

Omalizumab Protects against Allergen-Induced Bronchoconstriction in Allergic (Immunoglobulin E-Mediated) Asthma

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Key Words

Allergen · Allergic asthma · Bronchoconstriction · Immunoglobulin E · Omalizumab

Abstract

Background: Omalizumab has been shown to suppress responses to inhaled allergens in allergic asthma patients with pretreatment immunoglobulin E (IgE) ≤ 700 IU/ml. To extend current dosing tables, we evaluated the potential of high omalizumab doses to block allergen-induced bronchoconstriction in patients with higher IgE levels. **Methods:** Asthmatic adults (18–65 years; body weight 40–150 kg) were divided into groups according to screening IgE (group 1: 30–300 IU/ml; group 2: 700–2,000 IU/ml) and randomized 2:1 to omalizumab/placebo every 2 or 4 weeks for 12–14 weeks. Allergen bronchoprovocation (ABP) testing was performed before treatment and at weeks 8 and 16. The primary efficacy endpoint, the early-phase allergic response (EAR), was defined as the maximum percentage drop in forced expiratory volume in 1 s during the first 30 min after ABP. Serum free IgE was determined as a pharmacodynamic endpoint,

and the exhaled fractional concentration of nitric oxide (FE_{NO}) was an exploratory endpoint. **Results:** Fifty patients were included in the study. Omalizumab improved EAR; at week 8, EAR was 23.1% for placebo, 9.3% in group 1 ($p = 0.018$ versus placebo) and 5.6% in group 2 ($p < 0.001$). At week 16, EAR was 20%, 11.8% ($p = 0.087$) and 5.1% ($p < 0.001$), respectively. Free IgE decreased in groups 1 and 2 and remained < 50 ng/ml in all patients during weeks 6–16. Omalizumab completely suppressed FE_{NO} increases after ABP in both groups. **Conclusions:** Omalizumab blocked early asthmatic responses over a broad range of IgE/body weight combinations. Extending the dosing tables enables omalizumab to benefit a wider range of patients.

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Introduction

Allergic asthma is an inflammatory disease characterized by bronchial hyperresponsiveness, airway eosinophilia, goblet cell hyperplasia and production of allergen-specific immunoglobulin E (IgE). IgE is a key mediator of allergic responses and is central to the induction and maintenance of airway inflammation and asthma-related symptoms [1]. Inhibiting IgE represents a logical therapeutic approach to allergic asthma.

Omalizumab is a humanized anti-IgE monoclonal antibody approved in a number of countries throughout the world. In the EU, omalizumab is indicated for patients (≥ 6 years of age) with inadequately controlled severe allergic asthma (as described in the summary of product characteristics [2]), and in the USA, it is indicated for patients (≥ 12 years of age) with moderate-to-severe allergic asthma (as described in the prescribing information [3]). Adding omalizumab to current asthma therapy has been shown to be effective and well tolerated [4–9].

The dose and dosing frequency of omalizumab is determined by body weight and pretreatment serum IgE, using dosing tables [2]. Omalizumab was initially indicated for patients with IgE of 30–700 IU/ml, with a dose of 75–375 mg every 2 or 4 weeks. More recently, it was hypothesized that patients with inadequately controlled allergic asthma and high serum IgE (>700 IU/ml) may also benefit, but there has been no placebo-controlled demonstration of the efficacy of omalizumab in this subpopulation [10]. However, pharmacokinetic (PK)/pharmacodynamic (PD) modeling and correlation with clinical outcome indicated that it should be possible to treat patients with higher baseline IgE if doses above 375 mg can be administered [11]. Therefore, we evaluated the effects of omalizumab doses up to 600 mg every 2 weeks on early asthmatic responses using allergen bronchoprovocation (ABP) testing and assessed the safety of treatment in patients with allergic asthma and pretreatment IgE up to 2,000 IU/ml. The data from this study support the extension of the omalizumab dosing table in Europe [2], which was approved in 2010.

Methods

Study Design and Patients

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of omalizumab in two groups of patients with different pretreatment IgE concentrations. The study was designed, implemented and reported in accordance with good clinical practice, local regulations and the Declaration

of Helsinki. The protocol and informed consent form were reviewed and approved by institutional review boards and/or ethics committees. Written informed consent was obtained from patients before randomization.

