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Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany

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KEYWORDS

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Summary

Omalizumab is a humanized monoclonal anti-immunoglobulin E (IgE) antibody indicated in Europe for the treatment of uncontrolled severe persistent allergic (IgE-mediated) asthma despite optimal therapy with inhaled corticosteroids and long-acting β_2 agonists.

Between 2005 and 2007 280 patients (58% female, mean age 44 ± 16 yrs., 46% on oral corticosteroids, median serum IgE level 235 IU/ml) who met the EU criteria for add-on therapy with anti-IgE were treated prospectively with omalizumab by 134 physicians as part of a post-marketing surveillance trial and were followed-up for 6 months.

The median follow-up time was 195 days, the patients were treated with a median dose of 450 mg omalizumab every 4 weeks. After 6 months there was a marked effect of omalizumab treatment on daily (–76%) and nocturnal symptoms (–84%), exacerbations (–82%), unscheduled health care contacts (–81%), hospitalizations (–78%) and quality of life (Mini-AQLQ: score increase from 2.9 to 4.5). Overall, efficacy of omalizumab was rated as excellent or good by the majority of physicians (82%) and patients (86%). In 19 patients (7%) omalizumab-related adverse events were recorded.

This post-marketing surveillance trial confirms the marked and clinically relevant effect of omalizumab on asthma symptoms and level of asthma control in the majority of patients with severe persistent allergic (IgE-mediated) asthma in a real-life situation.

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Introduction

Asthma represents one of the most common chronic diseases.^{1,2} In the majority of patients control of asthma as defined by guidelines can be achieved with inhaled corticosteroids and β_2 -agonists.^{3–5} However, patients with severe persistent asthma who are inadequately controlled despite treatment according to current asthma guidelines

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are at high risk of severe exacerbations and asthma-related mortality and represent the greatest unmet medical need among the asthmatic population today.^{6,7}

Recently, the recombinant humanized monoclonal anti-immunoglobulin E (IgE) antibody omalizumab has been introduced as an add-on treatment for patients with inadequately controlled persistent allergic asthma despite GINA step 5 therapy. IgE plays a central role in the pathogenesis of allergic asthma.⁸ After sensitization, atopic patients respond to allergen exposure through a number of IgE-dependent mechanisms,⁸ making IgE a novel and attractive target for anti-allergic and anti-asthmatic treatments.⁹ Omalizumab interrupts the allergic cascade by binding free serum IgE.¹⁰ Clinical trials confirm that in patients with allergic asthma who have a significant unmet need despite best available therapy omalizumab as add-on therapy reduced asthma symptoms, clinically significant asthma exacerbations and emergency visits as well as hospitalizations due to asthma.^{8,9,11–17}

In 2005, omalizumab has been approved by the European Medicines Agency (EMA) as add-on therapy for patients 12 years and older with severe persistent allergic asthma who demonstrate a positive skin prick test or an *in vitro* reactivity to a perennial aeroallergen, a reduction in lung function ($FEV_1 < 80\%$), frequent daily symptoms or nightly awakenings, multiple severe asthma exacerbations despite treatment with high doses of inhaled corticosteroids and long-acting- β_2 agonists, and a treatable IgE burden as defined by total serum IgE and body weight within the therapeutic window.

Aim of the present prospective post-marketing surveillance trial was to verify the efficacy and tolerability of omalizumab in a real-life setting following the introduction of the drug to the German market in October 2005. It describes the characteristics of patients and the real-life effectiveness of omalizumab in the first large group of patients who received this treatment in Germany.

Methods

Patients

This observational study was performed according to Good Clinical Practice (GCP) standards, the declaration of Helsinki and was approved by the local ethics committee. All patients included in this study gave written informed consent.

