

Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma

Stephanie Korn, MD**; Christian Schumann, MD†; Cornelia Kropf, MD‡; Kathrin Stoiber, MD‡; Antje Thielen‡; Christian Taube, MD*; and Roland Buhl, MD, PhD*

Background: Omalizumab is approved for the treatment of severe allergic asthma.

Objectives: To compare the efficacy of omalizumab therapy in patients 50 years or older with patients younger than 50 years.

Methods: Between November 2005 and November 2007 a total of 174 asthma patients 50 years or older (40.7% male, 51.1% taking oral corticosteroids, and mean [SD] serum IgE level of 315 [353] U/L) and 297 asthma patients younger than 50 years (40.0% male, 50.5% taking oral corticosteroids, and mean [SD] serum IgE level of 363 [431] U/L) who met the European Union criteria for add-on therapy with anti-IgE were treated prospectively with omalizumab for 4 months as part of 2 postmarketing surveillance trials.

Results: Compared with the pretrial period omalizumab treatment reduced the rate of severe exacerbations in patients 50 years or older by 68.9% ($P < .001$) and in patients younger than 50 years by 75.4% ($P < .001$). After 4 months there was a marked reduction of daily asthma symptoms and nocturnal awakenings by 67.8% and 72.6% in the older and by 79.3% and 82.5% in the younger patients, respectively ($P < .001$, all 4 comparisons). In 60% of patients 50 years or older lung function improved compared with 69% of patients younger than 50 years. Efficacy of omalizumab was rated as excellent or good by most physicians in patients 50 years or older (68.4%) and younger than 50 years (76.8%, $P = .05$ elderly vs younger). Adverse events were reported in 35.5% of patients 50 years or older and 32.1% of patients younger than 50 years. There was a higher rate of discontinuation of omalizumab therapy in older patients (20.9% vs 11.1%, $P = .006$).

Conclusions: The present study confirms the clinical efficacy of omalizumab in patients with severe allergic asthma irrespective of age in a real-life setting outside the omalizumab trial program.

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INTRODUCTION

In the elderly population asthma is more prevalent than previously appreciated. Rates of asthma prevalence in individuals 65 years and older range from 3.8% to 7.1% in the United States¹ and from 6% to 7% in Germany.² The impact of asthma is greater in this age bracket than in younger patients as manifested by greater lung function impairment,³

greater hospitalization risk,⁴ reduced quality of life,⁵ and increased mortality. In most patients irrespective of age asthma is associated with allergic triggers and elevated IgE level.^{6,7} Recent data indicate that IgE-dependent disease mechanisms remain relevant in the elderly population. There is a substantial prevalence of allergic sensitization⁸ and a linear association with IgE levels and the risk of asthma.⁹

In most patients asthma control as defined by guidelines can be achieved with inhaled corticosteroids and β_2 -agonists.^{10–12} In contrast, patients with severe persistent asthma that is inadequately controlled despite treatment according to current asthma guidelines are at high risk of severe exacerbations and asthma-related mortality and represent the greatest unmet medical need among the asthmatic population today.^{13,14} This is true irrespective of age. However, the elderly patient group is most at risk of adverse effects not only due to high-dose inhaled and oral corticosteroids⁶ but also due to other asthma treatments and drug interactions due to a higher rate of comorbidities and consequent comedication.

The recombinant humanized monoclonal anti-IgE antibody omalizumab has been introduced as an add-on treatment for patients with inadequately controlled persistent allergic asthma despite Global Initiative for Asthma step 4 therapy. Clinical trials confirm that omalizumab reduced symptoms, exacerbations, emergency department visits, and hospitalizations due to asthma.^{15–23} Although in the clinical study program omalizumab was effective in patients in the 12- to

Affiliations: * Pulmonary Department, Mainz University Hospital, Mainz, Germany; † Pulmonary Department, Ulm University Hospital, Ulm, Germany; ‡ Novartis Pharma GmbH, Nürnberg, Germany.

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79-year age bracket,²³ previous clinical trials have not focused specifically on efficacy in older adults. The present analysis examines for the first time the influence of patient age (≥ 50 and < 50 years) on the results of add-on treatment with omalizumab in 2 prospective postmarketing surveillance trials designed to verify the efficacy and tolerability of omalizumab in a real-life setting after the introduction of the drug to the German market in October 2005.