Patients aged 18–65 years with a body weight of 40–150 kg were eligible if they had asthma, prebronchodilator forced expiratory volume in 1 s (FEV_1) $\geq 65\%$ predicted and had been asthma exacerbation-free for ≥ 4 weeks. Patients had to have had well-characterized skin reactivity to a specific allergen within 2 years before screening. At screening, patients had to demonstrate a 20% fall in FEV_1 in response to methacholine at a provocative concentration ≤ 16 mg/ml and a 20% fall in FEV_1 in response to an allergen at a cumulative provocative dose (PD_{20}) in a bronchoprovocation test [12, 13]. Exclusion criteria included history of an asthma attack requiring a visit to an emergency room in the 6 weeks before or during screening, history of an asthma attack requiring treatment with intubation and mechanical ventilation in the 12 months before day 1 of the study, asthma exacerbation requiring treatment with oral or intravenous corticosteroids in the previous 3 months and history of intolerance to methacholine or ABP. Current active smokers with a smoking history of ≥ 5 pack-years or patients with elevated IgE due to suspected parasitosis were also excluded.

Patients were divided into two groups: group 1 had low screening IgE (30–300 IU/ml) and group 2 had high screening IgE (700–2,000 IU/ml). A third group of patients (screening IgE 301–699 IU/ml) was also enrolled and treated with omalizumab as part of an exploratory investigation; however, the objective and study design for this group differed from those for groups 1 and 2, and therefore the third group was not included in the analyses presented here. Patients in groups 1 and 2 were randomized in a 2:1 ratio to omalizumab or placebo (both administered by subcutaneous injection). Doses and dosing frequencies (every 2 or 4 weeks) are given in table 1. Concomitant medication, including short-acting β -agonists (withheld for at least 6 h prior to visits for ABP), leukotriene modifiers (constant dosing throughout study period and withheld 48 h prior to ABP testing) and low-dose inhaled corticosteroids (ICSs; as defined by Global Initiative for Asthma guidelines, e.g. ≤ 400 μ g/day budesonide, ≤ 250 μ g/day fluticasone), was permitted provided it remained stable throughout the study.

Prohibited medications included high-dose (as defined by Global Initiative for Asthma guidelines) ICSs, long-acting β -agonists alone or in combination with ICSs, oral corticosteroids (within 4 weeks of the first study visit), antihistamines (within 24 h of bronchoprovocation visits or skin prick test) and theophylline.

The study comprised a screening period (28–6 days before first dose), baseline evaluation and 12- to 14-week treatment period followed by a study completion evaluation (12 weeks after last dose). At an initial screening visit, eligibility was assessed, a skin prick test was performed to identify allergens for ABP testing and standard spirometry and methacholine challenge were conducted. PD_{20} for specific allergen was determined at a second screening visit (≥ 24 h after methacholine challenge). Baseline evaluations included ABP, spirometry, serum total and free IgE and fractional concentration of exhaled nitric oxide (FE_{NO}).

Study Assessments

The primary efficacy endpoint was the early-phase allergic response (EAR; maximum percentage drop in FEV_1 during first 30

Table 1. Omalizumab dose (in milligrams) and regimen according to patient baseline IgE level and weight

Screening IgE	Body weight						
	>40–50 kg	>50–60 kg	>60–70 kg	>70–80 kg	>80–90 kg	>90–125 kg	>125–150 kg
Group 1							
30–100 IU/ml	150	150	150	150	150	300	300
>100–200 IU/ml	300	300	300	300	300	225	300
>200–300 IU/ml	300	300	225	225	225	300	375
Group 2							
>700–800 IU/ml		450	450	525	600	600	600
>800–900 IU/ml		450	525	600	600	600	600
>900–1,000 IU/ml	450	525	600	600	600	600	600
>1,000–1,100 IU/ml	450	600	600	600	600	600	600
>1,100–1,200 IU/ml	525	600	600	600	600	600	600
>1,200–2,000 IU/ml	600	600	600	600	600	600	600

Omalizumab was administered every 4 weeks (not shaded) or every 2 weeks (shaded).

min after ABP test), where $\text{EAR} (\%) = 100 \times [\text{FEV}_1 (\text{time } 0) - \text{minimum FEV}_1 (10, 15, 30 \text{ min})] / \text{FEV}_1 (\text{time } 0)$. The least squares mean change in FEV_1 area under the curve (AUC) over 30 min after ABP was also assessed at weeks 8 and 16. Secondary efficacy endpoints included the late-phase allergic response (LAR; maximum percentage drop in FEV_1 over 3–8 h after ABP test), where $\text{LAR} (\%) = 100 \times [\text{FEV}_1 (\text{time } 0) - \text{minimum FEV}_1 (3 \text{ to } 8 \text{ h})] / \text{FEV}_1 (\text{time } 0)$.