In the period between November 2005 and February 2007 280 patients with uncontrolled severe persistent allergic asthma were treated with omalizumab and were prospectively investigated by 135 physicians in Germany. Patients were selected for add-on therapy with omalizumab as approved by the EMA and as recommended by German¹⁸ and international guidelines² based on age (patients ≥ 12 years), positive skin prick test or *in vitro* reactivity against at least one perennial allergen, reduced lung function ($FEV_1 < 80\%$ pred.), frequent daily symptoms or nocturnal awakenings, severe asthma exacerbations despite high doses of inhaled corticosteroids and long-acting β_2 -agonists, total serum IgE between 30 and 700 IE/ml, and body weight between 20 and 150 kg.

Study design

Due to its mechanism of action, the EMA recommends that omalizumab treatment effectiveness be assessed after 16 weeks of treatment.¹⁹ Consequently, patients were investigated prior to start of treatment with omalizumab as well as after 4 and 6 months of the treatment phase. At the initial visit physicians completed a questionnaire regarding the 12 month-period prior to omalizumab treatment (baseline data) to collect demographics (date of birth, sex, smoking status), abnormal pulmonary function defined as an $FEV_1 < 80\%$ of predicted, asthma-related treatments (inhaled corticosteroids, long-acting β_2 -agonists, oral corticosteroids, sustained-release theophylline, leukotriene receptor antagonists), daily symptoms, nightly awakenings, days off school or work, number of exacerbations (as defined by $FEV_1 < 60\%$ of personal best, intermittent treatment with oral corticosteroids, unscheduled health care visits, emergency treatments, hospitalizations due to asthma), hospitalizations, unscheduled health care visits, and omalizumab dosing information (body weight of patient, total IgE). Quality of life (QoL) was assessed using the Mini Adult Asthma Quality of Life Questionnaire (Mini-AQLQ).²⁰ The quality of life score was calculated using the following equation: total score = total (question 1–question 10)/number (question 1–question 10). Both patients and investigators independently evaluated treatment effectiveness and tolerability of omalizumab after 4 and 6 months.

4 and 6 months after the start of omalizumab treatment physicians completed questionnaires providing information about treatment discontinuation (date, reason), date of last clinical evaluation whilst still under treatment, modification of asthma-related treatments (inhaled corticosteroids, long-acting β_2 -agonists, oral corticosteroids, slow-release theophylline, leukotriene receptor antagonists), daily asthma symptoms/nocturnal awakenings, and adverse events suspected to be linked to omalizumab treatment. Lung function changes were recorded as categorical variables, i.e. improved or deteriorated compared with baseline. At the end of the trial period after 6 months patients again provided information about days off school or work, and the number of exacerbations. As is typical for post-marketing surveillance trials and to reflect the real-life-situation in daily clinical routine instructions concerning diagnostic and therapeutic procedures were not issued.

Medication and dosing

Individual omalizumab doses were calculated according to a dosing table based on the patient's individual IgE load, i.e. on pre-treatment body weight and total serum IgE level at screening, as previously described.²¹ Depending on the omalizumab dose, the drug was administered by subcutaneous injection every 2 or 4 weeks. There were no restrictions on doses of ICS and LABA (taken separately or as a fixed combination) and other concomitant asthma medications during the treatment period.

Statistical analysis

In the study population, effectiveness of omalizumab over the treatment period as reflected by the reduction of

exacerbations was evaluated in all patients with follow-up data. Analyses were descriptive and annual rates calculated using patient-years. All patients treated with omalizumab at least once were considered for tolerability evaluation by monitoring of adverse events. Due to the observational character of the study neither a primary endpoint was defined nor a statistical power calculation was performed. Data analysis was performed by using SAS[®] software. Data description was primarily based on means and standard deviation or medians and quartiles for continuous endpoints and based on frequencies for categorical endpoints. The resulting pair wise comparisons were based on Wilcoxon test or *t* test and on Fishers exact test (*p* values < 0.05 indicate local statistical significance).

