Omalizumab in patients with severe asthma: the XCLUSIVE study

Christian Schumann[1], Cornelia Kropf[1], Thomas Wibmer[1], Stefan Rüdiger[1], Kathrin Magdalena Stoiber[1], Antje Thielen[2], Wolfgang Rottbauer[1] and Claus Kroegel[3]

1 Department of Internal Medicine II, University of Ulm Medical Center, Ulm, Germany
2 Novartis Pharmacy, Nuremberg, Germany
3 Department of Pneumology and Allergy, Medical Clinics I University, Jena, Germany

Abstract

Background and Aims: Although the efficacy and safety of omalizumab (OMA) in uncontrolled severe allergic asthma has been demonstrated in several randomised controlled trials (RCTs), information on the treatment in a practice-related setting is limited. Thus, the purpose of this prospective multi-centre study (XCLUSIVE) was to investigate the efficacy, compliance and utilisation of OMA therapy in real-life clinical practice in Germany.

Methods: One hundred ninety-five asthmatic patients initiated on anti-Immunoglobulin E (IgE) IgE treatment were followed-up for 6 months. Forced expiratory volume in 1 s (FEV_1), exacerbation rate, days of absence, asthma symptoms [Asthma Control Questionnaire (ACQ)], a Global Evaluation of Treatment Effectiveness (GETE) and medication use were assessed.

Results: Measured outcome variables improved after a 16-week treatment period with OMA (FEV_1 +13.7% predicted $P < 0.05$, exacerbation rate −74.9% $P < 0.0001$, days of absence −92.1% $P < 0.001$, ACQ −43.7% $P < 0.0001$). Investigators evaluated the effectiveness of OMA by GETE in 78.8% as excellent or good (responder), and in 12.6%/8.6% as moderate/poor or worse (non-responder). Responders demonstrated better improvement of FEV_1, exacerbation rate, days of absence, ACQ and reduction of oral corticosteroids compared with non-responders.

Conclusion: Results of effectiveness strongly suggest that the efficacy demonstrated in RCTs can be transposed to a clinical practice-related setting.

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Key words
omalizumab – real-life experience – safety – severe persistent asthma

Correspondence
Christian Schumann, MD, University of Ulm Medical Center, Department of Internal Medicine II, Albert-Einstein-Allee 23, 89081 Ulm, Germany
Tel: +49 731 500 45022
Fax: +49 731 500 45023
email: christian.schumann@uniklinik-ulm.de

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Christian Schumann and Claus Kroegel wrote the manuscript; Cornelia Kropf, Thomas Wibmer, Stefan Rüdiger, Kathrin Magdalena Stoiber, Antje Thielen and Wolfgang Rottbauer analyzed the data, performed the statistics and collaborated in the literature research.

Ethics
All subjects gave written informed consent prior to their inclusion in the study, and the study was approved by the local ethical committee in accordance with the standards laid down in the Declaration of Helsinki

Conflict of interest
CS has received reimbursement from Novartis for attending scientific conferences and holding talks. CK has been financially compensated by Novartis for giving talks at scientific conferences and for consultations. TW, SR and KS have no conflicts. SS and AT are employees at Novartis Pharma GmbH. The Clinic of Internal Medicine II at the University Clinic Ulm and the Pulmonary Department at the University Medical Clinic of the Friedrich-Schiller-University Jena received funds for services performed for participation in single- and multi-centre clinical phase I–IV trials organised by various pharmaceutical companies.

Introduction

Asthma is a chronic inflammatory disease that continues to show an alarming increase in incidence, severity and mortality in a few developed countries as well as in many developing countries (1). Exposure to tobacco smoke and occupational dust are the main self-inflicted environmental risk factors influencing the development and expression of asthma at present. However, in the future, it is likely that climatic changes related to global warming leading to an increase in environmental risk factors may represent a major hazard for asthmatics resulting in innumerable deaths (2, 3).

Epidemiological data show that a high proportion of patients with severe asthma are atopic (4). Immunoglobulin E (IgE), recognised as an important mediator of allergic reactions, is thought to be partially responsible for the induction and maintenance of chronic airway inflammation and asthma-related symptoms (5). Thus, in addition to reducing allergen load, an adequate diagnosis and treatment are necessary to achieve asthma control. The Global Initiative for Asthma (GINA) current treatment guidelines comprise both the severity of the underlying disease and its responsiveness to treatment (6).

Elevated levels of specific IgE in serum in response to common environmental aeroallergens are a key feature in the pathogenesis of allergic asthma (7–9). Omalizumab (OMA), a humanised anti-IgE antibody, has been introduced for treatment of patients with poorly controlled asthma (10, 11). Its use is currently limited to cases of severe asthma, inadequately controlled by means of inhaled corticosteroids (ICS) at high dosages and long-acting β_2-agonists (LABA). Following a Marketing Authorisation for OMA on 25 October 2005 for use within the European Union, the European Medicine Agency recommends the assessment of OMA efficiency after 16 weeks of treatment. Information regarding utilisation of OMA therapy with the consideration of Patient Information Leaflet, as well as data concerning the patient's adherence to treatment protocol in a real-life setting should be investigated. This study was carried out to evaluate utilisation for the treatment of OMA under real-life conditions in Germany, with a focus on tolerability and compliance. In addition, efficacy and safety were assessed to compare results with data from previous clinical trials.

Materials and methods

Study design and goals

This open, prospective German multi-centre post-marketing surveillance study was performed in patients with inadequately controlled severe asthma, who were eligible for anti-IgE treatment. The primary goal was to assess disease-related changes under add-on treatment with OMA. Additionally, the patient's compliance and utilisation of OMA were determined. Patients' symptoms were recorded using a shortened version of the Juniper Asthma Control Questionnaire (ACQ), and investigators assessed the efficacy of OMA using the Global Evaluation of Treatment Effectiveness (GETE). An overview of patients' data collected according to the hospital visit is available in Table 1.