PK and PD analyses consisted of total omalizumab serum concentrations and free and total (i.e. sum of free and omalizumab-bound) IgE. Blood samples for these analyses were collected before dosing on all dosing days, before the final ABP test (week 16, i.e. 2 or 4 weeks after the last dose) and 12 weeks after the last dose. Serum total omalizumab concentrations were determined using specific enzyme-linked immunosorbent assays, as described previously [11], with a lower limit of quantification of 15.6 ng/ml. Serum free and total IgE concentrations were determined using specific and sensitive immunoassays with lower and upper limits of quantification of 0.78 and 150 ng/ml for free IgE and a lower limit of quantification of 0.48 ng/ml for total IgE (1.0 IU/ml IgE corresponds to 2.42 ng/ml IgE). The free IgE assay allowed the detection of unbound IgE in the presence of omalizumab. Exploratory assessments of FE_{NO} were made 0, 8 and 24 h after ABP at baseline, week 8 and week 16. FE_{NO} was measured according to current guidelines [14] using the NIOX NO analyzer (Aerocrine, Solna, Sweden). Safety assessments consisted of recording of adverse events (AEs), physical examinations, medical history, vital signs, electrocardiograms (ECGs) and laboratory evaluations.

Allergen Provocation

Allergen provocation testing was performed using a standardized protocol [15] at screening (determination of PD_{20}), baseline, week 8 and week 16 with allergen extracts from grass, cat, birch or *Dermatophagoides farinae* (Allergopharma Joachim Ganzer KG, Hamburg, Germany), depending on the patient's sensitivity. Fifteen patients were challenged with birch allergen, 11 patients with cat allergen, 8 patients with grass allergen and 14 patients

with *D. farinae* allergen. All ABP tests were standardized with the Aerosol Provocation System® (CareFusion, Wuerzburg, Germany), which automatically determines administered allergen doses by measuring effective nebulization time and referring it to allergen concentration and nebulizer power [16]. All patients had significant responses to allergen challenge (PD_{20}) before treatment. FEV_1 was determined before allergen challenge, at 10, 15, 30 and 60 min, and then hourly for 8 h.

Statistical Analyses

In all analyses and summaries, group 1 and group 2 refer to the patients receiving omalizumab in these groups. Patients receiving placebo in the two groups were pooled for the analyses. The primary efficacy outcome (EAR) was analyzed using a linear model with a fixed effect for treatment group and baseline EAR as a covariate. EAR was compared between group 2 and placebo (two-sided test for superiority at the 5% α level). If this test was statistically significant, EAR was also compared between group 1 and placebo. The planned enrollment of 24 patients per group was based on 90% power to detect a 14% difference in EAR between omalizumab and placebo at the two-sided 5% α level and estimated drop-out rates. FEV_1 AUC for EAR was calculated using the linear trapezoidal method based on FEV_1 data between 0 (pre-ABP) and 30 min after ABP. Exploratory analyses were summarized descriptively (means and standard deviation (SD) or medians).

Results

Patient Disposition and Baseline Characteristics

Fifty patients were enrolled, 4 of whom withdrew prematurely (2 of the patients did not show sensitivity to the test allergen, 1 patient was discontinued due to the serious AE 'malignant melanoma', which was not suspected to be related to the study drug, and another patient was