Results

Study population

During the period between November 2005 and February 2007, 280 patients with physician-diagnosed severe persistent allergic asthma with a mean age of 43.9 ± 16.3 years (range 10–78 years, 3 patients ≤ 12 years) were followed up for a mean of 195 ± 60 days (Table 1). All patients had a documented sensitization to at least one perennial aeroallergen. 243 patients (86.8%) suffered from additional allergic diseases. Accordingly, in 226 patients (80.0%) attempts were made to reduce allergen exposure (e.g. mattress covers in 75.2% of patients). The median IgE level prior to treatment with omalizumab was 235.0 IU/ml

(interquartile range 130–457 IU/ml, min. 16 IU/ml, max. 5820 IU/ml), mean body weight was 73.1 ± 17.2 kg (range 27–150 kg). All patients were treated with high doses of inhaled corticosteroids and long-acting β_2 -agonists. The majority of patients (90.4%) were treated by at least 2 and upto 7 different classes of drugs. In retrospect 271 patients (96.8%) fulfilled the criteria for severe allergic asthma according to the omalizumab label (Table 1).

Pre-treatment asthma control

In the 12 months prior to initiation of omalizumab treatment 269 patients (96.1%) reported daily asthma symptoms and 242 patients (86.4%) nightly awakenings. Nearly all patients (90.0%) had experienced frequent severe asthma exacerbations (mean 4.5 ± 7.5 exacerbations/year), 67 patients (23.9%) were hospitalized due to exacerbations. In addition, 238 patients (85.0%) reported on average 4.4 ± 4.6 unscheduled health care contacts or emergency room visits due to asthma in the year prior to treatment with omalizumab. 171 patients (61.1%) had not been able to go to work or school for at least one day. Total pre-treatment quality of life score was 2.9 ± 0.9 points (Table 2).

Asthma control after 4 and 6 months of omalizumab treatment

Patients were administered a median of 450 mg omalizumab per month (range 150–850 mg per month). In 43 patients (14.9%) the IgE load was outside the recommended

Table 1 Study population.

	<i>n</i> [patients]	% Of patients
Patients	280	
Sex [female]	114	40.7
Smoking status [non-smokers, ex-smokers, still smokers]	209, 40, 13	79.8, 15.3, 4.9
Additional allergic diseases	243	86.8
Allergic rhinitis/rhinoconjunctivitis	228	93.8
Atopic dermatitis	84	34.6
Food allergy	77	31.7
Other	18	7.4
Sensitization to allergens	280	100
Mites	219	78.2
Animal dander	182	65.0
Molds	132	47.1
Grass pollen	201	71.8
Birch	191	68.2
Other	68	24.3
Asthma medication		
High doses	142	50.7
of inhaled corticosteroids		
Long-acting beta-2-agonists	124	44.3
Combination therapy	166	59.3
(inhaled corticosteroids and beta-2-agonists)		
Slow-release theophylline	122	43.6
Leukotriene receptor antagonists	136	48.6
Oral corticosteroids	129	46.1
(as maintenance therapy)		

Table 2 Results.

	Baseline [<i>n</i> = 280] ^a		After 4 months [<i>n</i> = 279] ^a		After 6 months [<i>n</i> = 241] ^a	
	<i>n</i> [patients]	% Of patients	<i>n</i> [patients]	% Of patients	<i>n</i> [patients]	% Of patients
Daily asthma symptoms	269	96.1	83	29.7	55	22.8
Nightly awakenings	242	86.4	67	24.0	33	13.7
Asthma exacerbations	252	90.0	—	—	44	18.3
Hospitalizations	67	23.9	—	—	12	2.5
Unscheduled health care contacts/emergency room visits	238	85.0	—	—	48	19.9
Days off school/work	171	61.1	—	—	40	16.6

^a Due to the observational character of the study not all information are available in a small number of patients.

dosing table, either because total serum IgE was too low or too high and/or body weight was too low or too high.

