ5	−1.7 ± 0.4 (−3.6–2.8)	0.1 ± 0.1 (−0.2–0.6)	<0.001
Mini-AQLQ	1.9 ± 0.4 (−1.8–3.7)	0.1 ± 0.2 (−0.5–0.9)	0.001
Parameter at week 16			
Free serum IgE (ng/ml)	58 ± 16 (7–272)	61 ± 12 (36–102)	0.869
Free serum IgE < 50 ng/ml (*n*, %)	10, 59%	2, 40%	0.624
Omalizumab concentration (μg/ml)	45 ± 8 (5–140)	22 ± 5 (9–36)	0.189

Values are means ± SEM (range) unless otherwise stated. FEV_1 denotes forced expiratory volume in 1 s. Exhaled NO denotes nitric oxide in exhaled air. *p*-values: responders vs. non-responders.

the treatment period. After 16 weeks free IgE was reduced in 21 patients by 81% (Table 3). In one patient (responder) free IgE was unchanged (baseline 45 ng/ml, 16 weeks 47 ng/ml).

There was no relation between free serum IgE concentrations and treatment effectiveness (GETE) after 16 weeks of treatment. In particular, free serum IgE levels were similar in responders and non-responders despite significant and/or clinically relevant differences in lung function, exhaled NO, asthma control, and quality of life (Table 2).

Omalizumab was detected in serum in 21 patients after the first injection and in all patients after 16 weeks of treatment (Table 3). Serum concentrations of free IgE and omalizumab reached a stable phase within 8 weeks, with no significant difference between responders and non-responders (Table 3).

Discussion

The treatment of severe allergic asthma with a humanized monoclonal anti-IgE antibody is supported by results of multiple phase II–IV clinical trials in the adult and pediatric population.[3,4,7,8,16,23,24] The results of the present study confirm that a majority of patients with severe allergic asthma characterized by compromised lung function and frequent exacerbations despite treatment with high doses of inhaled glucocorticosteroids and long-acting β2-agonists benefit from treatment with anti-IgE. Omalizumab reduced serum concentrations of free IgE to levels in the same range as were reported as part of the omalizumab phase II–IV clinical trial program. In addition, the present study demonstrated for the first time outside of clinical trials organized by the manufacturer of omalizumab that monitoring of serum concentrations of free IgE and omalizumab with a commercially available assay is feasible, and that anti-IgE treatment decreased serum concentrations of free IgE around 10-fold.

Table 3 Free serum IgE and omalizumab concentrations.

	Mean ± SEM	*p*-value (vs. baseline)
Free serum IgE (ng/ml)		
Baseline (week 0)	652 ± 136 (45–2078)	–
Change 1 h after first injection	−57 ± 26 (−300–105)	0.039
Trough second injection	108 ± 19 (8–309)	<0.001
Trough 16 weeks of treatment	58 ± 12 (7–272)	<0.001
Omalizumab (μg/ml)		
Trough second injection	18 ± 3 (0–55)	<0.001
Trough 16 weeks of treatment	40 ± 7 (5–>140)	<0.001

The therapeutic efficacy of omalizumab is mainly attributed to a reduction of free IgE secondary to the formation of IgE-anti-IgE immune complexes, thereby preventing downstream immunological reactions that eventually lead to allergic and asthmatic symptoms.[9,25] To simplify dosing, and ensure that free IgE reduction is achieved, an individualized tiered dosing table was developed based on phase II studies in which free serum IgE concentrations were quantified,[9,26] and in which patients, depending on weight and baseline IgE level, received omalizumab by subcutaneous injection every 2 or 4 weeks. Commercially available IgE assays recognize IgE-anti-IgE immune complexes, leading to false IgE measurements in patients treated with omalizumab.[27] Until recently it was impossible to routinely quantify free serum IgE as a means to guide long-term omalizumab dosing and monitor treatment. This trial addresses several of the ensuing questions and demonstrates that free IgE and omalizumab serum concentrations can be routinely monitored in asthma patients on omalizumab. Treatment with omalizumab lowered free serum IgE in all patients in accordance with the results of the omalizumab phase II–IV clinical trial program.[3,4,7–10,15,16,23,24] Interestingly, the clinical benefit of omalizumab was not related to serum concentrations of free IgE or serum concentrations of omalizumab. A similar pattern was seen in an earlier study following 23 patients on long-term treatment (range 4.5 months–7 years) with omalizumab, including all omalizumab responders identified in this trial. All patients had responded to anti-IgE