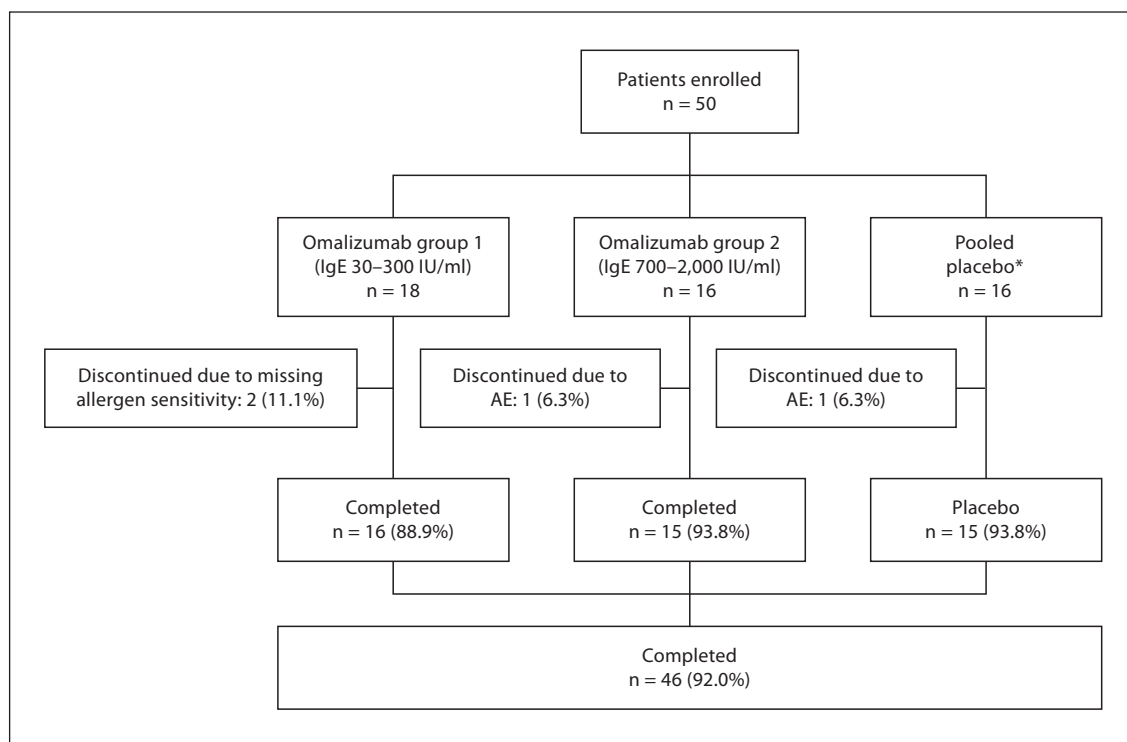


Fig. 1. Patient disposition. * Eight patients had low IgE (30–300 IU/ml) and 8 patients had high IgE (700–2,000 IU/ml).

Table 2. Baseline demographic and clinical characteristics

	Omalizumab		Placebo (pooled) ^a (n = 16)
	Group 1: low IgE (n = 18)	Group 2: high IgE (n = 16)	
Mean age $\pm$ SD, years	36 $\pm$ 11.9	29 $\pm$ 11.0	34 $\pm$ 10.4
Range	19–63	19–50	21–57
Sex, n (%)			
Male	13 (72)	6 (37.5)	9 (56)
Female	5 (28)	10 (62.5)	7 (44)
Race, n (%)			
Caucasian	18 (100)	16 (100)	15 (94)
Black	0	0	1 (6)
Mean weight $\pm$ SD, kg	83.6 $\pm$ 14.2	76.6 $\pm$ 16.4	76.5 $\pm$ 16.7
Range	58–109	48–100	44–109
Mean FEV ₁ $\pm$ SD, % predicted	94.2 $\pm$ 17.1	97.8 $\pm$ 12.5	96.6 $\pm$ 15.4
Median (range)	89.5 (74.1–132.2)	101.1 (72.7–113.7)	91.9 (68.8–125.2)
Mean FEV ₁ $\pm$ SD, liters	3.5 $\pm$ 0.82	3.4 $\pm$ 0.75	3.3 $\pm$ 0.85
Median (range)	3.2 (2.3–4.9)	3.4 (1.8–4.6)	3.1 (2.1–4.9)
Mean serum IgE at screening $\pm$ SD, IU/ml	131.4 $\pm$ 62.3	1,325.3 $\pm$ 312.4	598.5 $\pm$ 592.9
Median (range)	121 (41–270)	1,338 (882–1,940)	230 (63–1,766)

^a Eight patients had high IgE and 8 had low IgE.