METHODS

Patients

Patients were selected for add-on therapy with omalizumab as approved by the European Medicines Agency and as recommended by German²⁴ and international guidelines.²⁵ In line with the real-life approach of the trial the additional asthma treatment was at the discretion of participating physicians. The study was performed according to Good Clinical Practice standards and the Declaration of Helsinki and was approved by the local ethics committees. All patients included in the study gave written informed consent.

Study Design

Data from 2 postmarketing surveillance trials^{26,27} were merged, and only parameters collected in the same way in both trials were analyzed with particular emphasis on treatment outcomes and adverse events (AEs) in patients 50 years and older compared with patients younger than 50 years. Age brackets were chosen to achieve a representative number of patients in both subgroups.

Because of its specific mechanism of action, omalizumab treatment effectiveness is assessed after 16 weeks of treatment.²⁸ Consequently, although the total duration of the 2 studies was 6 months, patients were investigated before the start of treatment and after 4 months of treatment. At the initial visit physicians recorded a questionnaire regarding the 4-month period before omalizumab treatment (baseline data), demographics (date of birth, sex, smoking status), abnormal pulmonary function defined as a forced expiratory volume in 1 second (FEV₁) of less than 80% of predicted, asthma-related treatments (inhaled corticosteroids [ICS], long-acting β_2 -agonists [LABAs], oral corticosteroids, sustained-release theophylline, or leukotriene receptor antagonists), daily symptoms, nightly awakenings, number of exacerbations (as defined by an FEV₁ $< 60\%$ of personal best, intermittent treatment with oral corticosteroids, unscheduled health care visits, emergency department treatments, hospitalizations due to asthma), days off school or work, and omalizumab dosing (body weight and total IgE of patients). Study parameters were recorded based on questionnaires. Investigators completed the questionnaires based on the patients' responses to predefined questions.

After 4 months investigators evaluated treatment effectiveness of omalizumab,²⁹ including information about treatment discontinuation (date, reason), last clinical evaluation while still under treatment, daily asthma symptoms, nocturnal

awakenings, AEs suspected to be linked to omalizumab treatment, number of exacerbations, and days off school or work. Lung function changes were recorded at categorical variables only (ie, improved or deteriorated compared with baseline). As is typical for postmarketing surveillance trials and to reflect the real-life situation, instructions concerning diagnostic and therapeutic procedures were not issued.

Medication and Dosing

Individual omalizumab doses were calculated based on the patient's individual IgE load (ie, on pretreatment body weight and total serum IgE level at screening).³⁰ Depending on the total monthly dose, omalizumab was administered by subcutaneous injection every 2 or 4 weeks. There were no restrictions on doses of ICS and LABA or other concomitant asthma medications.

Statistical Analysis

Data analysis was performed using SPSS statistical software (SPSS Inc, Chicago, Illinois). Data description was based on means and standard deviations or medians and quartiles for continuous end points and on frequencies for categorical end points. The comparisons between the patient populations were based on Wilcoxon or *t* test for continuous end points and on the Fisher exact test for categorical end points; intra-individual comparisons were based on the sign or *t* test.

Effectiveness of omalizumab during the treatment period as reflected by the reduction of exacerbations was evaluated in all patients with follow-up data. Analyses were descriptive and 4-month rates were calculated. All patients treated with omalizumab at least once were considered for safety evaluation by monitoring of AEs. Because of the observational character of the study, neither a primary end point was defined nor a statistical power calculation performed. *P* $< .05$ indicated local statistical significance.

