

Original article

Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma

Background: Patients with poorly controlled asthma have greater morbidity and mortality. This study evaluated the efficacy and tolerability of omalizumab in patients with poorly controlled, moderate-to-severe allergic asthma.

Methods: This was a randomized, open-label, multicentre, parallel-group study. A total of 312 patients (12–73 years) receiving ≥ 400 $\mu\text{g/day}$ (adolescent) or ≥ 800 $\mu\text{g/day}$ (adult) inhaled beclomethasone dipropionate, or equivalent were included. Patients received best standard care (BSC) with or without omalizumab [at least 0.016 mg/kg/IgE (IU/ml) every 4 weeks] for 12 months.

Results: The annualized mean number of asthma deterioration-related incidents was reduced from 9.76 with BSC alone ($n = 106$) to 4.92 per patient-year with omalizumab ($n = 206$) ($P < 0.001$). Mean clinically significant asthma exacerbation rates were 2.86 and 1.12 per patient-year, respectively ($P < 0.001$). Omalizumab-treated patients (41.4%) required rescue medication < 1 day/week compared with 20.7% for BSC alone ($P < 0.001$). Omalizumab improved absolute forced expiratory volume in 1 s (FEV_1) compared with BSC alone (2.48 and 2.28 l, respectively; $P < 0.05$) and reduced symptom scores relative to BSC alone (decrease of 6.5 and 0.7 respectively; $P < 0.001$). Omalizumab was well-tolerated.

Conclusions: Omalizumab administered as add-on therapy to BSC benefits patients with poorly controlled, moderate-to-severe allergic asthma.

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Patients with poorly controlled (moderate-to-severe) asthma are commonly encountered in clinical practice and account for much of the morbidity, mortality and economic burden of this disease (1). Studies of new products addressed at the more severe end of the asthma clinical spectrum are relatively uncommon, a considerable unmet medical need therefore exists for this important subgroup of patients with asthma.

Approximately 90% of asthma is allergic in nature (2). Targeting of factors involved in the allergic response, such as immunoglobulin E (IgE) represents a novel approach for the development of new therapeutic agents

for allergic asthma and other IgE-mediated diseases (3). Omalizumab, a recombinant humanized monoclonal antibody, is the first anti-IgE agent to undergo clinical evaluation for asthma. Recent large-scale, placebo-controlled clinical trials with this agent, added to existing anti-asthma therapy, demonstrated a reduction in asthma exacerbations in patients with allergic asthma of varying severity (4–6). In the study of Solèr et al. (6), for example, patients treated with omalizumab experienced 58% fewer asthma exacerbations vs. placebo ($P < 0.001$) when the drug was added on to a constant dose of inhaled corticosteroid for 16 weeks. The beneficial effect of omalizumab was particularly apparent for patients at high risk of serious asthma-related morbidity and mortality. Holgate et al. demonstrated that high-risk patients treated with omalizumab and stable steroid therapy (with inhaled corticosteroids) experienced 51% fewer asthma exacerbations than patients who received

Abbreviations: BSC, best standard care; ADRI, asthma deterioration-related incident; IgE, immunoglobulin E; FEV_1 , forced expiratory volume in 1 s; ICS, inhaled corticosteroids; BDP, beclomethasone dipropionate; ND, not determined; CI, confidence interval.

placebo and stable steroid therapy (0.95 and 1.93 per patient-year, respectively; $P = 0.01$) (7).

However, clinical trials conducted thus far with omalizumab may have, through their rigorous design, limitations in their applicability to ‘real-life’ clinical practice. As such our aim was to investigate the efficacy and tolerability of omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma in an open-label study in which omalizumab was added to, and compared against, best standard care (BSC) as defined by the National Heart, Lung and Blood Institute (NHLBI).