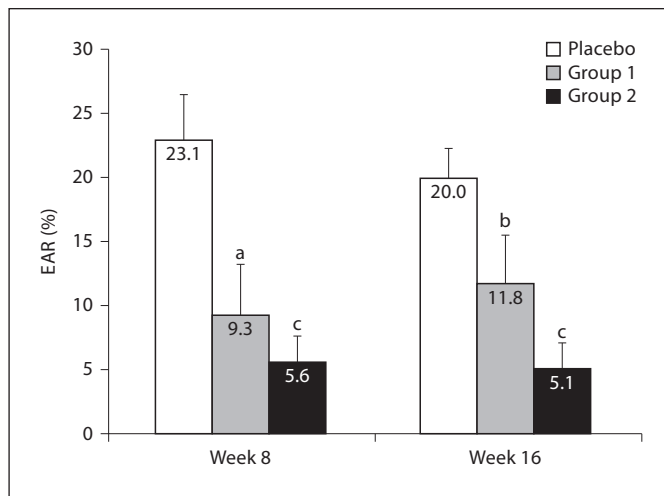


Fig. 2. EAR (defined as the maximum percentage drop in FEV₁ in the first 30 min after ABP testing) at weeks 8 and 16 in group 1 (low screening IgE, i.e. 30–300 IU/ml) and group 2 (high screening IgE, i.e. 700–2,000 IU/ml). Values are least squares means and standard errors. ^a $p = 0.018$, ^b $p = 0.087$, ^c $p < 0.001$ versus placebo.

withdrawn due to the AE ‘asthma exacerbation’; fig. 1). Two patients were replaced. Baseline characteristics are shown in table 2. ICSs were used by 8 of the 18 patients from group 1, 7 of the 16 patients from group 2 and 7 of the 16 patients receiving placebo. In subjects receiving ICSs, the mean dose was 262.5 µg for group 1, 314.3 µg for group 2 and 271.4 µg for the placebo group, referring to budesonide or budesonide-equivalent doses of other ICSs.

Efficacy Analyses

Primary Endpoint: EAR following ABP

At week 8, the least squares mean EAR in the placebo group was 23.1%, and omalizumab reduced it to 9.3% in group 1 and to 5.6% in group 2 ($p = 0.018$ and $p < 0.001$, respectively, versus placebo). At week 16, the least squares mean EAR in the placebo group was 20.0%, and omalizumab reduced it to 11.8% in group 1 and to 5.1% in group 2 ($p = 0.087$ and $p < 0.001$, respectively, versus placebo; fig. 2). Least squares means of FEV₁ AUC for EAR at weeks 8 and 16 were significantly higher for groups 1 and 2 compared with the placebo group (table 3).

Secondary Endpoint: LAR following ABP

LAR $\geq 15\%$ was observed in 16 patients at baseline, of whom 10 and 13 provided LAR data at weeks 8 and 16, respectively (table 4). Statistical analysis was not per-

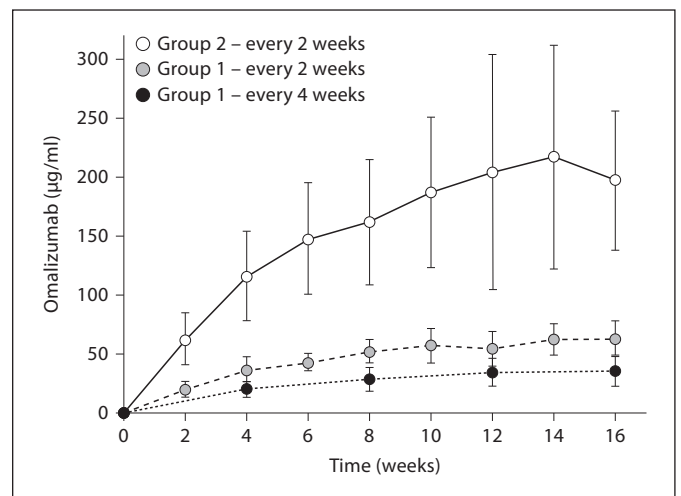


Fig. 3. Arithmetic means and SDs of omalizumab trough concentrations over time for group 1 (low screening IgE, i.e. 30–300 IU/ml) and group 2 (high screening IgE, i.e. 700–2,000 IU/ml). For group 1, results are shown separately for patients who received omalizumab every 4 weeks ($n = 10$ –12) and every 2 weeks ($n = 5$ –6). For group 2, $n = 15$ –16.

formed, as too few patients had LAR measurements. The available data indicated a trend for attenuation of LAR in patients receiving omalizumab.