Population and inclusion criteria

From October 2006 to January 2007, a total of 195 patients were included in the study at 85 participating centres in Germany. All patients had a history of severe asthma with a duration of at least 2 years, which remained uncontrolled, including multiple documented exacerbations, irrespective of receiving high doses of ICS and LABA (according to the treatment algorithm defined by GINA step 4).

Other inclusion criteria were:

(i) age > 12 years;*
(ii) impaired lung function with forced expiratory volume in 1 s (FEV_1) < 80% predicted;
(iii) total serum IgE level of 30–700 IU/mL;*
(iv) evidence of positive serum specific IgE (radioallergosorbent testing) for at least one perennial allergen;
(v) body weight of 20–150 kg;*
(vi) reported nocturnal and daytime symptoms.

Therapy of OMA

OMA was administered subcutaneously in the deltoid region or alternatively in the *vastus lateralis* area. The total dose, as well as schedule of treatment (every 2 or 4 weeks), was calculated using the dosing table in the package inserts, which is based on baseline serum IgE levels and body weight.

Efficacy assessment

Lung function (FEV_1)

FEV_1 (litres and % predicted) of all of the patients was assessed at baseline and after 16 weeks of treatment with OMA.

*After careful review and decision by the investigator, some patients were included in the study, despite deviations of inclusion criteria (weight, age or serum IgE level).

Table 1. Overview regarding data collection depending on the visit

	ACQ	Medications	GETE	Comorbidities	FEV_1	Exacerbations	Days of absence
Baseline	X	X		X	X	X	X
16 weeks	X	X	X		X	X	X
6 months	X	X		X			

ACQ, Asthma Control Questionnaire; GETE, Global Evaluation of Treatment Effectiveness; FEV_1, forced expiratory volume in 1 s.

Exacerbations

Only severe exacerbations, defined as worsening of asthma requiring systemic corticosteroids, an emergency room visit, hospitalisation or reduction of $FEV_1 < 60\%$ of personal best, were quantified 16 weeks before and after the beginning of treatment with OMA.

Absenteeism

Days absent from work or school were recorded. For baseline, all events during the last 16 weeks prior to enrolment were noted down. Moreover, for an assessment of efficacy, the total number of days absent from work or school up to the control visit at 16 weeks was also documented.

ACQ

A shortened version (symptoms only) of Juniper's ACQ was used to assess the patient's symptoms for the evaluation of asthma control (12). Patients were asked to reflect on their feelings of well-being since the previous visit, and to respond to each of the five questions on a 7-point Likert scale (0 = not impaired, 7 = severely impaired). The Juniper ACQ was completed by the patients at every visit and further, to highlight the question they considered the most relevant to themselves.

The following questions were asked:

(i) How often did you wake up in the night during the last week, due to your asthma?

(ii) How strong were your asthma symptoms in the mornings during the last week?

(iii) How many of your activities were restricted due to the asthma over last week?

(iv) How strong was your breathlessness in the last week?

(v) How often did you note a wheezing in the last week?

GETE

After a 16-week period, the investigators carried out a GETE of the OMA therapy, by completing a 5-point questionnaire. GETE graduates asthma control as follows: (i) excellent = complete asthma control; (ii) good = improved asthma control; (iii) moderate = slightly improved asthma control; (iv) poor = without improvement; and (v) worsening. Patients with a good or excellent GETE were categorised as responders, and the remaining patients as non-responders.

Medications

The use of asthma medications was recorded prior to study enrolment and after 16 weeks of treatment with OMA.

Concomitant allergic disorders

The severity of existing concomitant allergic disorders, as given in the patient's history, was assessed prior to and after 16 weeks of treatment with OMA.

Compliance and utilisation of OMA treatment

The investigator used an application schedule plan in a calendar format to record date, number of vials and total dose of OMA administered. Furthermore, the application schedule plan allowed a recording time gap between the visits, for the purposes of identifying the adherence to treatment protocol, tolerability of treatment and patient's compliance.

Safety

In order to assess the safety and tolerability of OMA, adverse drug reactions (ADRs), adverse events (AE) and serious adverse events (SAE) were recorded in the case report form 16 weeks after initiation of treatment with OMA.

Statistics

Descriptive analysis and figures were constructed using SAS software version 9.1 (SAS Institute Inc., Cary, NC, USA) for Windows and GraphPad Prism software

version 5.0a (GraphPad Software, San Diego, CA, USA) for Mac OS X. The Wilcoxon signed rank or the Mann–Whitney tests were used to compare differences between two paired or unmatched groups. A P value of <0.05 was considered to be statistically significant.

Results

A total of 195 patients were included in the study at 85 participating centres in Germany. All patients attended the control visit after 16 weeks, and 173 (88.7%) patients were followed-up for a period of 6 months.

Demographics, clinical characteristics and baseline serum IgE levels

Patients' characteristics and baseline data are summarised in Table 2. All patients were atopic, showing allergies against house dust mite (81%), animal dander (58.5%), moulds (46.2%), grass (61.5%) or birch (64.6%). The asthma was concomitant by allergic rhinitis ($n = 131$, 72.4%), atopic eczema ($n = 47$, 26.0%), urticaria ($n = 25$, 13.8%) and other disorders ($n = 18$, 9.9%).

