

Original article

The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma

Background: Patients with severe persistent asthma who are inadequately controlled despite treatment according to current asthma management guidelines have a significant unmet medical need. Such patients are at high risk of serious exacerbations and asthma-related mortality.

Methods: Here, we pooled data from seven studies to determine the effect of omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody, on asthma exacerbations in patients with severe persistent asthma. Omalizumab was added to current asthma therapy and compared with placebo (in five double-blind studies) or with current asthma therapy alone (in two open-label studies). The studies included 4308 patients (2511 treated with omalizumab), 93% of whom had severe persistent asthma according to the Global Initiative for Asthma (GINA) 2002 classification. Using the Poisson regression model, results were calculated as the ratio of treatment effect (omalizumab : control) on the standardized exacerbation rate per year.

Results: Omalizumab significantly reduced the rate of asthma exacerbations by 38% ($P < 0.0001$ vs control) and the rate of total emergency visits by 47% ($P < 0.0001$ vs control). Analysis of demographic subgroups showed that the efficacy of omalizumab on asthma exacerbations was unaffected by patient age, gender, baseline serum IgE (split by median) or by 2- or 4-weekly dosing schedule, although benefit in absolute terms appeared to be greatest in patients with more severe asthma, defined by a lower value of percentage predicted forced expiratory volume in 1 s (FEV_1) at baseline.

Conclusions: These results suggest that omalizumab may fulfil an important need in patients with severe persistent asthma, many of whom are not adequately controlled on current therapy.

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Patients with severe asthma often experience variable or continuous symptoms, airflow obstruction and limitations on daily activities. They are also at an increased risk of hospitalization for exacerbations or asthma death (1–9). The prevention of asthma exacerbations is a key goal of asthma management. However, in these patients, complete control may not be achievable and the goal is to obtain the best possible results in terms of symptoms, rescue medication use and lung function (10).

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody for use in IgE-mediated allergic diseases. Studies conducted in patients with allergic asthma showed that omalizumab reduced the incidence and frequency of clinically significant asthma exacerbations (11–14). Omalizumab was also shown to reduce inhaled corticosteroid (ICS) requirements, to improve asthma symptoms and lung function, and to improve

asthma-related quality of life in patients with allergic asthma (11–17).

The potential efficacy of omalizumab in patients with severe asthma was suggested in previous analyses in which omalizumab significantly reduced the level of exacerbations in patients deemed to be at high risk because of recent emergency treatment or prior intubation (18), and significantly reduced the level of severe exacerbations resulting in hospitalization or emergency medical care (19). A further analysis showed that the patient baseline features predicting the greatest likelihood of response to omalizumab were those features characterizing more severe asthma: lower forced expiratory volume in 1 s (FEV_1), recent emergency treatment and higher ICS dose (20).

Because exacerbation prevention is vitally important in the management of patients with severe asthma, and

because the clinical studies with omalizumab included a large proportion of patients with severe persistent asthma (10), we conducted a pooled analysis of the clinical database to examine the effect of omalizumab on exacerbations in 4308 patients, 2511 of whom were treated with omalizumab.

Methods

Study design

Details of the seven studies included in the analysis are shown in Table 1. Five were randomized, double-blind, placebo-controlled studies in which patients received subcutaneous injections of omalizumab or placebo. Two studies were randomized and controlled but open label; one study (study 2) had a naturalistic design to allow the impact of the dosing regimen and any related compliance or behavioural issues to be taken into account in the assessment of omalizumab therapy compared with current asthma therapy alone, and the other study (study 7) was designed primarily as a safety study. In all studies, omalizumab was given as add-on therapy to concomitant asthma treatment. Omalizumab was administered subcutaneously every 2 or 4 weeks to provide a dose of at least 0.016 mg/kg per IU/ml of IgE according to patients' bodyweight and baseline IgE levels using a dosing table (21). Readers are referred to the full publications of six of the studies for further details of the designs of study 1 (Humbert et al. this issue), study 2 (13), study 3 (14), study 4 (11, 22), study 5 (12, 23) and study 6 (15). Two of the placebo-controlled studies (studies 4 and 5) comprised core and extension periods, and data for the full 52-week treatment period are included in the present analysis. The unpublished study, study 7 or 'asthma subjects already treated with other therapies' ('ALTO'), was an open-label study in patients with moderate-to-severe asthma evaluating the addition of omalizumab to current therapy, which comprised moderate doses of ICS and/or daily oral corticosteroids, long-acting inhaled β_2 -agonists, a leukotriene modifier, a xanthine or sodium cromoglycate. This large study was conducted in patients aged 6–75 years, but only data from those aged 12 years or older are included here. Asthma exacerbation was the primary efficacy outcome measure in six of the studies, and a secondary efficacy variable in study 6.