PK/PD Analysis: Omalizumab Trough Concentrations, Free IgE and Total IgE

Omalizumab trough concentrations increased during treatment, indicating accumulation during repeated dosing (fig. 3). For group 1, concentrations are shown separately for patients receiving omalizumab every 2 weeks and every 4 weeks. As expected, trough concentrations were higher in group 2 than in group 1. Free IgE dropped after the first dose in both omalizumab-treated groups and remained low until week 16 (fig. 4a). At the end of the study (12 weeks after the last dose), an increase was observed, but levels remained below those at baseline. Mean free IgE remained stable in placebo-treated patients throughout the study. Free IgE was <50 ng/ml in all omalizumab-treated patients in group 1 during weeks 2–16 (means ranged from 12.6 to 22.7 ng/ml) and in all omalizumab-treated patients in group 2 during weeks 6–16 (means ranged from 19.0 to 23.3 ng/ml). Total IgE at 2 weeks increased from predose levels in groups 1 and 2 and remained at those levels until week 16. Total IgE was considerably higher in group 2 than in group 1 throughout the study. Placebo patients had little change in total IgE throughout the study (fig. 4b).

Table 3. FEV₁ AUC for EAR and treatment effect estimates from a mixed-model analysis for groups with low (30–300 IU/ml) and high screening IgE (700–2,000 IU/ml) treated with omalizumab compared with placebo

Week	Treatment	FEV ₁ AUC for EAR, LS mean	Difference versus placebo	p value
8	Placebo	89.5 (2.64)		
	Group 1: low IgE	103.0 (4.05)	13.5 (3.5–23.5)	0.010
	Group 2: high IgE	105.3 (5.61)	15.8 (2.5–29.2)	0.024
16	Placebo	89.9 (3.40)		
	Group 1: low IgE	100.7 (3.98)	10.8 (0.1–21.5)	0.049
	Group 2: high IgE	103.3 (5.16)	13.4 (0.6–26.2)	0.041

Values in parentheses represent standard errors or 95% confidence intervals, as appropriate. LS = Least squares.

Table 4. LAR in patients with LAR ≥15% at baseline allergen provocation testing in group 1 (omalizumab-treated patients with low screening IgE of 30–300 IU/ml), group 2 (omalizumab-treated patients with high screening IgE of 700–2,000 IU/ml) and the placebo group

	Omalizumab		Placebo (pooled)
	Group 1: low IgE	Group 2: high IgE	
Baseline			
n	8	3	5
Mean LAR, %	22.5 (6.12)	25.7 (12.62)	27.4 (7.27)
Week 8			
n	6	1	3
Mean LAR, %	5.3 (12.13)	–3.5 (–)	19.1 (13.42)
Week 16			
n	7	2	4
Mean LAR, %	0.23 (7.109)	1.5 (1.53)	12.3 (7.09)

Values in parentheses represent SDs.

Exploratory Analyses: Impact of Omalizumab Administration on FE_{NO} Production following ABP

The percentage change in median FE_{NO} 24 h after ABP testing relative to median pre-ABP FE_{NO} is shown in figure 5. At baseline, post-ABP FE_{NO} increased by between 31 and 67% compared to before ABP in all groups. Comparable values were observed with placebo at weeks 8 and 16 (42 and 64%, respectively). In omalizumab-treated patients, the post-ABP rise in FE_{NO} was attenuated at these

time points, leading to changes of –8 and –7% at weeks 8 and 16, respectively, in group 1, and 12 and –16% at weeks 8 and 16, respectively, in group 2 (fig. 5). At baseline, there was no numerical difference in median FE_{NO} after 8 h relative to pre-ABP values in group 1 or group 2 and a decrease of 6 parts per billion (ppb) in the placebo patients, compared with increases at 24 h of 15, 24 and 11 ppb in group 1, group 2 and the placebo group, respectively. Therefore, FE_{NO} measurements at 8 h seem to be less sensitive to bronchoprovocation and were not used to assess the omalizumab treatment effect.