Table 2. Baseline characteristics of the study population

	Omalizumab ($n = 195$)
Age (years)	
Mean (SD)	43.6 (16.9)
Median (range)	44.3 (6–78)
Sex, *n* (%)	
Male	78 (40.6)
Female	114 (59.4)
Weight (kg)	
Mean (SD)	74.4 (18.5)
Median (range)	73.0 (23–151)
Smoking history, *n* (%)	
Never smoked	142 (82.6)
Ex-smoker	22 (12.8)
Smoker	8 (4.7)
FEV_1 (L)	
Mean (SD)	2.0 (0.8)
Median (range)	1.9 (0.6–4.6)
FEV_1 (% predicted)	
Mean (SD)	63.1 (18.4)
Median (range)	62.0 (26–123)
<60, *n* (%)	77 (39.5)
60–80, *n* (%)	89 (45.6)
>80, *n* (%)	26 (13.3)
Total serum-IgE (IU/mL)	
Mean (SD)	329.1 (290.6)
Median (range)	245 (29.7–2104)
<30, *n* (%)	1 (0.5)
30–700, *n* (%)	173 (92.0)
>700, *n* (%)	14 (7.4)
ACQ	
Mean (SD)	3.6 (1.3)
Median (range)	3.8 (0–6)

ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 s; IgE, immunoglobulin E; SD, standard deviation.

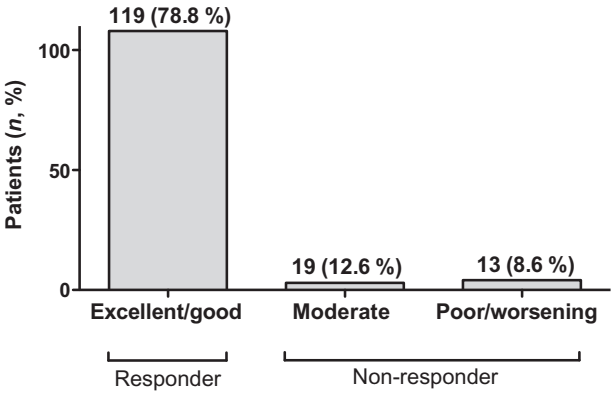

Figure 1. Global Evaluation of Treatment Effectiveness (GETE) by investigators recorded after the 16-week treatment period with omalizumab. Patients with excellent or good GETE were classified as responders to treatment, whereas patients with moderate and poor or worse GETE were classified as non-responders.

Efficacy

Lung function (FEV_1)

The absolute values of FEV_1 as well as the % predicted were found to be improved in patients after a 16-week treatment period. FEV_1 [mean ± standard deviation (SD)] increased from 2.05 L ± 0.77 L to 2.31 L ± 0.84 L, or 63.6% ± 18.3% to 73.7% ± 20.3%, representing a total difference of 270 mL, or an increase of 10.1% predicted, respectively that was statistically significant; $P < 0.05$ (Fig. 2A). Patients who did respond to OMA treatment had higher absolute FEV_1 values at baseline (2.11 L vs 1.87 L) and showed a higher expressed increase in % predicted of FEV_1 compared with non-responders (15.6% vs 13.7%) (Figs. 1C and 2B).

Exacerbation rate

The exacerbation rate (mean ± SD) at baseline was 3.99 ± 6.49 and decreased significantly to 1.0 ± 1.87 ($P < 0.0001$) after 16 weeks of treatment with OMA. A relative reduction of 74.9% in the exacerbation rate was achieved (Fig. 3A). Treatment responders showed a higher and significant reduction of exacerbation rate