Upon reevaluation of patients after 4 months there was a marked reduction of daily asthma symptoms and nocturnal awakenings by 69.1% and 72.3% resp. ($p < 0.001$ resp.). After 6 months there was a further reduction in daily symptoms and nocturnal awakenings down to a total reduction of 79.6% and 86.4% resp. ($p < 0.001$ resp.). During therapy with omalizumab concomitant allergy manifestations decreased significantly by 80.6% after 4 months and by 87.1% after 6 months ($p < 0.001$, both comparisons). In 177 patients (63.4%) lung function improved after 4 months and in 157 of 241 patients (65.1%) after 6 months. Compared with the 12 month pre-treatment period the rate of severe asthma exacerbations decreased by 82.0% to a mean of 0.3 ± 0.8 exacerbations/year (rate adjusted to a 1-year period; $p < 0.001$). During the whole follow-up period of 6 months 12 patients (5.0%) were hospitalized due to exacerbations, corresponding to a reduction of 77.5% ($p < 0.001$). Similarly, unscheduled health care visits and emergency room visits decreased by 80.8% ($p < 0.001$). Total days patients were not able to go to work or to school were reduced by 71.6% ($p < 0.001$) (Fig. 1). Accordingly, there was a marked improvement in quality of life. Mean total score increased to 4.5 ± 1.2 points ($p < 0.001$) (Fig. 2).

After 6 months efficacy and tolerability of omalizumab was rated as excellent or good by the majority of physicians (82.2% and 95.0%) and patients (85.9% and 93.7%) (Table 2).

Tolerability and discontinuations

In 100 patients (35.7%) a total of 198 adverse events and in 67 patients (23.9%) a total of 145 severe adverse events

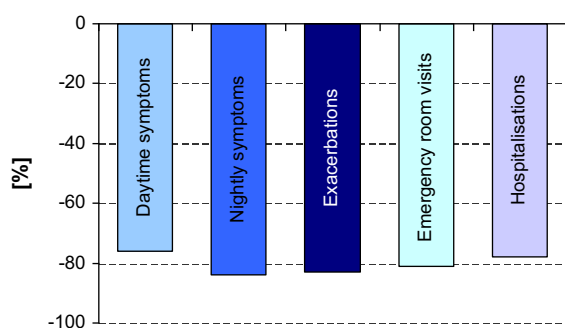


Figure 1 Effects [%] of omalizumab after 6 months of treatment compared with baseline.

(73.2%) were reported. In only 7 of all patients (2.5%) 33 adverse events (16.7% of all AEs) were considered to be related to omalizumab treatment (Table 3).

As expected, the respiratory system (37.6%) was the organ system most commonly affected by adverse events, with "asthma" being the leading complaint (65 patients).

47 patients (16.8%) discontinued omalizumab treatment after 4 months and 44 patients (18.3%) after 6 months, corresponding to a total discontinuation rate of 32.5%. Main reason for discontinuation was ineffectiveness (48.9% after 4 months, 38.6% after 6 months). Due to the small numbers of patients who discontinued treatment no statistical analyses could be performed to relate insufficient treatment response to a potential overdosing or underdosing of the study drug.

Discussion

Omalizumab has been successfully adopted into clinical practice, with more than 68,000 patients treated worldwide since June 2003. Clinical trials have shown important benefits for many patients with inadequately controlled severe persistent allergic asthma who respond to omalizumab therapy, and demonstrated a good safety profile. This supports the results from the comprehensive clinical trial programme, in which omalizumab significantly reduced asthma exacerbation and emergency visit rates, and significantly improved quality of life in patients with severe

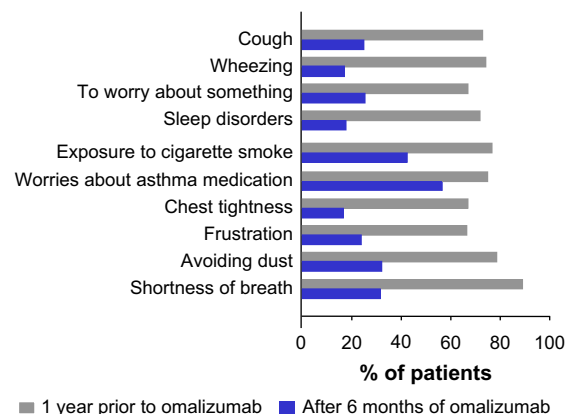


Figure 2 Mini AQLQ, 7 point score (1 = always, 2 = mostly, 3 = often, 4 = sometimes, 5 = rarely, 6 = hardly ever, 7 = never). Bars represent points 1–3.