Definition of asthma severity

In all but two of the studies, the patient population was originally described as having moderate-to-severe asthma. These were defined before Global Initiative for Asthma (GINA) 2002 guidelines were available, so classified severity by existing clinical features irrespective of current therapy, whereas the GINA guidelines now take into account both clinical features and asthma treatment. However, more than 90% of patients met the criteria for severe persistent asthma set out in the GINA 2002 guidelines (Table 1). The GINA 2002 severity guidelines and the patient populations studied in the individual clinical trials are shown in Table 2.

Definition of asthma exacerbations

In studies 1, 2 and 6, asthma exacerbations were defined as a worsening of asthma requiring treatment with systemic corticosteroids. In studies 3, 4 and 5, asthma exacerbations were defined as a worsening of asthma requiring treatment with systemic corticosteroids or a doubling of the baseline ICS dose (approximately 90% of exacerbations required systemic corticosteroids). In study 7, exacerbations were defined as a worsening of asthma requiring unscheduled medical care or an emergency room visit or hospitalization, and one or more of the following: doubling of ICS dose, increase in dose of oral corticosteroids, or initiation of systemic corticosteroids.

Statistical analysis

Absolute differences in annualized exacerbation rates between treatment groups were calculated for all studies individually and combined. Annualized exacerbation rates were used to enable comparison of results from studies of different duration, and are summarized with differences between groups shown as rate ratios (omalizumab : control). The relative rates of asthma exacerbations were analysed using the Poisson regression model. Estimates of the ratio of exacerbation rates in the treatment groups (omalizumab : control), together with 95% confidence intervals, were calculated for each individual study as well as for pooled studies. The Poisson regression model for pooled studies included terms for treatment, dosing schedule, country grouping and study. The Poisson regression model had been used previously in study 1 and was modified to enable application across all studies.

Table 1. Studies included in the analysis

Study	Patients (number randomized)	Patients with severe persistent asthma*, n (%)	Baseline ICS mean dose (μ g/day)†	Study treatment arms	Duration (weeks)
Study 1	Inadequately controlled severe asthma (n = 419)	419 (100)	2330	Omalizumab + ICS vs placebo + ICS	28
Study 2 (13)	Inadequately controlled severe asthma (n = 312)	294 (94.2)	2177	Omalizumab + current asthma therapy vs current asthma therapy alone	52
Study 3 (14)	Severe asthma and rhinitis (n = 405)	364 (89.9)	1088	Omalizumab + ICS vs placebo + ICS	28
Study 4 (11, 22)	Severe asthma (n = 525)	523 (99.6)	677	Omalizumab + ICS vs placebo + ICS	52 (28 + 24 extension)
Study 5 (12, 23)	Severe asthma (n = 546)	537 (98.4)	771	Omalizumab + ICS vs placebo + ICS	52 (28 + 24 extension)
Study 6 (15)	Severe asthma dependent on high-dose ICS (n = 341)	310 (90.9)	2785	Omalizumab + ICS vs placebo + ICS	32
Study 7 ALTO	Severe asthma (n = 1760)	1555 (88.4)	1406	Omalizumab + current asthma therapy vs current asthma therapy alone	24

ICS, inhaled corticosteroids; ALTO, asthma subjects already treated with other therapies; GINA, Global Initiative for Asthma.

* Severe persistent asthma according to GINA 2002 classification.

† Beclomethasone dipropionate (BDP) equivalent.

