

Immunological and Clinical Changes in Allergic Asthmatics following Treatment with Omalizumab

Oliver Noga Gerald Hanf Gert Kunkel

Allergy and Asthma Clinic, Charité, Humboldt University, Berlin, Germany

Key Words

Omalizumab · rhuMAb E25 · Allergic asthma · Asthma treatment

Abstract

IgE plays a key role in allergic asthma. We investigated whether omalizumab treatment of patients with moderate to severe allergic asthma leads to changes in inflammatory mediators and clinical symptoms. This sub-study was conducted on 35 patients with a positive skin prick test (SPT) requiring daily administration of beclomethasone dipropionate (500–1,000 µg), who participated in a multicentre, randomised, double-blind, placebo-controlled study. Omalizumab or placebo was administered at 0.016 mg/kg/IgE every 4 weeks. Patients recorded peak expiratory flow, asthma symptom score and β_2 -agonist use in daily diaries and spirometry was performed at each visit. β_2 -Agonist use and SPT wheal reaction decreased significantly ($p < 0.05$). Circulating levels of IL-5, IL-6, IL-8, IL-10, IL-13 and s-ICAM were measured before and after 16 weeks of treatment. IL-13 and s-ICAM were measured before and after 16 weeks of treatment. IL-13 decreased significantly ($p < 0.01$). IL-5 and IL-8 decreased in the omalizumab group compared to baseline. The other circulating mediators did not demonstrate any changes. Histamine release was significantly reduced ($p < 0.01$). Airway resistance ($p < 0.05$) and the

provocative concentration inducing a 20% decrease in FEV₁ ($p < 0.05$) were measured before, after 16 weeks, and 3 months after completion of treatment. Both parameters decreased significantly ($p < 0.05$). Peripheral eosinophil count decreased significantly compared to placebo ($p < 0.01$). These findings suggest that omalizumab has potential as a novel treatment for allergic asthma.

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Introduction

Allergic asthma is a common disease [1] with increasing prevalence [2] and marked association with elevated serum IgE levels and skin test reactivity [3]. Binding of allergens to antigen-binding sites of IgE on the surface of basophils and mast cells with subsequent cross-linkage of IgE and aggregation of high-affinity IgE receptors triggers the release of previously formed and newly synthesised mediators, with the onset of allergic symptoms [4]. Current therapies include corticosteroids, bronchodilators, theophylline, mast cell stabilisers, anti-leukotrienes and immunotherapy. Preventing allergen-induced liberation from target cells is a new strategy for the treatment of atopic diseases [5–7]. Recombinant humanised monoclonal anti-IgE antibody, omalizumab (Xolair®), also referred to as rhuMAb E25, is a non-anaphylactogenic anti-

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Correspondence to: Dr. Oliver Noga
Allergy and Asthma Clinic, Charité, Virchow Klinikum, Humboldt University
Augustenburger Platz 1
D-13353 Berlin (Germany)
Tel. +49 30 450 650 82, Fax +49 30 450 659 02, E-Mail oliver.noga@charite.de

IgE antibody that attenuates both the early- and late-phase responses to inhaled allergens in asthmatic subjects [8]. It is a construct of the murine antibody MAE11 that binds to circulating IgE on the Fc side (at the FcεRI binding site) of the IgE antibody [9]. As a result, binding to Fcε-receptors or to receptor-bound IgE is impossible. Its efficacy, safety, tolerability, pharmacokinetics as well as pharmacodynamics have been assessed in single- and multiple-dose studies with omalizumab [10–13].

The majority of asthmatics suffer from other atopic diseases, including allergic rhinitis, atopic dermatitis, drug and food allergies driven by allergen-specific IgE. By reducing IgE levels, omalizumab could potentially influence all of these disorders.