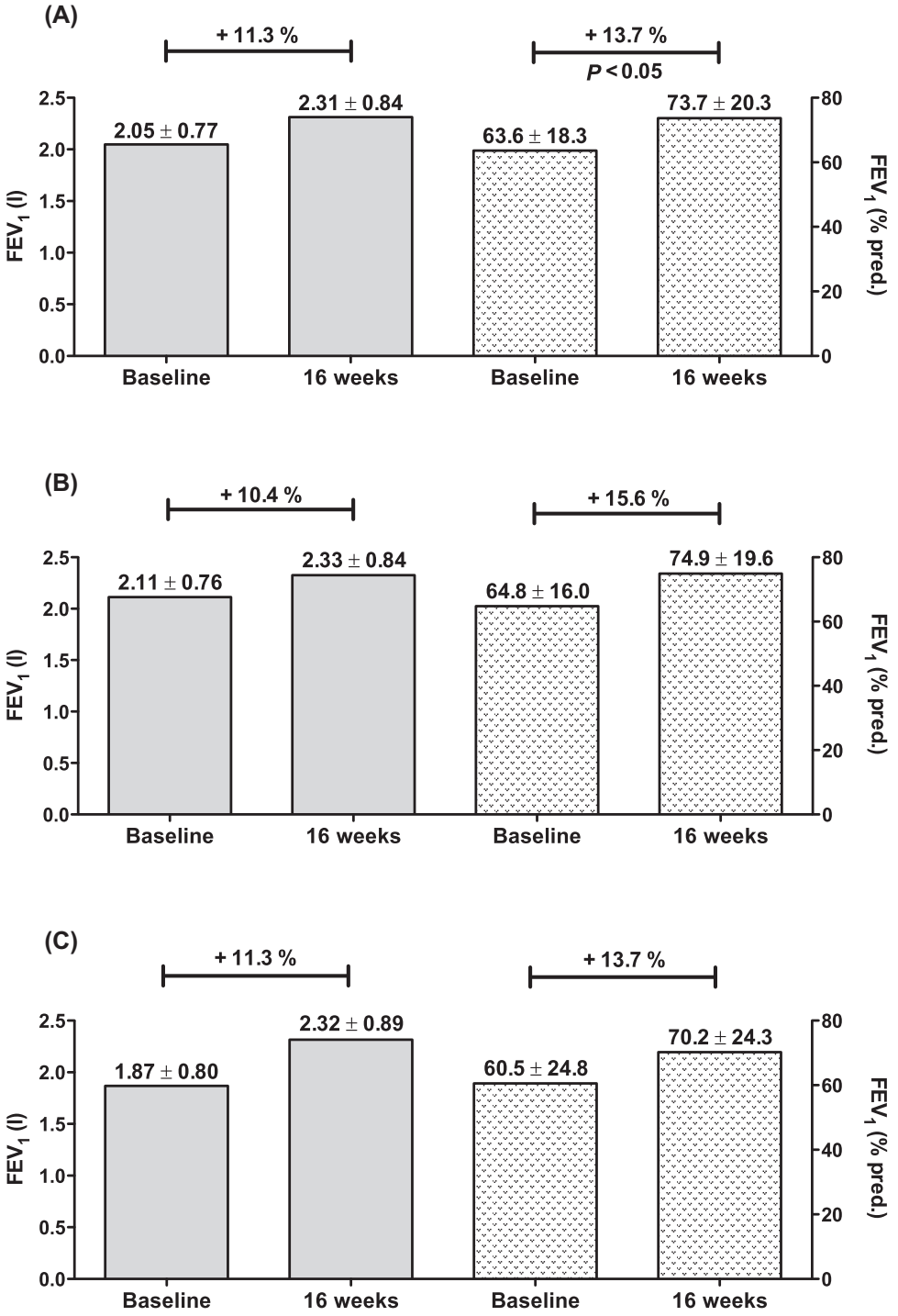

Figure 2. (A) Effect of omalizumab (OMA) treatment on forced expiratory volume in 1 s (FEV_1) as absolute values in litres and as % predicted during the 16-week treatment period; mean ± standard deviation, relative changes to baseline. (B) Effect of OMA treatment in patients who respond and (C) who do not respond to treatment (Global Evaluation of Treatment Effectiveness = excellent or good) on FEV_1 as absolute values in litres and as % predicted during the 16-week treatment period; mean ± standard deviation, relative changes to baseline.

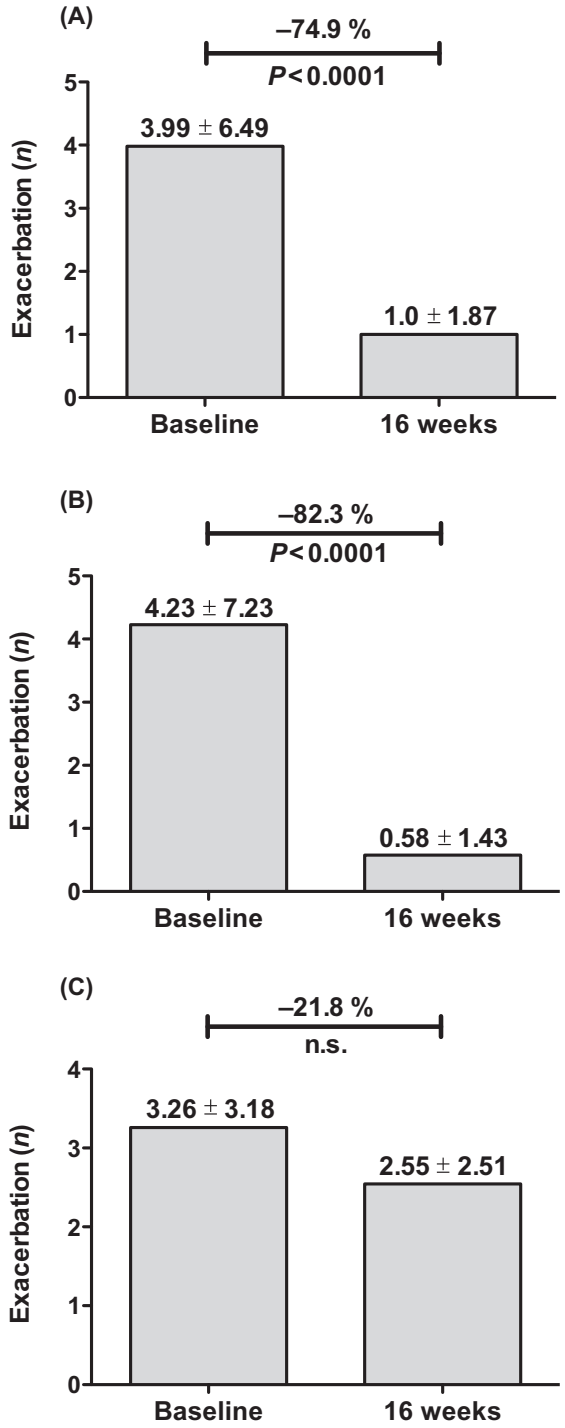

Figure 3. (A) Effect of omalizumab (OMA) treatment on the rate of asthma exacerbations during the 16-week treatment period; mean ± standard deviation, relative changes to baseline. (B) Effect of OMA treatment on the rate of asthma exacerbations in responders and (C) non-responders to treatment (Global Evaluation of Treatment Effectiveness = excellent or good) during the 16-week treatment period; mean ± standard deviation, relative changes to baseline. n.s., not significant.

(–82.3%, $P < 0.0001$) compared with non-responders, who had fewer improvements without significant reduction of exacerbation rate (–21.8%) (Fig. 3B,C).

Absenteeism

Missed work/school days could significantly ($P < 0.001$) be reduced from 6.21 ± 8.08 (mean ± SD) to 0.49 ± 1.34 following 16 weeks of treatment with OMA (Fig. 4A). Although treatment responders had significantly more days of absence at baseline compared with non-responders (7.12 vs 2.65, $P < 0.01$), they showed a significantly higher reduction in the days of absence during the course of treatment with OMA (–93.1% vs –78.9%, $P < 0.001$) (Fig. 4B,C).

ACQ

One hundred forty-two patients (72.8%) completed the ACQ at baseline. The total scores of the questionnaires at baseline, as well as changes after 16 weeks and after 6 months of treatment, are given in Fig. 5A. During treatment with OMA, the ACQ score significantly decreased from 3.58 ± 1.28 to 2.01 ± 1.05 after 16 weeks (–43.7%) and to 1.92 ± 1.13 after the 6-month treatment period (–46.3%) (both $P < 0.0001$). The most important question for the patients related to restriction in activity. Treatment responders showed greater and highly significant improvements of symptoms compared with non-responders even after 16 weeks (–46.9%, $P < 0.0001$ vs –36.1%, $P < 0.05$) or after 6 months (–55.4 per cent, $P < 0.001$ vs –24.7%), respectively (Fig. 5B,C).