Table 2. GINA 2002 asthma severity classification and patient populations studied

Baseline clinical features	Baseline asthma treatment*			
	Step 1	Step 2	Step 3	Step 4
Step 1: FEV ₁ (% predicted) ≥80% and daytime symptoms <1 per week and nocturnal symptoms ≤2 per month	Intermittent	Mild persistent Study 2 (1%)	Moderate persistent Study 2 (2%) Study 6 (9%) Study 7 (10%)	Severe persistent Study 1 (1%) Study 2 (1%) Study 6 (6%) Study 7 (3%)
Step 2: FEV ₁ (% predicted) ≥80% and daytime symptoms >1 per week with <1 per day, and/or nocturnal symptoms >2 per month but <1 per week	Mild persistent	Moderate persistent Study 2 (3%) Study 3 (10%) Study 5 (1%)	Severe persistent Study 2 (2%) Study 3 (3%) Study 6 (2%) Study 7 (6%)	Severe persistent Study 1 (1%) Study 2 (3%) Study 3 (3%) Study 6 (3%) Study 7 (3%)
Step 3: FEV ₁ (% predicted) ≥60% to <80% or daytime symptoms daily or nocturnal symptoms ≥1 per week	Moderate persistent Study 7 (1%)	Severe persistent Study 2 (4%) Study 3 (28%) Study 4 (27%) Study 5 (19%) Study 7 (1%)	Severe persistent Study 2 (19%) Study 3 (13%) Study 5 (3%) Study 6 (23%) Study 7 (26%)	Severe persistent Study 1 (23%) Study 2 (31%) Study 3 (10%) Study 6 (21%) Study 7 (17%)
Step 4: FEV ₁ (% predicted) <60% or nocturnal symptoms frequent	Severe persistent Study 7 (1%)	Severe persistent Study 2 (2%) Study 3 (14%) Study 4 (72%) Study 5 (68%) Study 7 (1%)	Severe persistent Study 2 (7%) Study 3 (11%) Study 5 (8%) Study 6 (22%) Study 7 (14%)	Severe persistent Study 1 (74%) Study 2 (27%) Study 3 (8%) Study 6 (14%) Study 7 (17%)

* Baseline asthma treatment was classified as follows. step 1: no ICS, theophylline, leukotriene modifier, regardless of LABA use; step 2: >0 to 1000 µg BDP or equivalent without LABA use, or <500 µg BDP or equivalent plus theophylline and/or leukotriene modifier, or ≥1 to <200 µg BDP or equivalent plus LABA use; step 3: >1000 µg BDP (or equivalent) without LABA use, or ≥500 to 1000 µg BDP (or equivalent) plus theophylline and/or leukotriene modifier, or ≥200 to 1000 µg BDP (or equivalent) plus LABA use; step 4: >1000 µg BDP (or equivalent) plus LABA use, or use of systemic corticosteroid.

FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting inhaled β₂-agonist; BDP, beclomethasone dipropionate.

Estimates for the asthma exacerbation rate ratio for each study were based on Poisson regression models with adjustments for patients who discontinued prematurely (imputation). The imputation method involved adding one exacerbation to the total number for that patient, unless that person had an asthma exacerbation in the 7 days prior to the premature discontinuation. The duration of the imputed exacerbation was deemed as 0 days. An analysis without imputations was also performed to assess the impact of discontinuations and the imputation rule.

For the subgroup analyses, efficacy data for the controlled studies were pooled for analysis by demographic subgroups. Subgroup analyses were performed for each of the following factors, by adding its interaction with treatment to the Poisson regression model: age (12 to <18 years, 18 to <65 years, ≥65 years), gender, predicted FEV₁ (<60%, 60 to <80%, ≥80%), total serum IgE (<median IgE, ≥median IgE) and dosing (2- or 4-weekly). No analysis of efficacy by racial subgroups was performed owing to the large difference between the percentage of patients in each racial group (85.8% Caucasian, 6.7% Black, 1.5% Oriental and 6.1% other races).