Inhibition of IgE by omalizumab is potentiated by down-regulation of high-affinity IgE receptors on circulating basophils and probably mast cells as well – the key

cells of allergic inflammation – with levels returning to baseline after the treatment is stopped [14, 15]. Omalizumab inhibits the early allergic response to allergens [16] and the late allergic response [8], which are characterised by tissue infiltration with eosinophils and T-cell activation. This suggests that omalizumab has anti-inflammatory effects. In a large multicentre study, omalizumab demonstrated a significant increase in FEV₁ and a decrease in β₂-agonist usage. The reduction in inhaled corticosteroids was significantly higher compared with the placebo group. Furthermore, positive effects on the frequency of exacerbations were detectable. However, the absolute increase in FEV₁ is only small. The aim of this sub-study was to strengthen these findings by using more sensitive parameters of lung function [17, 18], such as airway resistance (R_{aw}) and the provocative dose of acetylcholine (ACh) that causes a 20% decrease in FEV₁ (PC₂₀), and to define factors and mediators involved in immunological and cellular reactions in order to improve our understanding of the mode of action of omalizumab.

Table 1. Baseline characteristics of the study subjects

Characteristics	Omalizumab (n = 18)	Placebo (n = 17)
Female	11	5
Male	7	12
Age, years ¹	37 (26–59)	36 (23–61)
FEV ₁ , % predicted ¹	79 (41–103)	80 (57–108)
BDP, µg/day ¹	653 (500–1,000)	600 (500–1,000)
IgE, IU/l	183 (21–483)	148 (45–683)
Allergen		
House dust mite	14	12
Cat dander	17	10
Dog dander	11	8

¹ Median and ranges (shown in parentheses).

Methods

Study Design

A group of 35 patients suffering from moderate to severe allergic asthma participated in this sub-study (table 1) which was conducted as part of a large multi-centre randomised, double-blind, placebo-controlled, parallel-group trial [17, 18]. All patients had at least a 1-year history of allergic asthma, a positive skin prick test (SPT) to at least one of the tested allergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat or dog dander), specific IgE (CAP Pharmacia, Uppsala, Sweden), inhaled corticosteroids at doses equivalent to beclomethasone dipropionate requirement for treatment with 500–1,000 µg/day for at least 2 months and demonstrated a reversibility of >12% in FEV₁ over the baseline value within 30 min after taking 200 µg of salbutamol. The study design is outlined in table 2. The study was approved by the local Ethics Committee. All patients gave informed written consent.

Table 2. Study design

Week	–7	–6 to 0	0 to 16	16 to 28	28 to 52
Period	Screening	run-in	stable steroid phase	steroid reduction phase	extension
Study treatment	none	none	omalizumab or placebo	omalizumab or placebo	omalizumab or placebo
BDP	≥ 500 µg/day	500–1,200 µg/day	stable dose	week 16–24: tapered dose week 24–28 maintenance dose	as appropriate for maintenance

BDP = Beclomethasone dipropionate.

Omalizumab or placebo was administered subcutaneously at 2- or 4-week intervals. Body weight and total IgE at screening were considered to warrant omalizumab administration of at least 0.016 mg/kg/IgE (IU/ml) every 4 weeks. Patients monitored peak expiratory flow (PEF), asthma symptom score and short-acting β_2 -agonist use on diary cards till the end of steroid reduction. PEF was measured every morning and evening. Asthma symptom scores were monitored by patients using a 4-point scale to rate their symptoms from 0 (no symptoms), 1 (symptoms caused little or no discomfort), 2 (symptoms caused some discomfort), 3 (symptoms caused moderate discomfort) to 4 (breathing problems at rest). The score was computed as mean daily score. FEV₁ was measured prior to every injection. Mean values for each patient in the period before the first injection were set as baseline.

Circulating Mediators

Concentrations of IL-5 (Pierce, Rockford, Ill., USA), IL-6, IL-8, IL-10, s-ICAM (Biosource, Camarillo, Calif., USA), IL-13 (Diacalone, Besançon, France) were measured in the serum of patients (18 omalizumab, 17 placebo) before therapy and after 16 weeks of therapy with omalizumab or placebo. Tests were performed in duplicate by ELISA according to the manufacturer's instructions. Sensitivity was 2 pg/ml for IL-5, 0.104 pg/ml for IL-6, 100 fg/ml for IL-8, 0.208 pg/ml for IL-10, 1.5 pg/ml for IL-13, 0.04 ng/ml for s-ICAM.