GETE

GETE was performed in 151 of the 195 patients (77.4%) after 16 weeks of treatment with OMA. The investigators evaluated the effectiveness as good or excellent in 119 cases (78.8%), as moderate in 19 cases (12.6%) and as poor/worsening in 13 cases (8.6%), respectively (Fig. 1).

Medications

Asthma medications were adjusted in 103 (52.8%) patients in the course of the 16-week treatment duration with OMA. Theophylline ($n = 93$, 47.7% vs $n = 76$, 39%), oral corticosteroids ($n = 112$, 57.4% vs $n = 64$, 32.8%) and leukotriene antagonists ($n = 106$, 54.4% vs $n = 81$, 41.5%) could be reduced in the course of the study, whereas high-dosed ICS ($n = 51$, 26.2% vs $n = 49$, 25.1%), LABA ($n = 50$, 25.6% vs $n = 43$, 22.1%)

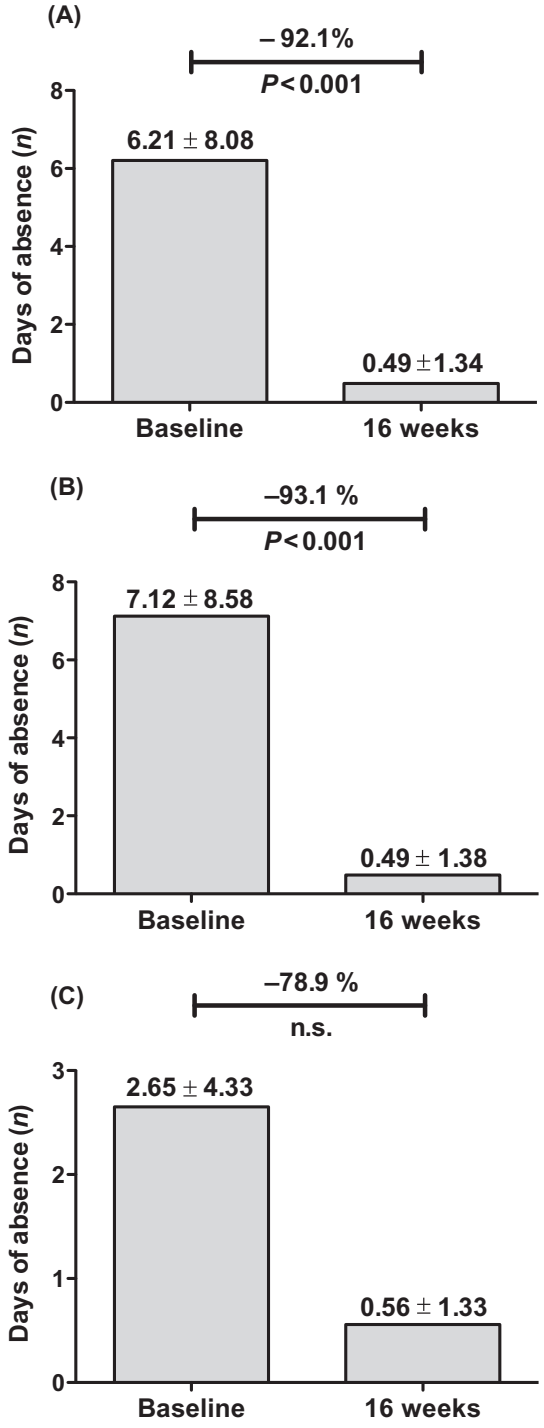

Figure 4. (A) Effect of omalizumab (OMA) treatment on days of school/work absence because of asthma during the 16-week treatment period; mean ± standard deviation, relative changes to baseline. (B) Effect of OMA treatment on the days of absence in responders and (C) non-responders to treatment (Global Evaluation of Treatment Effectiveness = excellent or good) during the 16-week treatment period; mean ± standard deviation, relative changes to baseline. n.s., not significant.

as well as the fixed dose combination of both ($n = 143$, 73.3% vs $n = 139$, 71.3%) remained mostly unchanged (Fig. 6).

Concomitant allergic disorders

Improvements of symptoms were seen for allergic rhinitis in 114 patients (91.2%), for atopic eczema in 30 patients (68.2%) and for urticaria in 16 patients (66.7%) after 6 months of treatment with OMA (Fig. 7).

Compliance and utilisation of OMA

Depending on the administered dose of OMA, 89 patients (45.6%) were scheduled to receive doses at two weekly intervals and 105 patients (53.8%) at four weekly intervals. The mean monthly dose of OMA was 398.9 mg. Forty patients (20.5%) received incorrect doses when referenced to the dosing table. Of these, 33 patients (16.9%) were under-dosed, and seven (3.6%) were overdosed. A total of 36 patients (18.5%) discontinued treatment: 20 patients (10.3%) at the control visit after 16 weeks and 16 patients (8.2%) at the final visit after 6 months. The most often cited single reason for discontinuation was lack of efficiency. Among those patients who discontinued, 12 (33%) were assigned to wrong schedules or were under-dosed.

Application schedule plan

The time gap (mean ± SD) between baseline and control visit after a 16-week treatment period and the total observation period (6 months) was 121.5 ± 25.8 days and 204.9 ± 49.8 days, respectively. Both were within the default time frame. From the overall 1168 visits for administration of OMA, the 638 visits (54.6%) documented as 2-week schedules and the 522 visits (44.7%) documented as 4-week schedules were both appropriate. Eight visits (0.7%) were not recorded. The mean time interval between the visits within the 2-week schedule was 17.4 days (range 13–16), and that within the 4-week schedule was 27.3 days (range 22–31). Overall, these results represent very good patient's compliance and adherence to protocol.