Safety

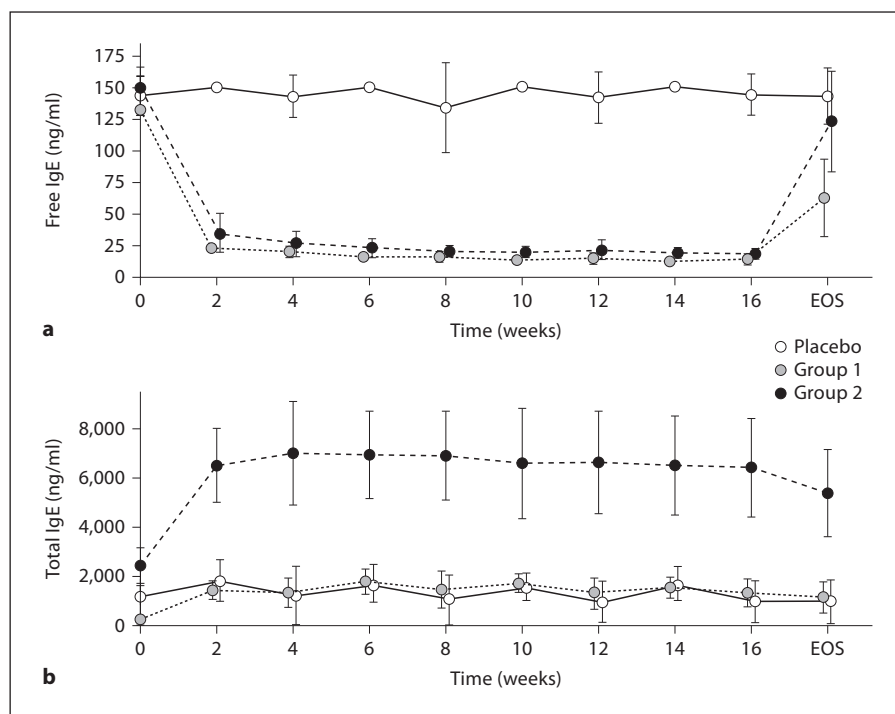
All treatments were well tolerated. The majority of AEs were considered mild or moderate and unrelated to the study drug, with no unexpected events. Nine patients in group 1, 16 in group 2 and 12 receiving placebo experienced an AE. Most AEs were categorized as ‘infections and infestations’, with nasopharyngitis the most frequent [12/50 patients (24%): 3 in group 1, 5 in group 2 and 4 in the placebo group]. One patient in each group had more than 1 nasopharyngitis event. The second most frequent category of AEs affected the respiratory system, although no single event was more frequent than any other. AEs were considered possibly treatment-related in 7 patients (1 in group 1, 2 in group 2, 4 in the placebo group).

The incidence of serious AEs was low; 1 patient from group 2 had a severe malignant melanoma and was withdrawn, while another patient (from group 1) had a previously planned overnight hospitalization for breast papilloma but was not withdrawn. None of these events was considered related to the study drug. Two placebo-treated patients experienced severe AEs; 1 had severe bronchospasm and a moderate asthma exacerbation that led to withdrawal, and another had severe bronchitis. None of these events was considered related to the study drug. There were no deaths and no clinically relevant changes in clinical laboratory tests, vital signs or ECGs.

Discussion

This randomized, double-blind, placebo-controlled study demonstrates the protective effects of omalizumab against allergen-induced bronchoconstriction in patients with allergic asthma and baseline IgE up to 2,000 IU/ml. Omalizumab suppressed the EAR to allergen at 8 weeks, with sustained suppression at 16 weeks compared to placebo. Protection against allergen-induced bronchoconstriction was also seen in patients with lower initial se-

Fig. 4. Arithmetic means and SDs of free IgE (**a**) and total IgE (**b**) over time for group 1 (low screening IgE, i.e. 30–300 IU/ml) and group 2 (high screening IgE, i.e. 700–2,000 IU/ml) compared with placebo. Values of free IgE above the upper limit of quantitation (150 ng/ml) were set to 150 ng/ml. All individual values of total and free IgE were above the lower limit of quantitation. For group 1, data from patients who received omalizumab every 4 weeks and every 2 weeks are pooled [$n = 15$ –18 for weeks 0, 4, 8, 12, 16 and end of study (EOS) and $n = 5$ –6 for weeks 2, 6, 10 and 14]. For group 2, $n = 15$ –16. For placebo, $n = 15$ –16 for weeks 0, 4, 8, 12, 16 and EOS and $n = 8$ –9 for weeks 2, 6, 10 and 14.



rum IgE (30–300 IU/ml) versus placebo at week 8; however, statistical significance was not reached at week 16, possibly due to the small sample size. Regarding FEV₁ AUC over 30 min after ABP, the protective effect of omalizumab reached statistical significance in both groups at weeks 8 and 16.

Our findings are consistent with a previous study in which patients with serum IgE <700 IU/ml underwent allergen challenge during 12 weeks of treatment with omalizumab [17]. In that study, early and late asthmatic responses were suppressed to 15.3 and 4.7%, respectively, following anti-IgE treatment ($p < 0.002$ compared with placebo). Other studies have also shown that omalizumab reduces early and late asthmatic responses [18, 19], with significant improvements in FEV₁ after allergen challenge during both phases [19].