Histamine Release of Basophils

Venous blood was collected from 15 volunteers participating in the study. Seven received omalizumab and 8 received placebo. Mixed leucocyte preparations were obtained by means of dextran sedimentation, as previously described [19]. After sedimentation of red cells (90–120 min), the supernatant containing basophils was carefully removed. Cells were washed with PBS and stimulated with specific allergen (house dust mite mix, cat or dog dander; Allergopharma, Reinbeck, Germany) in increasing amounts (0.1, 1, 10, 100, 1,000 IU) or with 100 IU/ml anti-IgE for 60 min.

The release process was stopped by centrifugation (800 g, 15 min, 4°C), and supernatants were removed for histamine analysis. Total histamine content was determined by lysing aliquots of the cells with 2% HClO₄. Cells incubated without challenge served as an index of spontaneous histamine release (<5% of the total histamine content). Histamine release was expressed as percentage of the total histamine content minus spontaneous release. All experiments were performed in duplicate. Histamine release was measured by an automated fluorometric method [19].

Skin Prick Test

An SPT to perennial allergens (house dust mite, cat and dog dander) was performed before therapy and after 16 weeks of treatment. A positive control was performed with histamine (1 mg/ml). A negative control was performed with diluent. The wheal reaction was read after 15 min, copied to a strip, and the wheal area was analysed using NIH image 1.6 software (National Institute of Health, N.Y., USA). Values were expressed as percentage of the histamine control.

Eosinophil Count

Blood was drawn five times: At the screening visit, at the randomisation visit, at the end of the stable treatment phase, at the end of steroid reduction, and at the visit when the last dose was administered. Blood eosinophil levels were counted as total counts and percentage of leucocytes.

R_{aw} and Non-Specific Airway Responsiveness

R_{aw} as well as PC₂₀ were determined by bodyplethysmography (Jaeger, Würzburg, Germany). Acetylcholine (Sigma) was inhaled with a breath-dependent nebuliser (ATS, Jaeger) at a dose of 0.02 µg/breath in incremental doses up to a 20% decrease in baseline FEV₁. Tests were performed before treatment, after 16 weeks of treatment with either omalizumab or placebo and 12 weeks after discontinuation of treatment.

Total and Free IgE Levels

Total IgE was measured by using a commercial kit (IMx Total IgE, Abbott Laboratories, Abbott Park, Ill., USA). Free IgE was measured by ELISA as previously described [8]. The detection limit was 2.4 ng/ml and the lower limit of quantitation was 1 ng/ml for free IgE.

Adverse Events

The incidence of adverse effects was recorded throughout the study.

Statistical Analysis

All calculations were made as between-group comparisons using the Mann-Whitney U test. $p < 0.05$, using two-tailed tests, was considered significant. Unless otherwise indicated, tests were performed at baseline and at week 16 and the results expressed as percentage change from baseline.

Results (table 3)

Circulating Mediators

IL-13 levels significantly decreased after 16 weeks of treatment ($p < 0.01$) in the omalizumab group compared to the placebo group (fig. 1). No difference was detected for IL-6, IL-10 and s-ICAM levels. IL-5 and IL-8 decreased in the omalizumab-treated group, however without reaching statistical significance.

Histamine Release from Basophils

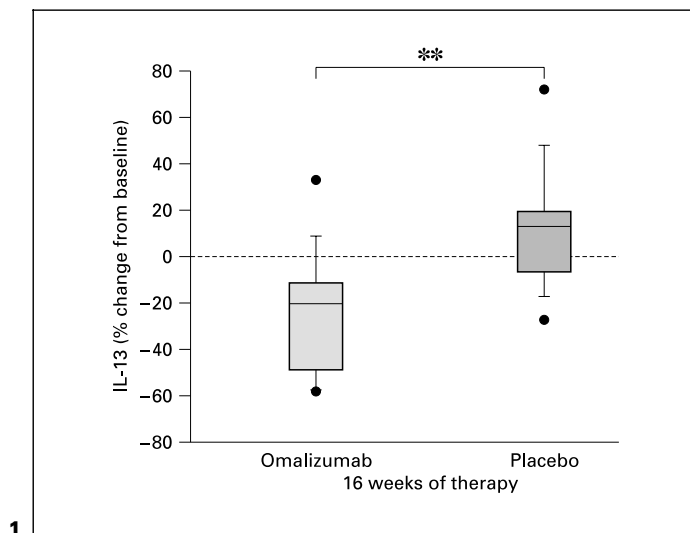
Histamine release from basophils was significantly decreased after 16 weeks of omalizumab treatment ($p < 0.01$) but returned to baseline levels 3 months after discontinuation of treatment (fig. 2).