RESULTS

Study Population

Between November 2005 and November 2007 a total of 484 patients with physician-diagnosed uncontrolled severe persistent allergic asthma (mean [SD] age, 43.8 [16.5] years; range, 6-78 years; 9 patients ≤ 12 years) were treated prospectively with omalizumab and investigated by 220 physicians as part of 2 postmarketing surveillance trials. Thirteen patients had to be excluded from the analysis because of missing data. Treatment effects were evaluated in 174 patients 50 years or older and 297 patients younger than 50 years after 4 months. All patients had a documented sensitization to at least 1 perennial aeroallergen. Sensitizations differed slightly but not in a conceptual way between the 2 populations. Similarly, patients 50 years and older had significantly fewer allergic comorbidities. All patients were treated with high ICS doses (at least 1000 μg of beclomethasone dipropionate per day) and LABAs. Approximately half of the patients in both groups were additionally treated with oral corticosteroids. Mean baseline IgE level, body weight, and median total

Table 1. Baseline Characteristics of the Study Population

Characteristics	Patients, No. (%)		P value (≥50 years vs <50 years)
	≥50 Years old	<50 Years old	
Patients	174 (36.9)	297 (63.1)	
Male patients	70 (40.7)	118 (40.0)	.92
Smoking status, nonsmokers and ex-smokers/continuous smokers	118 (76.1)/37 (23.9)	233 (83.8)/45 (16.2)	.06
Asthma medication			
High doses of inhaled corticosteroids	59 (33.9)	130 (43.8)	.04
Long-acting β_2 -agonists	49 (28.2)	109 (36.7)	.07
Combination therapy (inhaled corticosteroids and β_2 -agonists)	115 (66.1)	191 (64.3)	.76
Slow-release theophylline	88 (50.6)	124 (41.8)	.07
Leukotriene receptor antagonists	89 (51.1)	157 (52.9)	.77
Oral corticosteroids (as maintenance therapy)	89 (51.1)	150 (50.5)	.92

omalizumab dose per month were comparable in the 2 populations (Table 1 and Table 2).

Pretreatment Asthma Control

Before omalizumab treatment 94.7% of patients 50 years and older reported daily asthma symptoms and 76.4% reported nightly awakenings. A total of 90.3% of younger patients had daily symptoms and 79.6% had nightly awakenings. In both groups nearly all patients had experienced frequent severe asthma exacerbations (1.07 [2.19] exacerbations per 4 months in the elderly and 0.92 [1.65] exacerbations per 4 months in the younger patients). Approximately one-third of patients 50 years and older and approximately two-thirds of patients younger than 50 years had not been able to go to work or school for at least 1 day in the 4 months before the start of the study (Table 3).

Asthma Control After 4 Months of Omalizumab Treatment

After 4 months of treatment with omalizumab there was a marked and similar reduction of daily asthma symptoms and

nocturnal awakenings in all patients (Table 3, Figure 1). In 60% of patients 50 years and older lung function improved after 4 months compared with 69% of patients younger than 50 years ($P = .06$). Compared with the pretrial period the rate of severe exacerbations was reduced by approximately 67% in both groups (Table 3, Figure 1). Total days patients were not able to go to work or school were reduced in a comparable way in the older and younger patients (Table 3, Figure 1). Efficacy of omalizumab was rated as excellent or good by most physicians in patients 50 years and older (68.4%) and younger than 50 years (76.8%) ($P = .051$).

Discontinuation of Study Drug Use and Safety

The frequency of AEs was similar in both groups (Table 4 and Table 5). The AEs related to organ systems were not significantly different between the 2 groups. In 1.2% of the older patients 7 AEs (5.9% of all AEs) and in 1.7% of the younger patients 26 AEs (14.6% of all AEs) were considered to be severe and related to omalizumab treatment ($P = .54$).

Table 2. Allergic Comorbidities and Sensitizations in the Study Population^a

	Patients, No. (%)		P value (≥50 years vs <50 years)
	≥50 Years old	<50 Years old	
Allergic comorbidities			
Allergic rhinitis or rhinoconjunctivitis	118 (67.8)	249 (83.8)	<.001
Atopic dermatitis	36 (20.7)	98 (33.0)	.004
Urticaria	27 (15.5)	76 (25.6)	.01
Sensitization to allergens			
House dust mites	124 (71.3)	244 (82.2)	.008
Animal dander	81 (46.6)	204 (68.7)	<.001
Molds	80 (46.0)	111 (37.4)	.08
Grass pollen	94 (54.0)	213 (71.7)	<.001
Birch	100 (57.5)	206 (69.4)	.01
Other	41 (23.6)	72 (24.2)	
IgE level, mean (SD) [range], U/mL	315 (353) [16–2793]	363 (431) [25–5820]	.56
Body weight, mean (SD) [range], kg	79.0 (17.3) [40.0–151.0]	70.6 (17.3) [23.0–124.0]	.49
Total dose per month, median (range), mg	300 (150–750)	300 (150–750)	.39

^a Data are number (percentage) of patients unless otherwise indicated.