Safety

AE and SAE were recorded in 39 (20%) and 11 (5.6%) of patients. An ADR was seen in 14 (7.2%) patients, although this was not noted as being serious. The most frequently cited preferred terms for ADR were: general

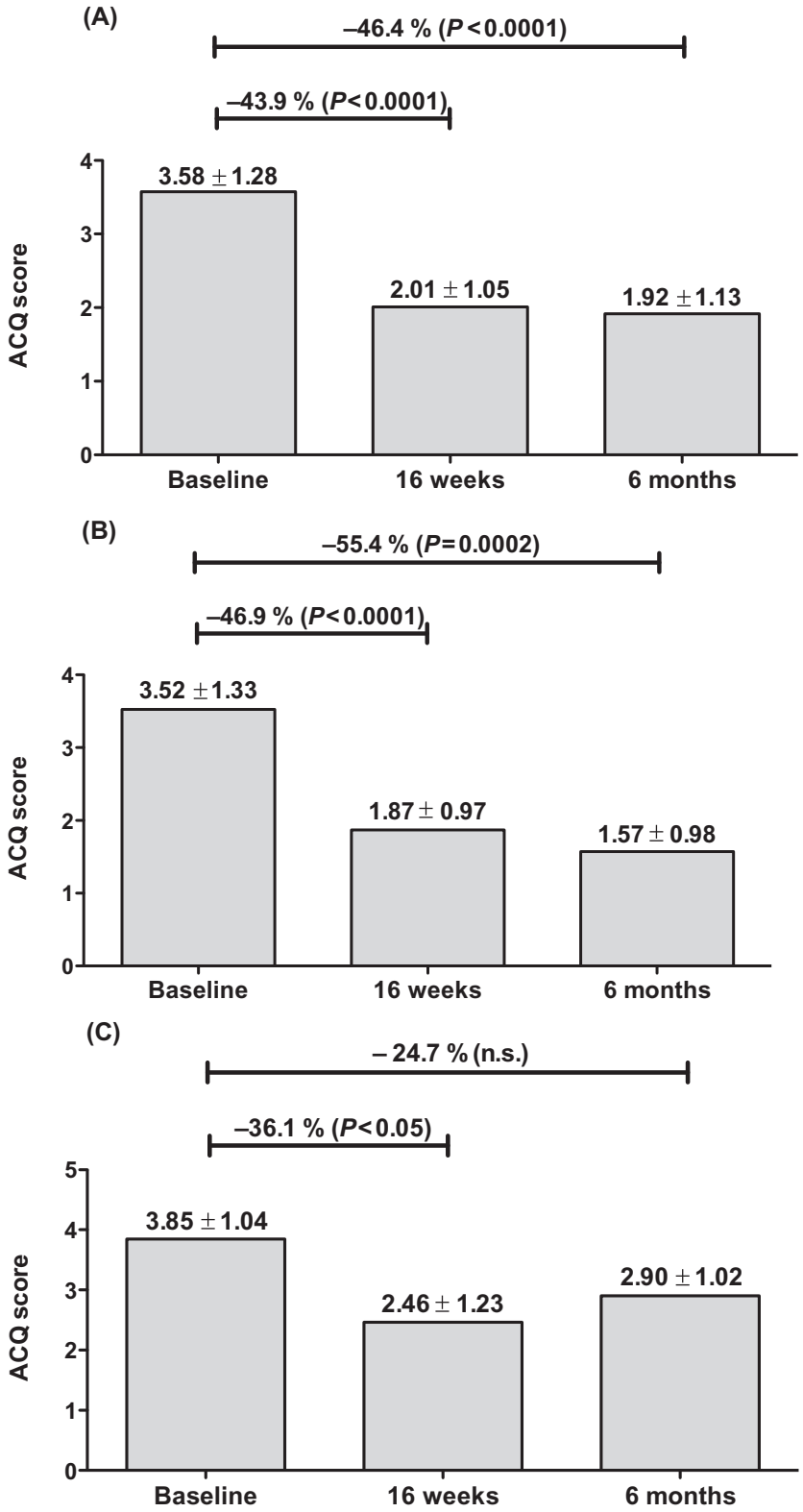

Figure 5. Effect of OMA treatment on asthma symptoms, assessed by the modified Asthma Control Questionnaire (ACQ), during the 16-week and 6-month treatment periods; mean ± standard deviation, relative changes to baseline. Graph (A) represents all patients; graph (B) represents responders; graph (C) represents non-responders. n.s., not significant.

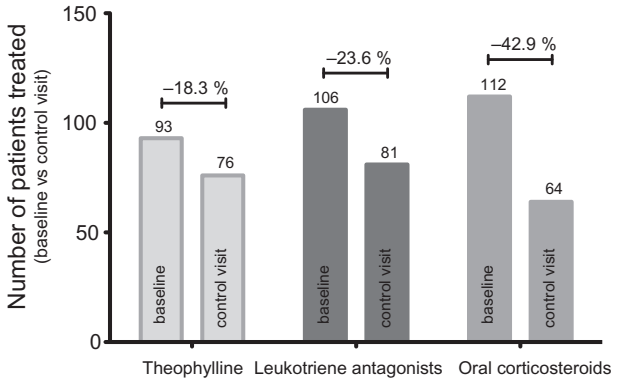

Figure 6. Omalizumab enables reduction of additional controller medication. The absolute number of patients receiving theophylline, leukotriene antagonists and oral corticosteroids at baseline and control visit is given and their relative changes under treatment.

disorders and administration site conditions ($n = 6$), nervous system disorders ($n = 4$), infections and infestations ($n = 3$) and gastrointestinal disorders ($n = 3$). Table 3 gives a detailed overview of all ADRs.