Skin Prick Test

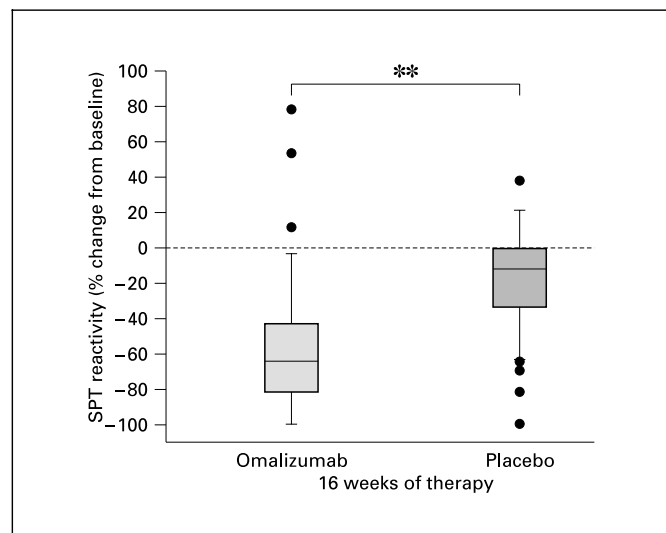
In the omalizumab group, the area of the wheal reaction decreased significantly for all 3 allergens after 16 weeks of treatment ($p < 0.01$) (fig. 3).

Eosinophil Count

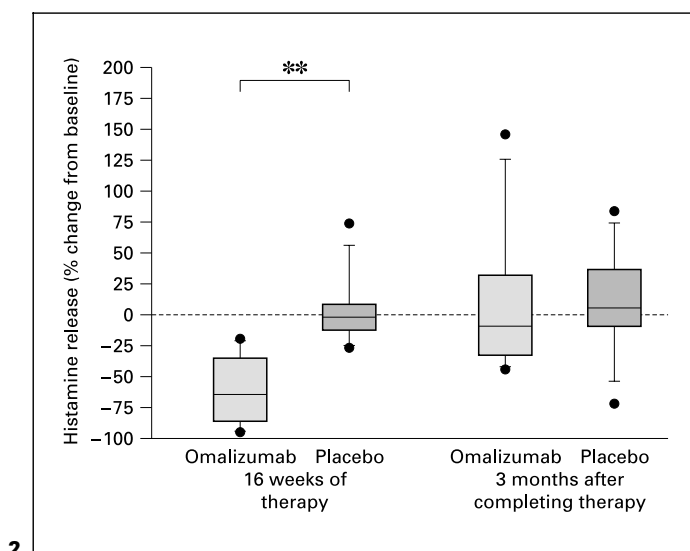
Blood eosinophil count was significantly decreased compared to placebo after 16 and 52 weeks of treatment ($p < 0.01$) (fig. 4).