Methods

Patients

Eligible subjects were aged 12–75 years with persistent (> 2 years) moderate-to-severe allergic asthma [according to the NHLBI guidelines (8)], whose disease was poorly controlled. Poor control was defined as ≥ 1 emergency room visit/hospitalization and ≥ 1 additional course of oral corticosteroids because of asthma in the last year. All patients had forced expiratory volume in 1 s (FEV₁) reversibility of $\geq 12\%$ within 30 min of taking inhaled salbutamol (up to 400 μg via pressurized metered dose inhaler or up to 5 mg via nebulizer) and were receiving ≥ 400 $\mu\text{g}/\text{day}$ (adolescent, age < 18 years) or ≥ 800 $\mu\text{g}/\text{day}$ (adult) inhaled beclomethasone dipropionate (BDP) (or equivalent). Further inclusion criteria included a positive skin prick test to at least two clinically relevant antigens, a serum total IgE level of 30–700 IU/ml and body weight suitable for optimum dosing of omalizumab. Exclusion criteria included pregnancy and lactation, female patients of child-bearing potential not using an adequate means of contraception, patients with a history of smoking of ≥ 10 pack-years, active lung disease other than allergic asthma or any other significant systemic disease, patients who were immunocompromised, and elevated serum IgE levels for reasons other than atopy. Patients receiving desensitization immunotherapy were also excluded from enrolment.

Each patient, or their parents or guardians when appropriate, provided written informed consent prior to any study-related procedures.

Study design

This was a randomized, open-label, parallel-group study conducted at 49 centres in five European countries (France, $n = 10$; Germany, $n = 9$; Spain, $n = 7$; Switzerland, $n = 3$; UK, $n = 20$). Following a screening period of 4 weeks and baseline assessments of lung function (spirometry) and Wasserfallen asthma symptom score (9), eligible patients were randomized (2 : 1) to receive BSC with or without subcutaneous omalizumab for 12 months. Best standard care was defined by the NHLBI guidelines (8), which advocate a stepwise approach to the classification and long-term management of asthma. All patients (except one in the omalizumab group) were treated according to steps 3 and 4, i.e. daily treatment with moderate-to-high doses of inhaled corticosteroids with or without a long-acting bronchodilator. Those patients in the most severe category (step 4) received daily systemic corticosteroids. One patient in the omalizumab group did not receive inhaled corticosteroids at baseline (step 1) and entered the trial in error. While this patient was included in intention-to-treat analyses, they were excluded from analyses including treatment step in the model.

Bodyweight (kg)	30–60	> 60–70	> 70–80	> 80–90	> 90–150	
Baseline IgE (IU/ml)	Mg/dose				Frequency of dosing	
≥ 30 –100	150	150	150	150	300	Every 4 weeks
> 100–200	300	300	300	300	225	Every 2 weeks
> 200–300	300	225	225	225	300	
> 300–400	225	225	300	300		
> 400–500	300	300	375	375		Not dosed
> 500–600	300	375				
> 600–700	375					

Figure 1. Individualized dosing strategy for omalizumab (mg/dose), according to patient bodyweight and baseline (total) immunoglobulin E (IgE) level.

Omalizumab was administered during office visits and was dosed according to patient body weight and serum total IgE at screening (Fig. 1). Patients requiring a monthly dose of < 300 mg were treated once every 4 weeks, while higher doses were split and administered every 2 weeks, to reduce injection volumes and the number of injections at each administration. This approach ensured that patients received a dose of at least 0.016 mg/kg for every IU/ml of total IgE every 4 weeks. Therefore, in addition to the scheduled study physician visits that all patients undertook, those treated with omalizumab were seen every 2 or 4 weeks by a study nurse solely for omalizumab administration.

Rescue medication use with salbutamol (delivered by pressurized metered dose inhaler) was permitted throughout the study, each patient recorded salbutamol usage (and any other concomitant asthma treatment) in daily diary cards. Patients returned to the study centre for evaluation of diary data and repeat assessments of lung function and Wasserfallen asthma symptom score after 3, 6, 9 and 12 months’ treatment (and upon completion of a 4-week follow-up phase).

The study was performed in accordance with good clinical practice and the latest amendments to the Declaration of Helsinki, the protocol having been approved by independent ethics committees/institutional review boards for each centre.

Efficacy assessments

The primary efficacy variable was the annualized number of asthma deterioration-related incidents (ADRI) (10). The ADRI were recorded in patient daily diary cards, and were defined as ≥ 1 of the following events because of asthma: course of systemic corticosteroids or antibiotics for ≥ 2 days, ≥ 2 missed school/work days (or significantly reduced performance for nonworking adult patients, as judged by the patient), unscheduled physician visit, or hospitalization/emergency room visit. Consecutive ADRI were counted as individual incidents if they were separated by at least 2 ADRI-free days. The ADRI may also have been recorded as asthma worsening adverse events. If the asthma worsening adverse event required the administration of systemic corticosteroids, it was also recorded as an asthma exacerbation adverse event. For patients on maintenance systemic corticosteroids, only short-term supplemental bursts of systemic corticosteroids related to an asthma exacerbation were included within the definition of an ADRI/asthma exacerbation.