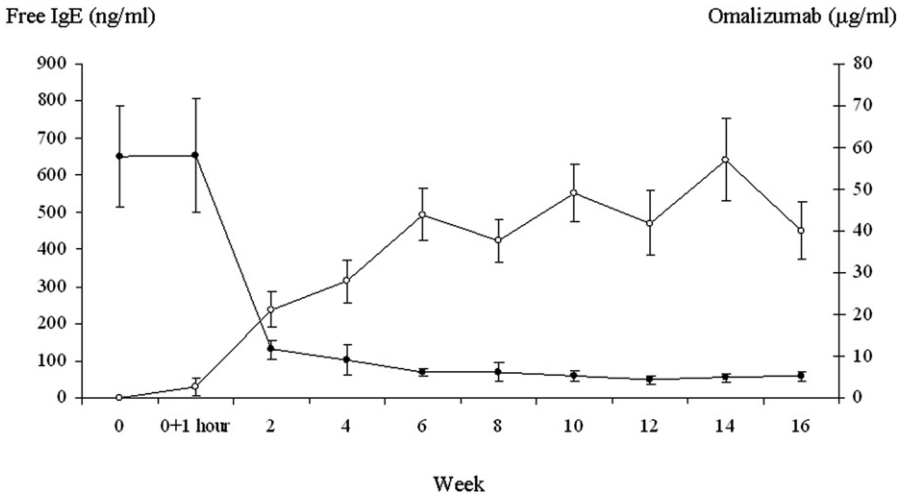

Figure 1 Free serum IgE and omalizumab concentrations shown are mean ± SEM concentrations of free serum IgE (ng/ml) and omalizumab (μg/ml) during the whole treatment period. Black circles: Free serum IgE concentrations White circles: Omalizumab concentrations.

therapy as judged by the GETE score. Again, there was no correlation between free serum IgE levels and pre-treatment total IgE, omalizumab dose, or duration of therapy.[28] Free serum IgE was quantified at least twice to evaluate variability concentrations showed a stable pattern over time.

It cannot be excluded that an increase of omalizumab doses in patients with free serum IgE above target range may improve treatment results, more so since there is an insignificant numerical difference between omalizumab serum concentrations in responders and non-responders. However, the similar magnitude of treatment effects in responders below and above the 50 ng/ml threshold does not support this hypothesis. Nevertheless, a long-term trial to test the clinical potential of monitoring free serum IgE in omalizumab patients is warranted. This further trial is important since *in vitro* results demonstrate down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE.[29] It is tempting to speculate that long-term treatment with anti-IgE may decrease the doses of omalizumab necessary to uphold a sufficient treatment response. In line with this are clinical reports that even three years after treatment with omalizumab was stopped 12/18 patients reported improved or unchanged asthma control compared with ongoing anti-IgE treatment,[30] further underlining the clinical relevance of trials following free serum IgE in relation to response criteria.

The results of this trial again highlight the question why a significant number of patients with severe allergic asthma carefully selected as recommended by recent guidelines[2] did not respond to omalizumab treatment', despite the fact that serum free IgE concentrations were within or only slightly above the therapeutic target range. A plausible explanation suggests that in non-responders non-allergic pathomechanisms dominate, while the clearly present allergic disposition is not clinically relevant. Alternative hypotheses suggest that the reduction of free serum IgE is not the only mechanism responsible for the omalizumab effects,[25,31] that the ratio between total and specific IgE may play a role,[32] and that criteria used to define the patient population in which a therapeutic trial with omalizumab is justified are inadequate. The results of this study confirm that in asthma the absolute reduction in free serum IgE is insufficient to explain and predict clinical response and to separate responders from non-responders. As yet, a loose correlation between free serum IgE concentrations and clinical benefit has only been shown in few studies[21] and in models developed on the basis of single-dose studies.[10] Additional parameters need to be identified to properly select patients that will likely benefit from treatment with omalizumab. The hypothesis of clinically relevant effects of omalizumab independent of IgE reduction is supported by observations that anti-IgE can be effective in relatively low doses,[33] in diseases characterized by serum total IgE concentrations outside of the dosing table,[34] and even in diseases without obvious allergic pathomechanisms.[35]

This study has several limitations. Firstly, although based on a valid sample calculation, the number of patients included in this study is small. However, the results of this study are well in accordance with results of the omalizumab phase II—IV clinical trials. Secondly, the assay used to quantify free serum IgE has not yet been validated in larger scale clinical trials prior to this study. It may well be that the absolute free IgE serum concentrations obtained with this assay differ from the assay(s) used in the omalizumab clinical trials. Nevertheless, the pattern of free serum IgE levels seen as part of the present study are well in line with the results of these trials, indicating at least a good proportional correlation. Thirdly, although the observation period of 4 months is based on the omalizumab license it cannot be excluded that the number of responders will increase with duration of treatment. This is true despite the fact that the percentage of responders in this study is well in line with reports in other trials. Finally, this was an open study, a fact known to influence patient's response to treatment, and there was no placebo control.

However, in the omalizumab study program there was no effect of placebo on free serum IgE, and it was therefore considered unethical to include a placebo arm in a study including patients with severe asthma.

Conclusion

It is feasible to routinely monitor serum concentrations of free IgE and omalizumab in patients with severe asthma treated with omalizumab. In this study this information does not predict clinical response nor does it add to the clinical decision to continue or stop treatment. However, routine measurements of free IgE may be clinically relevant to demonstrate an adequate reduction in free IgE in patients not responding to omalizumab therapy. For the time being treatment responses to omalizumab have to be judged solely based on clinical scoring systems. It remains unclear if the absolute reduction of free IgE is the only clinically relevant mechanism of action.

Authors contributions

SK, CT and RB made substantial contributions to concept and design of study. SK and IH performed study visits and collected data. GB, PS and AS analyzed serum samples. SK, CT and RB contributed to the analysis and interpretation of data. All authors critically reviewed the report and approved the final version.

Conflict of interest

SK, CT and RB have received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Novartis Pharma GmbH. IH and FF have no conflict of interest. GB, PS and AS are employed by BioTeZ Berlin-Buch GmbH as stated in the affiliations.

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