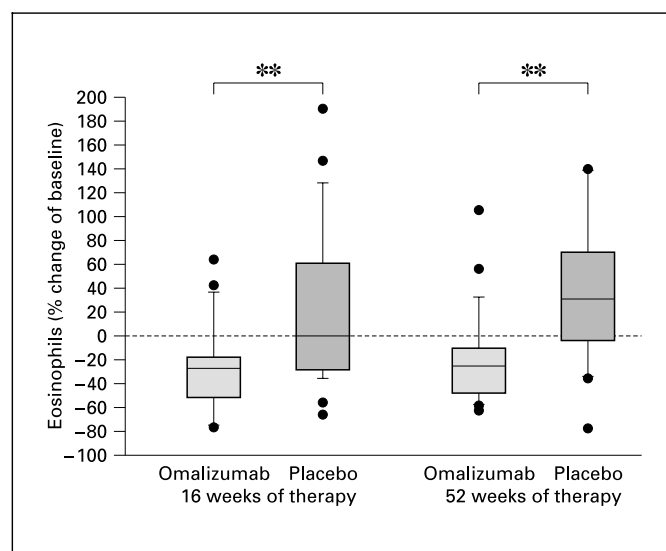
1



3



2



4

Fig. 1. Percentage change from baseline in circulating IL-13. Samples were taken before therapy and after 16 weeks of therapy with omalizumab or placebo. The omalizumab group (n = 18) demonstrated a significant decrease compared to placebo (n = 17).

Fig. 2. Histamine release to specific allergen as percentage of the total histamine content before therapy, after 16 weeks treatment and 3 months after completing trial treatment. After 16 weeks of therapy with omalizumab (n = 7) a significant decrease was seen. After discontinuing omalizumab therapy, the values returned to baseline. No change was seen in the placebo group (n = 8).

Fig. 3. SPT reactivity. Values were calculated as percentage of histamine-induced wheal area before therapy and after 16 weeks of therapy. The omalizumab-treated group (n = 18) demonstrated a significant decrease compared to the placebo group (n = 17).

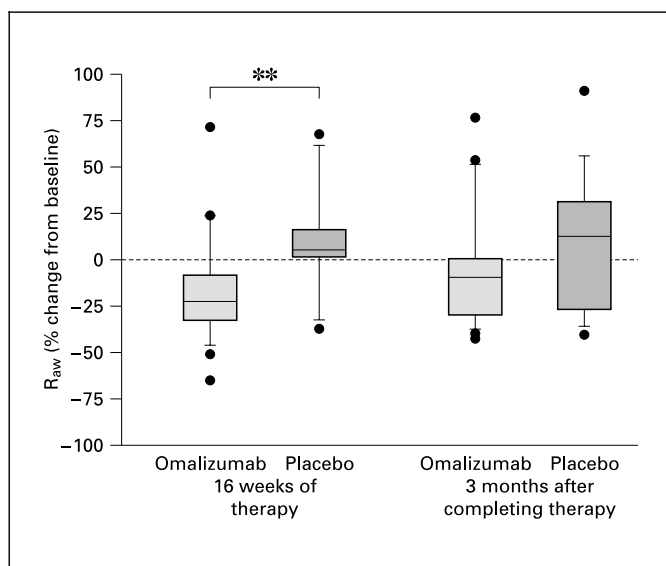
Fig. 4. Peripheral blood eosinophil levels as a percentage change from baseline before and during therapy with either omalizumab (n = 18) or placebo (n = 15). The omalizumab-treated group demonstrated a significant decrease in blood eosinophils compared to the placebo group.

R_{aw} and Non-Specific Airway Responsiveness

R_{aw} decreased significantly in the omalizumab-treated group compared to placebo ($p < 0.01$). Three months after discontinuation of therapy, R_{aw} had almost returned to baseline levels (fig. 5).

PC_{20} significantly increased after 16 weeks compared to the placebo group ($p < 0.05$). After discontinuation of the therapy, no difference between treatment groups was observed (fig. 6).

5



6

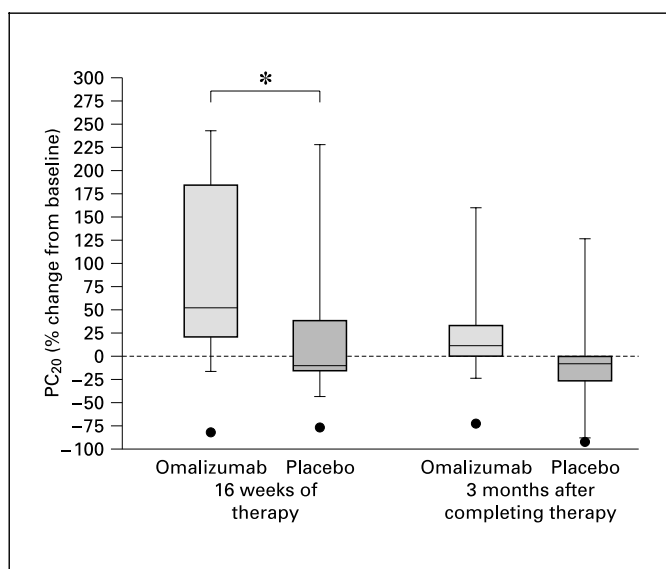


Fig. 5. R_{aw} as a percentage change from baseline after 16 weeks of therapy and 3 months after completing the treatment either with omalizumab ($n = 18$) or with placebo ($n = 14$). A significant decrease was demonstrated in the verum group compared to placebo.