Secondary efficacy variables included the annualized number of clinically significant asthma exacerbations, which were defined as episodes of asthma worsening requiring treatment with systemic corticosteroids. The minimum separation between consecutive exacerbations was 7 days from ending the preceding steroid burst. Further, secondary efficacy variables were lung function (morning FEV₁), use of rescue salbutamol, and Wasserfallen asthma symptom score (9). In a subgroup of patients with comorbid asthma and

rhinitis at baseline, asthma and rhinitis symptoms were evaluated using the Wasserfallen symptom score (9).

Safety and tolerability

Safety was evaluated from adverse event reports. All spontaneously reported and investigator-observed adverse events were recorded. Routine laboratory tests (haematology, clinical chemistry, urinalysis) were completed at screening and study end and analysed for clinically relevant trends.

Statistical analysis

All efficacy analyses were completed on an intention-to-treat basis. For the annualized mean number of ADRI, an imputation method was applied to account for patients who were prematurely withdrawn. Thus, an ADRI with a duration of zero was assigned to the patient if no ADRI was recorded within 7 days of discontinuation. Subsequently, ADRI rates per patient-year at risk were calculated. Between-group differences were analysed using Poisson regression. An identical analysis evaluated the effect of omalizumab on the annualized number of clinically significant asthma exacerbations. Poisson regression was also used to determine the effect of concomitant asthma medications on asthma exacerbation rates in patients receiving omalizumab treatment. Time to first ADRI and clinically significant exacerbation was compared between the two treatment groups using Kaplan–Meier survival curves and the log-rank test.

The effect of add-on therapy with omalizumab on change from baseline in lung function parameters and symptom scores was analysed using an analysis of covariance model (using baseline value as covariate), while the effect of omalizumab on unscheduled physician visits, emergency room visits, hospitalizations, and absenteeism and was determined using a Chi-square test. The effect of omalizumab on rescue salbutamol use was analysed for the last 14 days up to study completion using the Wilcoxon rank sum test.

Results

A total of 312 patients with poorly controlled (moderate-to-severe) allergic asthma were enrolled into this study, all but one of whom were being treated according to steps 3 and 4 of the NHLBI guidelines (8). Baseline doses of inhaled corticosteroids (BDP equivalent) are given in Table 1, with 38.8% (119 of 312) receiving a daily dose of 2000 µg BDP, 30.1% (94 of 312) receiving 1000 µg and 16.0% (50 of 312) receiving 4000 µg. Additionally, 77.9% of patients (243 of 312) were receiving concomitant medication with long-acting β-adrenoceptor agonists and 21.2% (66 of 312) were receiving systemic corticosteroids. Overall, 206 patients were randomized to receive omalizumab in addition to BSC; the remainder ($n = 106$) received BSC alone. The two treatment groups were comparable in terms of baseline demographic and clinical characteristics, including history of poor asthma control (Table 2).

Asthma deterioration-related incidents

A total of 280 patients (omalizumab, $n = 191$; BSC alone, $n = 89$) provided diary data and were included in the

Table 1. Baseline doses of inhaled corticosteroids (ICS)

Baseline ICS dose (µg/day) (BDP or equivalent)	Omalizumab ($n = 206$)	Best standard care ($n = 106$)
0	1	
400	2	1
500	1	2
800	4	1
1000	55	39
1200		1
1250	1	
1400	1	
1500	4	2
1600	5	1
2000	85	34
2400	1	
2500	2	
3000	3	3
4000	32	18
4500		1
5800		1
6000	3	
6500	1	
8000	4	2
10 000	1	

ICS, inhaled corticosteroid; BDP, beclomethasone dipropionate.

analysis of ADRI. Overall, those treated with omalizumab experienced 4.84 fewer ADRI per patient-year compared with BSC alone, a reduction of 49.6% [95% confidence interval (CI): 27.8–64.8%]. Significantly more omalizumab-treated patients remained ADRI-free during the study compared with BSC alone [36.1% (69 of 191) compared with 20.2% (18 of 89) respectively]. Likewise, significantly fewer omalizumab-treated patients experienced multiple (≥ 2) ADRI [40.8% (78 of 191) and 66.3% (59 of 89), respectively; $P = 0.001$]. Kaplan–Meier survival analysis showed a significant ($P = 0.03$) prolongation of the time to first ADRI with omalizumab vs. BSC alone (median time to first ADRI of 126 and 75 days, respectively; Fig. 2).