Although the seven individual trials shared many common design features, there were some differences. A test of homogeneity performed by fitting the treatment by study interaction was suggestive of a lack of homogeneity. Further exploration of the standard error and treatment effect estimates indicated that, as might be expected, the largest studies (studies 5 and 7) with the smallest standard error, and study 2 with the largest treatment effect, contributed to this finding. However, this finding is not necessarily the result of any underlying design issue and the treatment differences in all seven studies were in the same direction. In addition, pooling of data provided sufficient

number of patients to explore the effect of omalizumab treatment in different demographic subgroups within the overall population.

With the exception of study 1 (protocol excluded 63 pre-amendment patients) and study 7 [exclusion of patients <12 years of age (7% of study population)], results are presented for the intention-to-treat (ITT) population, which comprised all randomized patients.

Results

Patients and patient disposition

The demographic and background characteristics of the pooled patient population are shown in Table 3. From a total of 4308 patients, 2511 and 1797 were randomized to receive omalizumab or control, respectively. Treatment was discontinued in 549 patients, who were approximately equally divided between omalizumab (12%) and control (14%) groups. Most discontinuations were due to reasons other than adverse events or inadequate efficacy (which accounted for 15.5% and 0.9% of withdrawals, respectively).

Asthma exacerbations

The effect of omalizumab on the annualized rate of asthma exacerbations and rate ratios in the individual

studies and the pooled analysis is shown in Table 4. Meaningful differences in exacerbation rates between the omalizumab and control groups were observed across all studies. These differences were broadly comparable in the placebo-controlled studies [studies 1 (adjusted and

Table 3. Demographic and baseline characteristics of the pooled patient population

	Omalizumab (n = 2511)	Control (n = 1797)	Total patients (n = 4308)
Age (years)			
Mean (SD)	41.6 (14.83)	40.9 (14.43)	41.3 (14.67)
Range	12–79	12–76	12–79
Sex, n (%)			
Males	1018 (40.5)	738 (41.1)	1756 (40.8)
Females	1493 (59.5)	1059 (58.9)	2552 (59.2)
Race, n (%)			
Caucasian	2137 (85.1)	1526 (84.9)	3663 (85.0)
Black	173 (6.9)	114 (6.3)	287 (6.7)
Oriental	36 (1.4)	27 (1.5)	63 (1.5)
Other	165 (6.6)	130 (7.2)	295 (6.8)
Serum total IgE (IU/ml)			
Mean (SD)	198.2 (161.43)	198.8 (158.95)	198.5 (160.42)
Range	20–1118	19–815	19–1118
Baseline ICS in BDP equivalent (µg/day)			
Mean (SD)	1464.4 (1050.97)	1458.9 (1004.06)	1462.1 (1031.51)
Range	0–10 000	88–8000	0–10 000
Baseline LABA use, n (%)			
Yes	1537 (61.2)	933 (51.9)	2470 (57.3)
No	974 (38.8)	864 (48.1)	1838 (42.7)
FEV ₁ , % of predicted			
Mean (SD)	70.3 (17.65)	70.0 (17.34)	70.2 (17.52)
Range	12–139	14–130	12–139
Reversibility (%)			
Mean (SD)	24.0 (19.29)	23.6 (18.93)	23.8 (19.12)
Range	–100 to 158.3	–100 to 177.9	–100 to 177.9

IgE, immunoglobulin E; ICS, inhaled corticosteroids; BDP, beclomethasone dipropionate; LABA, long-acting β_2 -agonist; FEV₁, forced expiratory volume in 1 s.