Discussion

The XCLUSIVE study performed in an outpatient setting typical for the situation in Germany was an extension of a recently completed analysis by Korn *et al.* (13). This study with a large cohort of patients was carried out in parallel to the market entry of OMA. The OMA 'real-life' study, as opposed to a clinical trial, adds clinical experience to data relating to the safety and effectiveness of OMA for the treatment of severe persistent asthma. The results presented confirm that

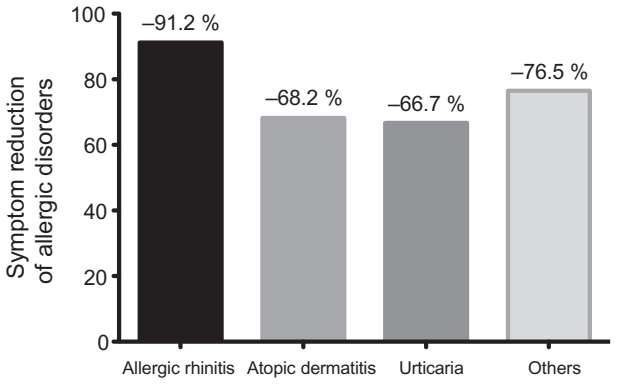

Figure 7. Effect of omalizumab on symptoms of concomitant allergic disorders. The improvements, illustrated as relative reduction of symptoms between baseline and control visit are given.

Table 3. Adverse drug reactions

Patients with at least one ADR	14 (7.2% of study population)	
	n	%
Patients with serious ADR	0	0
Total number of ADRs (on single event basis)	21	100
Respiratory, thoracic and mediastinal disorders	2	9.5
Infections and infestations	3	14.3
General disorders and administration site conditions	6	28.6
Nervous system disorders	4	19.0
Eye disorders	1	4.8
Surgical and medical procedures	0	0.0
Gastrointestinal disorders	3	14.3
Musculoskeletal and connective tissue disorders	0	0.0
Immune system disorders	0	0.0
Cardiac disorders	0	0.0
Injury, poisoning and procedural complications	0	0.0
Investigations	0	0.0
Skin and subcutaneous tissue disorders	1	4.8
Vascular disorders	1	4.8

ADRs, adverse drug reactions.

OMA treatment in a real-life setting offers an effective therapeutic option for a severe form of asthma that is currently uncontrolled using existing treatment options.

This study is comparable in a few aspects to its predecessor by Korn *et al.* (13): both are non-interventional studies that investigated OMA in patients with severe asthma in a real-life setting. Therefore, it is not surprising that the data of the few commonly investigated questions are in accordance with each other (e.g. treatment effectiveness). However, this study differs from the preceding study by the use of ACQ and analysis of treatment adherence. Furthermore, FEV1 was analysed and in respect to exacerbations, we sought to compare equal time periods before and after the beginning of OMA therapy. These points were investigated to help judgment and guidance of treatment with OMA.

The study included subjects with uncontrolled asthma receiving an elevated mean daily dose of ICS and those who had a high rate of asthma-related events in the year preceding OMA treatment, such as an increased rate of exacerbations, numerous emergency visits and hospitalisations. Thus, in line with results obtained from the INNOVATE study (11) and other large multi-national randomised controlled trials (RCTs) (14–16) comparing OMA with placebo, the study population investigated in the XCLUSIVE study represents the unmet clinical need in patients with severe allergic asthma uncontrolled by guideline-based treatment. Moreover, the approximately 200 patients enrolled in the study compared well with the number of patients enrolled in the verum arm of the INNOVATE study (11) and other open-label studies (13, 17, 18). In the majority of patients, the XCLUSIVE study data demonstrate a reduction in the rate of severe exacerbations, a significant decrease in severe asthma exacerbations, a decline in the frequency of day- and nighttime symptoms, as well as an improvement in symptoms related to asthma and concomitant allergic conditions leading to improved lung function, an enhanced quality of life (QoL) and a better physician-rated treatment effectiveness.

It is important to note that the proportion of participants responding to treatment with OMA was greater than anticipated compared with results from large efficacy (11, 14, 16) and open-label studies (17, 18). Moreover, improvements in asthma-related parameters were, in part, better than those previously reported in the INNOVATE study (11) and other large efficacy studies (14–16). Specifically, the XCLUSIVE study shows improved physician-rated effectiveness (17, 18), an enhancement in the QoL (11, 17, 19) and more pronounced reductions in exacerbation rates than previously reported (11, 18–20). The 74% reduction of the overall exacerbation rate observed herein was lower than that reported in the INNOVATE study (11). Similarly, the magnitude of improvement in lung function observed herein (improvement of FEV_1 10.1% predicted) was not achieved in RCTs (11, 14, 16, 21–24), in which changes of FEV_1 ranging between 2.5% and 4.3% of predicted were demonstrated.

There are several reasons to explain the discrepancy for the above findings. First, our data were collected in an open post-marketing surveillance study and hence reflect the real-life conditions associated with asthma therapy. In contrast, generally in phase III studies such as INNOVATE, the selection of patients enrolled is based on a well-defined asthma type. Thus, the disparity of the results from the current study compared with RCTs may partly be influenced by the subjective nature of the patients' narration with regard to their symptoms and any ensuing improvement, or it may be because of a physician-based assessment bias. Second, often in RCTs, the choice of medications and dosages permitted is restricted. For instance, in the INNOVATE study, patients requiring more than 20-mg oral corticosteroid dose were not included, whereas in The XCLUSIVE study almost 15% of the population received more than 20 mg oral maintenance corticosteroids. In addition, former phase III OMA trials disallowed oral maintenance corticosteroids or a revision of anti-asthmatic medication during the study period. A third potential explanation for the inconsistencies may relate to the factor concerning patient's selection. The treating physician chose participants included in the present study for inclusion. Subjects presented with a higher rate of asthma-related events, a lower baseline pulmonary function, an increased exacerbation rate and higher IgE levels. In addition, a greater number of patients receiving maintenance oral corticosteroid therapy were included compared with RCTs. Thus, although treatment benefit with OMA cannot be reliably predicted according to baseline characteristics (25), factors indicative of more severe asthma (history of emergency treatment, FEV_1 and high-dose ICS) may allow a greater relative response to add-on OMA than has been suggested by the pooled analysis of earlier randomised placebo-controlled trials (14, 21). Finally, it is tempting to speculate that controlled studies potentially underestimate the OMA effect and overestimate the effects of standard treatment in placebo or comparator arms because of the high adherence and the expert guidance that is inherent in controlled trials. While monthly injections scheduled according to the patients' individual needs favour treatment adherence, in a real-life setting, patient adherence to treatment with anti-asthmatic drugs is notoriously poor (26).