Findings for the individual outcomes that comprised the composite of ADRI are summarized in Table 3.

Clinically significant asthma exacerbations

All patients were included in the analysis of clinically significant asthma exacerbations (omalizumab, $n = 206$; BSC alone, $n = 106$). Overall, the annualized mean number of such exacerbations was significantly lower with omalizumab than with BSC alone (1.12 and 2.86 per patient-year, respectively; $P < 0.001$), which equated to a reduction of 60.8% (95% CI: 46.9–71.0%). Significantly more patients treated with omalizumab remained exacerbation-free during the study compared with those who received BSC alone [49.5% (102 of 206) and 26.4% (28 of 106), respectively; $P = 0.001$], and fewer patients experienced multiple (≥ 2) exacerbations [20.4% (42 of

Table 2. Summary of baseline demographic and clinical characteristics

	Omalizumab (<i>n</i> = 206)	Best standard care alone (<i>n</i> = 106)
Females, <i>n</i> (%)	148 (71.8)	72 (67.9)
Median age, years (range)	37.5 (12–73)	39.3 (12–71)
Median equivalent BDP dose, µg/day (range)	2000 (0–10 000)	2000 (400–8000)
Median total serum IgE, IU/ml (range)	167 (27–686)	ND
Median FEV ₁ , % predicted (range)*	70.5 (14.6–139.3)	72.3 (26.6–129.7)
Concomitant medications, <i>n</i> (%)†		
Systemic corticosteroids	47 (22.8)	19 (17.9)
Long-acting β-adrenoceptor agonists	160 (77.7)	83 (78.3)
Aspects of poor asthma control‡		
≥1 emergency room visit, <i>n</i> (%)	186 (90.3)	97 (91.5)
≥1 hospitalization, <i>n</i> (%)	87 (42.2)	48 (45.3)
Median number of oral corticosteroid courses (range)	3 (1–24)	2 (1–24)
Median number of missed school/work days (range)	10 (0–365)	15 (0–365)
Mean Wasserfallen asthma symptom score (SD)	17.4 (10.6)	17.0 (10.2)

* Data missing for two patients in the omalizumab group and one patient in the best standard care alone group.

† In the 2-week period prior to the baseline visit, and in addition to inhaled corticosteroids and short-acting β-adrenoceptor agonists.

‡ Due to asthma in the last year.

BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E; *n*, number of patients; ND, not determined; SD, standard deviation.

There were no statistical differences between the two groups.

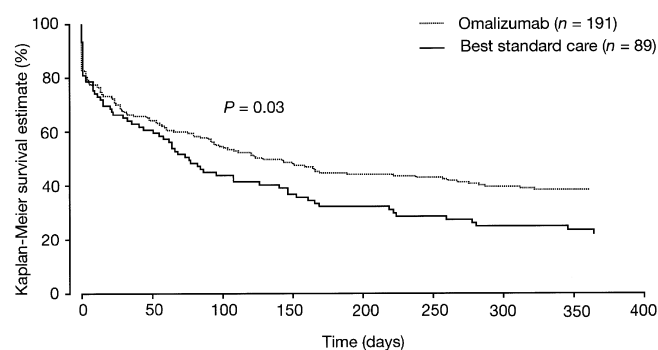


Figure 2. Kaplan–Meier survival curves of time to first asthma deterioration-related incident in patients with poorly controlled (moderate-to-severe) allergic asthma treated with best standard care, alone or in combination with omalizumab.

206) and 42.5% (45 of 106), respectively; $P = 0.001$]. Median time to first clinically significant asthma exacerbation with BSC alone was 266 days, but could

not be estimated in the omalizumab group as fewer than 50% of patients experienced such an event ($P = 0.001$; Kaplan–Meier survival analysis).