Trough omalizumab concentrations appeared to reach a plateau between 14 and 16 weeks, indicating that a PK steady state has been reached. Assuming that it takes 5 times the elimination half-life to reach steady state, the estimated half-life of omalizumab would be about 20–22 days, which is in the range of values reported previously (18.2 days [20] and 26 days [2]).

Clinical benefit with omalizumab is observed when serum free IgE is reduced to ≤ 50 ng/ml [21, 22]. In our study, protection against allergen-induced bronchocon-

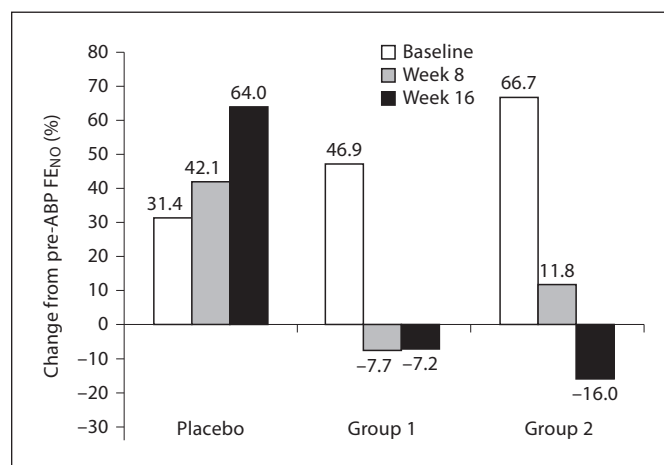


Fig. 5. Percent change in median FE_{NO} 24 h after ABP relative to median pre-ABP FE_{NO} at baseline and after 8 and 16 weeks of treatment with placebo or omalizumab. Group 1: low screening IgE, i.e. 30–300 IU/ml; group 2: high screening IgE, i.e. 700–2,000 IU/ml.

striction was accompanied by consistent reductions of free IgE in both groups. All omalizumab-treated patients had free IgE levels <50 ng/ml, at the latest from week 6 onwards. This reduction is consistent with previous evidence that omalizumab reduces serum free IgE by 89–

99% in patients with allergic asthma [5, 9]. The increase in total IgE (reaching a plateau after 2 weeks) in the current study is also consistent with previous studies, and results from the formation of biologically inert omalizumab-IgE complexes that are cleared slowly compared with free IgE [11]. Both free and total IgE levels measured after omalizumab administration are the result of the interaction of the antibody with IgE and cannot be used for dose determination or adjustment (for more details, see the summary of product characteristics [2] and prescribing information [3]).

Omalizumab has been shown to reduce airway inflammation, particularly eosinophilic inflammation, in patients with asthma [17, 23–25]. In the current study, omalizumab reduced airway inflammation as measured by FE_{NO}, a noninvasive marker of airway inflammation. This is the first clinical study demonstrating that increases in FE_{NO} normally seen after ABP are completely abolished by anti-IgE treatment, with effects sustained throughout the 16-week study.

There were no unexpected safety issues in the current study, and the proportion of serious AEs was low in all groups. Patients who received higher doses of omalizumab, based on their higher baseline IgE levels, had a slightly greater frequency of AEs than those who followed the previously established dosing regimen. ‘Infections and infestations’ was the most frequent AE class. Data from another study have shown that omalizumab at high doses in patients with IgE/body weight combinations outside the initially approved dosing table had a safety, PK and PD profile consistent with that previously reported [26].

Our findings indicate that omalizumab is effective in a broader range of IgE/body weight combinations than specified in the original dosing tables. In the pivotal Investigation of omalizumab in Severe Asthma Treatment study, 20.5% of patients failed screening because their total IgE levels and/or body weight fell outside the original dosing table limits (Novartis data on file). Furthermore, in a large observational study in patients ≥ 6 years of age with severe or difficult-to-treat asthma (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens), at least a third of patients would have fallen outside the original dosing table because of IgE levels or body weight [27] had omalizumab been available at the time.

In conclusion, this study demonstrates that omalizumab blocks early asthmatic responses over a broad range of IgE/body weight combinations and downregulates airway inflammation. Expanding the dosing tables has the potential to enable access to omalizumab for patients with unmet medical needs. Our study was part of the development program for the extended omalizumab dosing table that was recently approved in Europe.

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