Table 3. Number of Patients With Daily Symptoms, Nightly Awakenings, Asthma Exacerbations, and Days Off School or Work

	Patients, No. (%)				Reduction, %		P value for reduction	
	Baseline ^a		After 4 months ^a		≥50 Years	<50 Years	≥50 Years	<50 Years
	≥50 Years	<50 Years	≥50 Years	<50 Years				
Daily asthma symptoms	143 (94.7)	241 (90.3)	46 (39.0)	50 (16.8)	67.8	79.3	<.001	<.001
Nightly awakenings	113 (76.4)	211 (79.6)	31 (26.3)	37 (18.5)	72.6	82.5	<.001	<.001
Days off of school or work	44 (76.4)	155 (64.9)	12 (26.3)	36 (14.5)	72.7	76.7	<.001	<.001
Asthma exacerbations	161 (92.5)	276 (94.2)	50 (34.2)	67 (25.0)	68.9	75.4	<.001	<.001
No. of exacerbations (per patient per 4 months), mean (SD) ^b	0.9 (1.7)	1.1 (2.2)	0.7 (1.6)	0.4 (1.0)				

^a Because of the observational character of the study, not all information is available in all patients.

^b Number of exacerbations was based on a 4-month period before omalizumab therapy and 4 months after treatment with omalizumab.

In total, 14.8% of patients discontinued omalizumab treatment after 4 months, mainly because of ineffectiveness and AEs. The discontinuation rate was higher in older patients (20.9% vs 11.1%, $P = .006$).

Underdosing and Overdosing of Omalizumab

In line with the real-life character of this trial, patients who had been underdosed or overdosed were not excluded from the analysis. In 25 patients 50 years or older (15.2%), the IgE load was outside the recommended dosing table compared with 49 patients younger than 50 years (17.0%) ($P = .92$). This was either because the total serum IgE and/or body weight was too low or too high. Twenty-three (13.9%) of the elderly and 42 (14.5%) of the younger patients (elderly vs younger $P = .89$) received a lower and 9 (5.5%) of the elderly and 7 (2.4%) of the younger patients received a higher dose of omalizumab than recommended ($P = .12$). Underdosing and overdosing had no impact on outcomes and did not change results when inappropriately dosed patients were ex-

cluded from analysis. This is true also for patients treated outside the European Union license at the time of study.

DISCUSSION

Omalizumab is approved as add-on therapy to improve control of severe persistent allergic asthma that remains inadequately controlled despite treatment with high-dose ICSs and a LABA in patients 6 years and older. Previous clinical trials have not focused specifically on efficacy in older adults. With the exception of a post hoc analysis of the omalizumab phase 3 study program,⁷ there is no evidence supporting the use of the drug in this subpopulation. The present study prospectively investigated the clinical effectiveness of omalizumab in 2 cohorts of German patients 50 years and older with severe allergic asthma.^{26,27} To our knowledge, this is the first analysis of the therapeutic effects of omalizumab in a real-life setting outside clinical trials.

Several aspects of this study are of particular clinical relevance. First, recent analyses of serologic markers of sensitization to common inhaled antigens in a group of middle-aged men identified an increase in atopy in this group during the past quarter century, reinforcing the importance of IgE-mediated allergic disease in older individuals.³¹ The results of the present study support the concept that IgE-mediated mechanisms play an important role in asthma in patients 50 years and older. Baseline IgE levels and rates of sensitization to common aeroallergens were only slightly lower and allergic comorbidities only slightly less frequent in the elderly subgroup, well in line with previously reported incidences of allergen sensitization and allergic comorbidities.^{2,32–34}