The reduction in the asthma exacerbation rate with omalizumab treatment was not affected by concomitant asthma medication use. Concomitant long-acting β₂-agonists were used by the majority of patients at baseline [77.7% (160 of 206) omalizumab-treated patients and 78.3% (83 of 106) of patients in the BSC group]. Anti-leukotrienes and systemic steroids were used by 29.1% (60 of 206) and 22.8% (47 of 206) in the omalizumab group respectively, and by 28.3% (30 of 106) and 17.9% (19 of 106) in the BSC group, respectively. The relative rates of asthma exacerbations among omalizumab-treated patients compared with BSC were 0.4 ($P < 0.01$) for patients using concomitant long-acting β₂-agonists, 0.38 ($P < 0.01$) for patients using concomitant leukotriene receptor antagonists and 0.43 ($P = 0.02$) for patients receiving concomitant systemic steroids. These effects were similar to those

Table 3. Use of systemic corticosteroids, medical resource utilization and absenteeism due to asthma

	Omalizumab (<i>n</i> = 191)	Best standard care alone (<i>n</i> = 89)	<i>P</i> -value
Use of systemic corticosteroids, <i>n</i> (%)	99 (51.8)	58 (65.2)	0.037
Unscheduled physician visits, <i>n</i> (%)	64 (33.5)	45 (50.6)	0.007
Median number of days with unscheduled physician visits (range)*	2 (1–12)	3 (1–135)	–
Emergency room visits, <i>n</i> (%)	24 (12.6)	17 (19.1)	NS
Median number of days with emergency room visits (range)*	1 (1–46)	2 (1–33)	–
Hospitalizations, <i>n</i> (%)	16 (8.4)	8 (9.0)	NS
Median number of days of hospitalization (range)*	7 (1–53)	8 (1–21)	–
Absenteeism from work/school, <i>n</i> (%)†	83 (43.5)	51 (57.3)	0.031
Median number of days of absenteeism (range)*	14 (1–365)	28 (1–259)	–

* For patients experiencing this outcome.

† Includes significantly reduced performance for nonworking patients.

n, number of patients; NS, not significant.

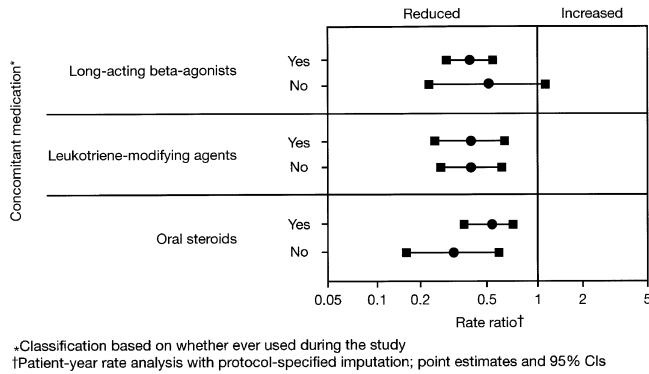


Figure 3. Effect of concomitant asthma medications (long-acting β -agonists, leukotriene receptor antagonists and systemic steroids) on the relative asthma exacerbation rates, in patients with poorly controlled (moderate-to-severe) asthma, receiving omalizumab therapy.

observed among patients not using these concomitant medications (Fig. 3).

Other efficacy variables

Rescue bronchodilators were required <1 day/week by 17% (30 of 179) of omalizumab-treated patients and 11% (9 of 83) of patients receiving BSC alone at 14 days postbaseline (no diary data collected prebaseline). At study completion, this had increased to 41.4% (75 of 181) of omalizumab-treated compared with 20.7% (18 of 87) of patients treated with BSC alone ($P < 0.001$). The median of mean number of puffs per day of rescue bronchodilator used during treatment was consistently lower in patients receiving omalizumab than patients receiving BSC alone (Fig. 4). At study completion, median rescue bronchodilator use was 0.60 puffs per day for patients receiving omalizumab vs 3.00 puffs per day for patients receiving BSC alone ($P < 0.001$).