Fig. 6. PC_{20} as a percentage change from baseline after 16 weeks of therapy and 3 months after completing the treatment either with omalizumab ($n = 18$) or with placebo ($n = 14$). The omalizumab-treated group demonstrated a significant increase compared to placebo.

Total and Free IgE Levels

As demonstrated in previous studies, free IgE levels decreased significantly ($p < 0.01$) to <10 IU/ml in all omalizumab-treated subjects while no significant change was observed in the placebo-treated group.

Self-Monitored Asthma Parameters and FEV_1

Over the whole study period, no changes in FEV_1 were seen in the omalizumab group or in the placebo group. PEF increased significantly compared to placebo after 12, 18, 20, 22 and 26 weeks of treatment with omalizumab. The usage of β_2 -agonists decreased significantly beginning with week 12. Symptom score decreased in the omalizumab group at weeks 12, 16 and 26. Daily beclomethasone dipropionate dose reduction was significantly higher in the omalizumab group compared to placebo. These results confirm the data of the main study [17].

Adverse Events

No subject was withdrawn from the study. Adverse events were infrequent and not significantly different in the omalizumab and placebo groups (table 4).

Discussion

Our results confirm that treatment with omalizumab improves allergic asthma symptoms [17, 18]. The use of β_2 -agonists and inhaled corticosteroids decreased significantly. FEV_1 remained stable in spite of the reduced corticosteroid usage. PEF demonstrated a slight increase, reaching statistical significance even under steroid reduction.

In the presented study we were additionally able to demonstrate a significant improvement in R_{aw} measured under tidal breathing conditions which therefore represents a physiological breathing pattern. PC_{20} also improved significantly. The influence of omalizumab on the early allergic response was demonstrated by a decrease in histamine release from basophils and the magnitude of the wheal reaction on the SPT compared to the placebo group. The influence on SPT reactivity was demonstrated for the first time. This confirms that tolerance to allergen exposure is increased and could explain the significant reduction in rescue medication and degree of hyperresponsiveness. Furthermore, we were able to demonstrate a significant decrease in IL-13 in the omalizumab-treated group. It also has to be considered that the cytokine levels in serum could be influenced by the inhalation of beclomethasone dipropionate and β_2 -mimetics. The significant reduction in eosinophils in the omalizumab group might be explained by a reduction in IL-5, while the increase in the placebo group is due to the decreased beclomethasone dipropionate intake.

Treatment was well tolerated and there was no difference in the incidence of adverse events between the treatment groups.