Second, the present study confirms that omalizumab is as effective in an elderly population as it is in younger asthma patients, with a similar magnitude of reduction of asthma exacerbations of all degrees of severity in both groups. This is also true for other clinically relevant patient-centered asthma outcomes. Elderly patients demonstrated a significant reduction of daily and nightly symptoms and significant improvements in lung function after addition of omalizumab to their treatment regimen. In particular, the high rate of exacerbations highlights

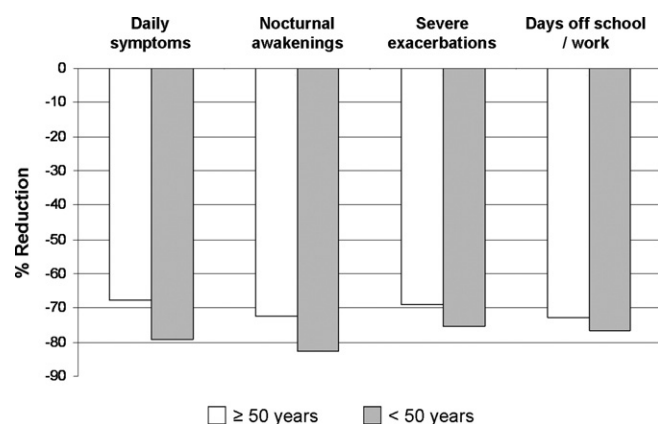


Figure 1. Effects of omalizumab after 4 months of treatment compared with baseline. P values are based on the comparison of patients 50 years and older vs younger than 50 years. Study parameters were recorded based on questionnaires. Investigators completed the questionnaires based on patient response to predefined questions.

Table 4. Number of Adverse Events

Adverse events	Patients with adverse events, No. (%)		P value	Adverse events, No. (%)		P value
	≥50 Years	<50 Years		≥50 Years	<50 Years	
Total adverse events	61 (35.5)	93 (32.1)	.31	119 (100.0)	178 (100.0)	.32
Total severe adverse events	25 (14.5)	49 (16.5)	.60	67 (56.3)	104 (58.4)	.45
Severe adverse event related to omalizumab	2 (1.2)	5 (1.7)	>.99	7 (5.9)	26 (14.6)	.54

the fact that asthma in patients older than 50 years was uncontrolled despite their already high use of antiasthmatic medication. Furthermore, the study population reflects both the huge unmet clinical need in patients with severe allergic asthma uncontrolled by guideline-based treatment^{25,35} and the potential for improvement after the institution of guideline-based treatment including omalizumab. The present analysis supports the few observations made by others regarding treatment effects in elderly patients.^{7,26}

Third, almost half of the elderly population and the younger patients received oral maintenance corticosteroids. This fact again highlights the severity of the underlying disease and underscores the clinical relevance of the present study because treatment with oral corticosteroids was an exclusion criterion for most of the phase 3 omalizumab trials. Furthermore, systemic and to a lesser degree even ICS may cause side effects. In an elderly population, because of older age and comorbidities and consequent comedication, these AEs may be more consequential than in younger patients.¹² The results of this trial confirm preliminary evidence that omalizumab is effective in severe allergic asthma irrespective of age and concomitant treatment with systemic corticosteroids.²³ Omalizumab can, therefore, be considered for the treatment of inadequately controlled severe allergic asthma, regardless of oral corticosteroid use and regardless of age.

Fourth, these findings coincided with a significantly improved response to treatment as judged by the investigators. Patients 50 years and older demonstrated a favorable re-

sponse that is in line with a response rate of greater than 60% of the general study population³⁶ and the younger patients in the present trials. This is particularly important because older patients may have more fixed airway disease that is poorly responsive to treatment, a potential reason why the overall response to omalizumab in the older patients was slightly less and the discontinuation rate higher than in patients younger than 50 years.