Patients treated with omalizumab also showed a significant improvement in morning FEV₁ throughout

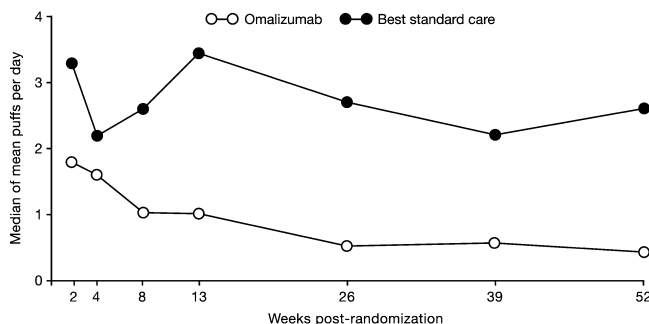


Figure 4. Effect of omalizumab, in addition to best standard care, on the median of mean number of puffs per day of short-acting β_2 -agonists used by patients with poorly controlled (moderate-to-severe) allergic asthma.

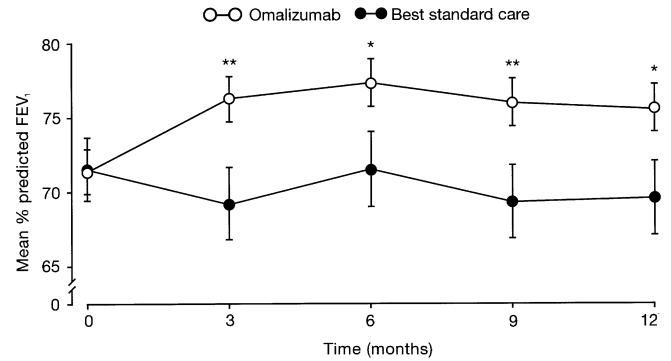


Figure 5. Effect of omalizumab, in addition to best standard care, on mean ($\pm$ SEM) predicted forced expiratory volume in one second (FEV₁) in patients with poorly controlled (moderate-to-severe) allergic asthma; * $P < 0.05$, ** $P < 0.01$ vs. best standard care alone.

treatment (Fig. 5). At study completion, a significant difference in absolute FEV₁ of 0.2 l was observed in the omalizumab group vs. BSC alone (2.48 and 2.28 l, respectively; $P = 0.02$).

Analysis of the change from baseline in asthma symptom scores at study end showed significant improvement for omalizumab over BSC alone (mean reduction in score of 6.2 and 0.7, respectively; $P < 0.001$). Of the total 312 patients, 205 (65.7%) had asthma and rhinitis comorbidity (omalizumab, $n = 135$; BSC, $n = 70$). Baseline symptom scores were similar for both treatment groups for the asthma scores, rhinitis scores and the total combined asthma and rhinitis scores. Omalizumab as an add-on to BSC significantly improved asthma, rhinitis and combined asthma and rhinitis clinical symptom scores at each visit whilst on treatment ($P < 0.001$ for all comparisons).

Patients treated with omalizumab ($n = 173$) experienced a reduction in mean daily dose of inhaled corticosteroid at study end relative to baseline ($-342 \mu\text{g/day}$) whereas those treated with BSC alone ($n = 76$) showed a slight increase ($+68 \mu\text{g/day}$). Despite no formal requirement to reduce steroid use, the between-group difference for change from baseline in daily dose of inhaled corticosteroid was statistically significant ($P < 0.001$).

Safety and tolerability

The percentage of omalizumab-treated patients experiencing ≥ 1 adverse event was comparable with BSC alone [85.0% (175 of 206) and 77.4% (82 of 106), respectively; $P = 0.116$, Table 4]. The profile of adverse events (which were typically of mild-or-moderate intensity) was comparable for the two treatment groups although headache, cough and nausea were more frequent among omalizumab recipients. Aggravated asthma was the most frequent adverse event in both treatment groups but

Table 4. Number (%) of patients with most frequently occurring adverse events ($\geq 5\%$ in any treatment group)

	Omalizumab, <i>n</i> (%) (<i>n</i> = 206)	Best standard care alone, <i>n</i> (%) (<i>n</i> = 106)
Total adverse events	175 (85.0)	82 (77.4)
Asthma aggravated	90 (43.7)	65 (61.3)
Nasopharyngitis	56 (27.2)	22 (20.8)
Lower respiratory tract infection	33 (16.0)	20 (18.9)
Headache	36 (17.5)	6 (5.7)
Rhinitis	9 (4.4)	14 (13.2)
Pharyngitis	19 (9.2)	9 (8.5)
Bronchitis	18 (8.7)	7 (6.6)
Cough	16 (7.8)	2 (1.9)
Sinusitis	14 (6.8)	3 (2.8)
Nausea	14 (6.8)	1 (0.9)
Upper respiratory tract infection	13 (6.3)	5 (4.7)
Influenza	12 (5.8)	6 (5.7)
Dyspnoea	12 (5.8)	3 (2.8)
Chest pain	11 (5.3)	1 (0.9)

showed lower frequency, as did report of rhinitis, among those treated with omalizumab.