Our study further suggests that there is heterogeneity in the effects observed for treatment regimens relating to OMA. Despite the physician's overall (GETE) assessment of OMA, therapy effectiveness (based on exacerbation rates, unscheduled health-care utilisation and other asthma control measures) was 'excellent' or 'good' in more than three-quarters of the patients (78.8%), and treatment response in the remainder was conceived as 'poor' or 'worse'. In addition, 17 patients (8.7%) discontinued OMA because of a treatment response. This observation is in agreement with other open-label studies (13, 17, 18, 27), RCTs (11, 14, 16, 21–24) and a corresponding meta-analysis (25). Collectively, the data suggest that approximately one-quarter of the patients treated with OMA show either no or a less favourable response. The reasons for the

lack of efficacy of OMA are not completely understood. It may be argued that physicians' assessment of treatment response may be subjective. However, the overall assessment of OMA therapy by physicians has been shown to be the most meaningful measure of response to OMA therapy, while pre-treatment baseline characteristics such as baseline total IgE load, allergen-specific IgE levels, daytime and night-time symptom scores, QoL and FEV_1 were less reliable (25, 28). Another conceivable possibility is associated with variations in serum IgE levels that could, in turn, lead to inaccurate anti-IgE dosing (29). Further, it may be because of the predominance of the relative pathogenic significance of a single allergen-specific IgE type. This point is illustrated by the finding that despite a reduction of free serum IgE level below 10 kU/L under appropriate OMA therapy (30), about a quarter of the sensitised population still have enough specific IgE levels to initiate a clinically relevant inflammation (31). Thus, regardless of adequate anti-IgE treatment, a critical portion of free IgE molecules may remain active in certain patients.

A final cause for an unsatisfactory therapeutic response could relate to OMA under-dosing relative to body weight and total serum IgE level. In fact, approximately one-fifth of the patients included in this study (16.9%) had been treated with doses below the range given in the dosing table. The nature of the present study, as a post-marketing investigation granting more flexibility to the prescriber compared with RCTs, can substantiate these data. However, undertreatment appears to represent a common phenomenon in daily clinical practice (13, 17, 18, 27). Although the causal relationship between under-treatment and unsatisfactory therapeutic effect could have been strengthened by a more formal assessment of disease control at inclusion and follow-up of this study, such intervention is likely to have modified prescriber behaviour and detract from the real-life nature of the study.

A further clinically significant aspect relates to the impact of OMA therapy on non-asthmatic atopic manifestations, such as rhinitis, urticaria, angioedema, food allergy and atopic dermatitis. In the present study, nearly all asthma patients demonstrated a marked reduction of symptoms correlated with concomitant rhinitis (91.2%), atopic eczema and urticaria as well as other related conditions (>60% of the patients). A similar beneficial effect of OMA on non-asthmatic allergic manifestations has been reported in several case reports and in small-scale studies (24, 32). Taken together, the data available to date strongly suggest that IgE-mediated mechanisms play a pivotal role in the pathogenic mechanisms underlying these concurrent conditions, and in the majority of the patients, extend the beneficial effect of OMA from its anti-asthmatic action to include other allergic manifestations.

OMA as add-on therapy had a good safety and tolerability profile in the present study. Despite the open-label design and the recall bias related to the more frequent visits for the OMA-treated group, AE were similar in frequency and profile to those observed in other trials (13, 17, 18, 25, 27). The imbalance in certain commonly ADRs observed may be because of the increased opportunity for reporting these events during add-on OMA therapy. The most frequent negative effects reported referred to common medical complaints and those expected of a patient population with poorly controlled asthma such as general discomfort, fatigue, local injection site reaction, headache and nausea. Side effects reported were of a mild nature. However, a total of 19 patients discontinued treatment for this reason during the study period of 6 months.

The clinical strength of the present study in comparison with RCTs consists of the evaluation of the effects of exposure to respiratory-related drugs in real-life clinical practice. However, this approach is also associated with a number of inherent limitations, which need to be considered when interpreting the results. One important aspect using observational data refers to the complex situation encountered in real-life. Thus, it cannot be ruled out that certain factors relating to recruitment and follow-up such as the placebo effect, or a stricter compliance to existing medications because of a more frequent physician, were not taken into account. We also cannot completely disregard the possibility that a selection bias on the part of the participating physician may have played a part in the results observed. The recruitment criteria in 85 different centres most likely differed according to the clinical experience of the participating physician. Nevertheless, prescribing practices as seen in this trial are representative of the German situation and, thus, reflect real-life conditions of use. Furthermore, participation in this trial was offered to all pulmonary and allergy specialists in Germany, and they were allowed to include as many patients as they thought appropriate. Therefore, patients enrolled in this study are not representative of a German sample, but rather of a selected collective of patients who were by no means randomised. Nevertheless, in many respects, the large number of patients makes this sample characteristic of the German situation.

In conclusion, the XCLUSIVE study of OMA therapy in a real-life setting confirms other data and strongly underlines the clinical benefit of the drug for use in very poorly controlled severe allergic asthmatic

patients. In addition, the treatment results demonstrate that the magnitude of improvement in symptoms because of OMA was at the very least comparable with that observed in phase III RCTs, and that the data can be transposed to a clinical practice-related setting. The study also shows that treatment with OMA is associated with excellent compliance, and that OMA administration can be achieved in a real-life setting. Finally, treatment with OMA may be considered in patients with inadequately controlled severe persistent allergic asthma, irrespective of pre-existing drug use.

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