Table 3 Adverse events.

Adverse events	<i>n</i> [patients]	% Of patients	<i>n</i> [adverse events]	% Of adverse events
Total adverse events	100	35.7	198	100.0
Total severe adverse events	67	23.9	145	73.2
Severe adverse event related to omalizumab	7	2.5	33	16.7
Organ systems most commonly affected by adverse events (multiple response)				
Respiratory, thoracic and mediastinal disorders	67	23.9	73	37.6
General disorders and administrations site conditions	40	14.3	48	24.7
Infections and infestations	14	5.0	14	7.2
Nervous system disorders	8	2.9	17	8.8
Skin and subcutaneous tissue disorders	7	2.5	10	5.2

persistent allergic asthma. Pooled analyses confirm the results of the omalizumab clinical trial program.^{9,17} Consequently, omalizumab is indicated in the EU as add-on therapy to improve control of severe persistent allergic asthma that remains inadequately controlled despite treatment with high-dose ICS and a LABA.

The present study summarizes the clinical experience with omalizumab in a large cohort of German patients with severe allergic asthma following the approval of the drug within the European Union and its launch in Germany. It is the first analysis of the therapeutic effects of omalizumab in a real-life setting in Germany outside of clinical trials.

Several aspects of this study are clinically relevant:

In contrast to the controlled trials performed as part of the omalizumab clinical trial program patient recruitment into the present study was not based on in – and exclusion criteria derived from study hypotheses. The patients included in this trial were selected according to the approved European omalizumab label, and, with very few exceptions, the patients' characteristics are well in line with the criteria recommended for the use of omalizumab by the European Medicines Agency (EMA).¹⁹ This is reflected in the study population by the mean daily dose of inhaled corticosteroids and the high rate of asthma-related events in the year preceding omalizumab treatment. In particular the high rate of exacerbations including emergency visits and hospitalizations highlights the fact that asthma in these patients was uncontrolled despite their already high use of anti-asthmatic medication. Further, the study population reflects both the huge unmet clinical need in patients with severe allergic asthma uncontrolled by guideline-based treatment^{2,22} and the potential for improvement following the institution of guideline-based treatment including omalizumab. Importantly, almost half of the study population was on oral maintenance corticosteroids, an exclusion criterion for most of the phase III omalizumab trials. The results of this trial indicate and confirm preliminary evidence that omalizumab is effective in severe persistent allergic asthma irrespective of

concomitant treatment with systemic corticosteroids.¹⁷ Omalizumab can, therefore, be considered for the treatment of inadequately controlled severe persistent allergic asthma, regardless of OCS use.

This was a real-life study reflecting daily clinical practice in an outpatient setting typical for the situation in Germany. In some aspects, the extent of clinical improvement experienced by the majority of patients following treatment with omalizumab was even more pronounced than what was observed in controlled clinical trials.^{11,17} Results similar to what was seen in the German cohort were observed in a comparable situation in France.²³ It is tempting to speculate that controlled studies potentially underestimate the omalizumab effect and overestimate the effects of standard treatment in placebo or comparator arms due to high adherence and expert guidance that is inherent to controlled trials. In a real-life setting adherence in particular to inhaled corticosteroids is notoriously poor²⁴ while monthly injections that can be scheduled according to the patients' individual needs may favor treatment adherence. The pronounced effect on the rate of severe asthma-related events including hospitalizations is equally relevant in the context of the ongoing discussion about the cost-effectiveness of omalizumab.²⁵ However, a detailed analysis of cost and effectiveness of this new treatment was beyond the scope of this investigation.