One patient died during the study (coronary artery stenosis; omalizumab group), but the death was not considered to be study-drug related by the investigator. A total of 48 patients [omalizumab, 34 of 206 (16.5%); BSC alone, 14 of 106 (13.2%)] experienced nonfatal serious adverse events during the study, most commonly aggravated asthma. Five omalizumab-treated patients were withdrawn because of nonfatal serious adverse events (aggravated asthma, $n = 2$; orbital oedema, $n = 1$; pulmonary embolism/thrombosis, $n = 1$; supra-ventricular tachycardia and pregnancy, $n = 1$). Ten additional omalizumab-treated patients discontinued because of non-serious adverse events, most commonly skin and subcutaneous tissue disorders.

An analysis of vital signs and routine laboratory tests showed no clinically relevant trends for either treatment group between screening and study end.

Discussion

The present study evaluated the efficacy and tolerability of anti-IgE therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma, in which the drug was added to, and compared against, BSC. For all but one patient, BSC followed treatment steps 3 or 4 of the NHLBI guidelines (8), i.e. moderate-to-high daily doses of inhaled corticosteroids often in combination with systemic corticosteroids and/or long-acting β -adrenoceptor agonists, yet patients were still inadequately controlled prior to enrolment. Overall, our findings show that adding omalizumab to the therapeutic regimen of these 'difficult-to-treat' patients improved indices of asthma control, and had concomitant effects

in terms of lowering the use of health care resources (unscheduled physician visits) and rates of school/work absenteeism. The improvement in asthma control, evidenced by significantly fewer ADRI and clinically significant asthma exacerbations, was accompanied by significantly improved symptoms and decreased use of rescue bronchodilators vs BSC alone. A clinically meaningful improvement in lung function was also seen in the omalizumab group, despite less use of rescue bronchodilators and a significant reduction in dose of inhaled corticosteroid. Overall, the findings of the present study are in agreement with previous studies with omalizumab in patients with allergic asthma of varying severity (4–6).

However, there are certain aspects of this study that are worthy of comment. This was an open-label study with no placebo treatment arm. There was a higher frequency of injection-only visits for patients randomized to omalizumab therapy (to allow injections to take place every 2 or 4 weeks). However, this approach was consistent with our attempt to perform the study under conditions as close to the real-life situation as possible in a population of patients with continued unmet medical need despite currently available therapy. Furthermore, as the placebo effect tends to be high in most placebo-controlled asthma studies (possibly because of improved compliance with inhaled corticosteroid therapy in such a setting), the results of the present study are more likely to have reflected the real-life situation. Also related to our attempt at a real-life study situation are the exclusion criteria (i.e. patients with a history of smoking of 10 pack-years, active lung disease other than allergic asthma, FEV₁ reversibility of 12% within 30 min of inhaled salbutamol). Although in reality one would encounter patients with these conditions as well as asthma, they were excluded here in an attempt to avoid misdiagnosing conditions with symptoms similar to poorly controlled moderate-to-severe asthma (e.g. chronic obstructive pulmonary disease).

The major finding was that add-on anti-IgE therapy with omalizumab halved the annualized rate of ADRI, from 9.76 events per patient-year with BSC alone to 4.92 events per patient-year ($P < 0.001$). Patients treated with omalizumab also had a significantly prolonged median time to first ADRI [126 days (18 weeks) vs. 75 days (around 11 weeks) for BSC alone], with over one-third (36.1%) remaining free of ADRI during the study compared with 20.2% of those who received BSC alone. Although use of patient-provided diary card data as a main variable can be inherently difficult to analyse, this primary variable of ADRI was chosen because it encompasses numerous aspects of poor asthma control directly relevant to patients in their everyday lives, such as unscheduled physician visits and absenteeism from school or work. The findings for ADRI were supported by a reduction in clinically significant asthma exacerbations which were based on objectively determined episodes of asthma worsening requiring systemic