Table 3. Patient data at baseline and after 16 weeks of therapy¹

Parameter	Study group	Baseline	16 weeks
FEV ₁ , % predicted	O	79.0 (41.2–102.8)	77.4 (53.5–110.4)
	P	77.2 (56.9–107.9)	76.6 (52.2–112.7)
PEF, % of predicted	O	90.3 (53.4–108.0)	93.6 (55.6–112.3)
	P	84.78 (59.9–105.0)	85.0 (60.5–98.2)
β ₂ -Agonist usage, puffs/day	O	1.5 (0–8.2)	0.4 (0–9.2)
	P	3.4 (0–7.5)	2.0 (0–9.2)
Symptom score (score 0–4)	O	0.8 (0.3–3)	0.5 (0–2.6)
	P	1.1 (0–2.0)	0.9 (0–2.9)
BDP, puffs 100 µg/day	O	6 (5.5–10)	0.5 (0–4)
	P	6 (5–10)	4 (0–7)
Histamine release, % of complete	O	11.3 (2.13–70.7)	3.0 (0.32–40.3)
	P	12.9 (2.0–69.36)	13.9 (1.8–66.1)
R _{aw} , kP·s/l	O	0.46 (0.22–0.72)	0.37 (0.19–0.57)
	P	0.4 (0.29–0.76)	0.42 (0.17–0.65)
PC ₂₀ , mg ACh	O	1.0 (0.29–2.5)	1.43 (0.36–3.03)
	P	0.99 (0.32–2.0)	1.06 (0.27–2.5)
SPT, % of histamine area	O	130.1 (30.1–321.8)	56.5 (0–377.6)
	P	148.5 (19.2–658.4)	121.4 (0–614.6)
IL-5, pg/ml	O	8.95 (1.6–27.0)	6.3 (0.48–24.7)
	P	7.9 (0.7–101.6)	6.76 (0–130.9)
IL-6, pg/ml	O	1.1 (0.53–5.9)	1.2 (0.4–10.1)
	P	1.4 (0.4–4.1)	1.2 (0.5–3.5)
IL-8, pg/ml	O	3.74 (0.8–20.1)	2.1 (0–5.1)
	P	2.6 (0.65–14.6)	1.84 (0–4.7)
IL-10, pg/ml	O	2.1 (0.9–35.6)	1.6 (0.6–37.1)
	P	2.1 (0.4–50)	1.2 (0.3–50)
IL-13, pg/ml	O	9.4 (4.8–15.9)	7.0 (3.82–10.81)
	P	7.16 (4.8–12.6)	8.5 (5.1–10.6)
s-ICAM, pg/ml	O	142.5 (57.8–234.9)	146.6 (50.7–229.8)
	P	136 (80.5–230.9)	143.3 (65.8–250.4)
Eosinophils, %	O	6.2 (2–9.5)	1.3 (1–11)
	P	3.5 (0.5–16.7)	6.0 (0.3–12.6)
IgE, IU/ml	O	183 (21–483)	6.4 (0.4–9.3) ²
	P	148 (45–683)	131 (21–471)

O = Omalizumab; P = placebo; BDP = beclomethasone dipropionate.

¹ Medians and ranges.

² Free IgE.

Our results indicate that subcutaneously administered omalizumab is a well-tolerated therapy to control asthma symptoms by decreasing immediate mediator release of mast cells and basophils and improving symptoms [20]. The beneficial therapeutic effect of omalizumab can be

understood as an anti-inflammatory effect due to decreased IgE levels, reduced cytokines (IL-13) and cellular activation. Additionally, IgE inhibition might potentiate the effects due to the negative feedback of reduced IgE levels on the production of IgE [21] and its receptors [22].

Table 4. Number of patients experiencing an adverse event

Effect	Placebo	Omalizumab
Post-injection phenomenon	1 (5.9%)	1 (5.6%)
Gastroenteritis	1 (5.9%)	1 (5.6%)
Viral infection	3 (17.6%)	2 (11.1%)
Moniliasis	0 (0%)	1 (5.6%)
Dizziness	0 (0%)	1 (5.6%)
Bronchitis	1 (5.9%)	1 (5.6%)
Pharyngitis	0 (0%)	1 (5.6%)
Upper respiratory tract infection	1 (5.9%)	2 (11.1%)
Angio-oedema	1 (5.9%)	0 (0%)
Transient deafness	1 (5.9%)	0 (0%)
Total ¹	9 (52.9%)	7 (38.9%)

¹ A patient with multiple adverse events within a body system is counted only once in the total row.

Inhibition of IgE-mediated release of previously formed or newly synthesised mediators from target cells might lead to decreased levels of circulating mediators and cytokines. Modulating mechanisms of released mediators and the modulation of high- and low-affinity IgE receptors which are expressed on various immune cells are able to regulate inflammatory mechanisms [23]. Another important aspect is the decrease in the circulating Th₂ cytokines IL-5 and IL-13, which can act indirectly via B cells, mast cells and eosinophils to change the asthma phenotype. Alternatively, IL-13 may act directly on the airways [24, 25].

Treatment with omalizumab provides a new strategy to treat allergic asthma and improves the present pharmacological tools with the possibility of targeting different organs simultaneously.

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