A French historic-prospective study has provided initial data on the real-world effectiveness of omalizumab. In the French study, the annual exacerbation rate decreased by 62%, emergency visits by 65% and hospitalizations by 29% for the 146 patients who had been prescribed omalizumab for severe allergic asthma. Additionally, 48.1% of patients reduced or discontinued maintenance OCS.²³

Analyses of patients treated in clinical trials have shown that it is difficult to predict which patients, within the label population, will derive greatest benefit from omalizumab based on pre-treatment patient characteristics. As recommended in the EU, the most accurate means of ensuring that omalizumab treatment is beneficial to evaluate the

response after a 16-week therapeutic trial. Treatment should be continued in patients who are judged by the physician to have achieved a marked improvement or complete asthma control. Using this method of assessment, approximately 60% of patients can be expected to be identified as responders to omalizumab. The reason why not all patients respond to omalizumab therapy is unclear.²⁶ Well in line with this experience, 32.5% of patients treated in the present study discontinued omalizumab treatment, mostly due to unsatisfactory therapeutic response. As was seen in the French trial, incorrect dosing may contribute to an insufficient response to the drug.²³ In our cohort, 14.9% of patients who were treated did not fall within the range of the recommended dosing table that considers total IgE concentration and body weight.²⁷ Potentially, both over-treatment and under-treatment may be explained by the design of the present study which was close to a post-marketing surveillance to give flexibility to the prescriber. However, the small number of patients who discontinued treatment or were incorrectly dosed precluded any statistical analyses to relate insufficient treatment response to a potential overdosing or underdosing of the study drug. Although the potential relationship between under treatment and unsatisfactory therapeutic response could have been formally strengthened at inclusion and follow-up visits, such as an intervention could have modified prescriber behavior and compromise the real-life nature of the study. It is, therefore, essential that the correct dose of omalizumab is calculated and administered for each individual patient.

Finally, the present trial confirmed the favorable safety profile of omalizumab. Frequency and severity of adverse events observed were similar to that seen in the omalizumab phases II and III study program and in many respects comparable to what was reported by patients receiving placebo or best available therapy.²⁸

This study has several limitations. Clearly, its results strongly suggest that the clinical efficacy of omalizumab demonstrated in randomized controlled trials (RCTs) is reproduced in a real-life setting. The magnitude of the improvements seen when compared with the previous year was at least comparable to that observed in RCTs. However, the results of this trial are based on retrospective comparisons within the same patient population instead of a comparison with a control group or a prospectively defined baseline period. Furthermore, confounding factors such as the placebo effect or a more strict compliance to existing medications due to more frequent physician contacts could not be taken into account. Nevertheless, prescribing practices participating in this trial are representative of the German situation and thus reflect real-life conditions of use.

Another limitation of the study is the way study centers and patients were recruited. In principle, participation in this trial was offered to all German pulmonary and allergy specialists. Neither study centers nor patients fulfill the criteria of a random German sample but represent a selection of physicians who agreed to participate in this trial and who included as many patients as they thought were appropriate. Again, however, the large number of patients makes this sample in many respects representative for the German situation.

Conclusion

In summary, in a German 6-month real-life follow-up study conducted between 2005 and 2007 treatment of 280 patients with severe persistent allergic asthma uncontrolled by inhaled corticosteroids and long-acting β_2 -agonists with omalizumab were generally well tolerated and reduced daily and nocturnal symptoms, asthma exacerbation and emergency visit rates, and improved quality of life. Treatment efficacy was rated as excellent or good by the majority of both physicians and patients, thus confirming the clinically relevant effect of omalizumab.

Conflict of interest

SK has received reimbursement for attending and a fee for speaking at a scientific conference in 2009. AT and SS are employees at Novartis Pharma GmbH. CT has received reimbursement for attending scientific conferences, and/or fees for speaking from Novartis. OK has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Novartis. RB has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Novartis. The Pulmonary Department at Mainz University Hospital received financial compensation for services performed during participation in single- and multi-center clinical phase I-IV trials organized by various pharmaceutical companies.

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