corticosteroids, thereby avoiding the analytical difficulties associated with patient diary data. Interestingly, the rates of clinically significant asthma exacerbations in the present study were similar to those in a pooled analysis of omalizumab therapy in patients similarly at high risk of serious asthma-related morbidity and mortality (7). In the latter analysis, the annualized rate of asthma exacerbations for patients receiving placebo and omalizumab was 1.93 and 0.95 per patient-year respectively (7). Corresponding rates in the present study were 2.86 and 1.12 per patient-year, respectively, for BSC alone and omalizumab. Thus, while this was an open-label study, the beneficial effect of omalizumab was comparable with that in a quite similar, but placebo-controlled population.

Given that ADRIs is a collective term, it was of interest to evaluate the effect of omalizumab on individual outcomes that comprised this variable. Overall, treatment with add-on omalizumab was associated with fewer patients needing systemic corticosteroids, and for a shorter median duration, compared with BSC alone. Interesting trends were apparent in terms of usage of medical resources. For example, there were significantly fewer patients with unscheduled physician visits for those treated with add-on omalizumab, although emergency room visits and hospitalizations were comparable for the two groups. Analysis of asthma-related absenteeism also showed a significant reduction in favour of add-on omalizumab therapy. Such findings therefore highlight the various ways in which poor asthma control directly affects patients in their everyday lives, most aspects of which may be improved with anti-IgE therapy.

Omalizumab as add-on therapy was safe and well-tolerated in the present study. Adverse events were similar in frequency and profile to those observed with BSC alone, with most events consisting of common medical complaints or those expected of a patient population with poorly controlled asthma. While the frequency of some adverse events during add-on omalizumab therapy was higher relative to BSC alone, this may be due to the open-label design or a recall bias related to the more frequent visits for the omalizumab-treated group. Indeed, while nursing staffs were requested not to question patients regarding tolerability at 2- or 4-weekly injection visits, spontaneously offered information on adverse events was recorded. This potential increased opportunity for reporting of adverse events during add-on omalizumab therapy may explain the imbalance in certain commonly reported adverse events within an otherwise healthy population.

In conclusion, the findings of this study indicate that therapy with omalizumab, combined with BSC, is well-tolerated and offers the potential to improve disease control and symptoms in patients with poorly controlled (moderate-to-severe) allergic asthma.

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References

1. BARNES PJ, JONSSON B, KLIM JB. The costs of asthma. *Eur Respir J* 1996;**9**:636–642.
2. HOLT PG, MACAUBAS C, STUMBLES PA, SLY PD. The role of allergy in the development of asthma. *Nature* 1999;**402**(Suppl.):B12–17.
3. JARDIEU PM, FICK RB Jr. IgE inhibition as a therapy for allergic disease. *Int Arch Allergy Immunol* 1999;**118**:112–115.
4. BUSSE W, CORREN J, LANIER BQ, McALARY M, FOWLER-TAYLOR A, CIOPPA GD et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;**108**:184–190.
5. HOLGATE ST, CHUCHALIN A, HÉBERT J, LÖTVALL J, CHUNG RF, BOUSQUET J et al. Omalizumab (Xolair®, RhuMab-E25), a novel therapy for severe allergic asthma [abstract]. *Am J Respir Crit Care Med* 2001;**163**(Suppl):A812.
6. SOLÈR M, MATZ J, TOWNLEY R, BUHL R, O'BRIEN J, FOX H et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;**18**: 254–261.
7. HOLGATE ST, BOUSQUET J, WENZEL S, FOX H, LIU J, CASTELLSAGUE J. Efficacy of omalizumab, an anti-immunoglobulin antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin* 2001;**17**:233–240.
8. National Institutes for Health, National Heart, Lung, and Blood Institute. Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. NIH Publication no. 97-4051, 1997.
9. WASSERFALLEN JB, GOLD K, SCHULMAN KA, BARANIUK JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. *J Allergy Clin Immunol* 1997;**100**:16–22.
10. LAHDENSUO A, HAAHTELA T, HERRALA J, KAVA T, KIVIRANTA K, KUUSISTO P et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. *BMJ* 1996;**312**:748–752.

Appendix

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