Fifth, clinical trials have shown that it is difficult to predict which patients, within the label population, will derive greatest benefit from omalizumab based on pretreatment patient characteristics.³⁵ The most accurate means of ensuring that omalizumab treatment may be beneficial is 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.²⁹ Using this method of assessment more than 60% of patients can be expected to respond to omalizumab.²⁹ The reason why not all patients respond is unclear.³⁶ Well in line with this experience, 20.9% of patients 50 years or older and 11.1% younger than 50 years treated in the present study discontinued omalizumab treatment, mostly because of unsatisfactory therapeutic response. As was seen in a French real-life trial, incorrect dosing may contribute to an insufficient treatment response.³⁷ In the present cohort, small subpopulations of both age groups did not fall within the range of the recommended dosing table based on total IgE concentration and body weight.³⁸ Both overtreatment and undertreatment may be explained by the design of the present study, which was close to a postmarketing surveillance to give flexibility to the prescriber and reflect the real-life situation. The small numbers of patients who discontinued treatment or were incorrectly dosed precluded any statistical analyses to relate insufficient treatment response to overdosing or underdosing of the study drug. Although the potential relationship between undertreatment and unsatisfactory therapeutic response could have been formally strengthened at inclusion and follow-up visits, such an intervention could have modified prescriber behavior and compromised the real-life nature of the study. It is, however, essential that the correct dose of omalizumab is calculated and administered for each patient.

Sixth, the present trial confirmed the favorable safety profile of omalizumab. Frequency and severity of AEs observed were similar to the omalizumab phase 2 and 3 study program irrespective of age and in many aspects comparable to what was reported by patients receiving placebo or best available

Table 5. Classification of Adverse Events

Classification	Adverse events, No. (%)	
	≥50 Years	<50 Years
General disorders and administration site conditions	32 (26.9)	47 (26.4)
Respiratory, thoracic, and mediastinal disorders	55 (46.2)	88 (49.4)
Skin and subcutaneous disorders and musculoskeletal and connective tissue disorders	8 (6.7)	10 (5.6)
Cardiac and cerebral disorders	3 (2.5)	3 (1.7)
Nervous system disorders	8 (6.7)	8 (4.5)
Gastrointestinal disorders	2 (1.7)	4 (2.2)
Other	11 (9.2)	18 (10.1)

therapy.³⁹ The safety profile of a medication established in a broader patient population may or may not be applicable to a subgroup of an older population. The present analysis showed that the proportion of drug-related AEs was similar in the older and younger populations, in line with previous data.⁷ The results of this trial confirm and extend the results of controlled trials in which comorbidities and comedications were exclusion criteria. The present real-life study reflects daily clinical practice in an outpatient setting typical for the situation in Germany (ie, for a highly developed health care system with full reimbursement of drugs prescribed by physicians). Previously, almost all omalizumab efficacy data are based on controlled trials (ie, compliance by definition, questions of reimbursement, comorbidities, comedication, and many other factors relevant to a real-life-situation had not been evaluated). In some aspects, the extent of clinical improvement experienced by most patients after treatment with omalizumab in this real-life setting was even more pronounced than what was observed in controlled clinical trials^{15,23} even in elderly patients.^{6,7} Similar results were seen in a French cohort.³⁷ 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 because of high adherence and expert guidance that is inherent to controlled trials.

The present study has several limitations: In contrast to the controlled trials of the omalizumab clinical trial program, patient recruitment was not based on inclusion and exclusion criteria derived from study hypotheses. With few exceptions, the patient characteristics are well in line with the criteria recommended for the use of omalizumab,²⁸ confirming that the clinical efficacy of omalizumab demonstrated in controlled trials can be reproduced in a real-life setting. However, the analysis of this trial is 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.

Another limitation is the way study centers and patients were recruited. Participation 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 by physicians who agreed to participate in this trial and who included as many patients as they thought appropriate. Again, however, the large number of patients makes this sample in many respects representative of the German situation.

In summary, the present analysis of 2 German clinical trials including patients 50 years and older with severe allergic asthma uncontrolled by ICS and LABA demonstrated for the first time in a real-life situation that treatment with omalizumab reduced asthma exacerbations and daily and noctur-

nal symptoms, improved lung function, and was well tolerated irrespective of age. Omalizumab in elderly patients with IgE-mediated asthma is an effective addition to treatment when symptoms persist despite guideline-based treatment.

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Requests for reprints should be addressed to:
 Stephanie Korn, MD
 Pulmonary Department
 Mainz University Hospital
 Langenbeckstrasse 1
 D-55131 Mainz, Germany
 E-mail: Stephanie.Korn@unimedizin-mainz.de

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