Table 4. Analysis of asthma exacerbations using Poisson regression for individual studies and pooled data [intention-to-treat (ITT) population]

Study	Exacerbation rate per year			Ratio (95% CI)	P-value
	Omalizumab	Control	Treatment difference		
Study 1 (adjusted baseline*)	1.357	1.847	0.491	0.734 (0.547–0.985)	0.039
Study 1 (unadjusted baseline)	1.554	1.925	0.370	0.808 (0.601–1.085)	0.156
Study 2 (13)	0.979	2.470	1.491	0.396 (0.293–0.536)	<0.0001
Study 3 (14)	0.491	0.785	0.294	0.625 (0.412–0.949)	0.027
Study 4 (11, 22)	0.592	0.992	0.400	0.597 (0.453–0.786)	0.0002
Study 5 (12, 23)	0.514	1.212	0.698	0.424 (0.329–0.548)	<0.0001
Study 6 (15)	1.176	1.600	0.424	0.735 (0.476–1.135)	0.165
Study 7	1.017	1.201	0.184	0.847 (0.705–1.018)	0.077
Pooled†	0.910	1.474	0.564	0.617 (0.535–0.712)	<0.0001

* Adjusted study 1 result to adjust for exacerbations at baseline. Study 1 results vary slightly from those published in Humbert et al. (this issue) due to different methods of grouping centres (fewer larger groupings) used here.

† Pooled analysis included unadjusted study 1 data.

unadjusted), 3, 4, 5 and 6] where they ranged from 0.294 to 0.698. The annualized rate of asthma exacerbations was significantly lower in patients receiving omalizumab compared with control patients in studies 1 (adjusted) 2, 3, 4 and 5. Pooled data showed a significantly lower rate for omalizumab-treated patients than for control patients [0.910 vs 1.474 (treatment difference 0.564); ratio 0.617; $P < 0.0001$ vs control]. In study 1, pre-treatment exacerbation history was imbalanced between the treatment groups and the primary efficacy variable was re-analysed with adjustments for baseline exacerbation history. However, the pooled analysis includes the unadjusted data and is therefore slightly biased in favour of control group. Of note were the results in open-label study 2, where the addition of omalizumab to best standard care led to an almost 2.5-fold decrease in exacerbation rates. Study 6 was primarily designed to evaluate the ICS-sparing effects of omalizumab in an optimally controlled population, and was not powered to detect an effect on exacerbation rate. In study 7, specifically designed to evaluate safety, the rate of asthma exacerbations was lower in the omalizumab group, but did not attain statistical significance ($P = 0.077$).

Emergency visits

The pooled population did not include study 3, which did not collect these data. For the pooled population as shown in Table 5, omalizumab had a statistically significant effect compared with control therapy in reducing each type of emergency visit ($P < 0.05$) and for the total emergency visits ($P < 0.0001$). Annualized rates for total emergency visits were 0.332 for omalizumab group and 0.623 for the control group, corresponding to a 47% reduction in total emergency visits with omalizumab. Omalizumab reduced hospital admissions by 52% ($P = 0.041$), emergency room visits by 61% ($P = 0.013$) and unscheduled doctor visits by 47% ($P = 0.0003$).

Table 5. The rate of hospitalizations and other unscheduled visits for the pooled population using Poisson regression

Type of visit	Rate per year			Ratio (95% CI)	P-value
	Omalizumab	Control	Treatment difference		
Total emergency visits	0.332	0.623	0.291	0.533 (0.401–0.709)	<0.0001
Hospital admission	0.030	0.062	0.032	0.489 (0.246–0.972)	0.041
Emergency room visits	0.026	0.066	0.040	0.397 (0.192–0.820)	0.013
Unscheduled doctor visits	0.252	0.443	0.191	0.568 (0.417–0.774)	0.0003

Data for study 3 were not collected. Randomized patients who did not receive study medication were excluded from the Poisson regression model.

Table 6. Analysis of asthma exacerbations using Poisson regression by demographic subgroup (intention-to-treat, ITT population)

Demographic subgroup	Exacerbation rate per year			Ratio (95% CI)	P-value
	Omalizumab (n = 2511)	Control (n = 1797)	Treatment difference		
Age group (years)					
12 to <18 (n = 298)	0.736	1.566	0.830	0.470 (0.318–0.695)	0.0002
18 to <65 (n = 3734)	0.914	1.465	0.551	0.624 (0.539–0.722)	<0.0001
≥65 (n = 241)	1.006	1.534	0.528	0.656 (0.415–1.036)	0.071
Gender					
Male (n = 1740)	0.795	1.285	0.490	0.619 (0.507–0.756)	<0.0001
Female (n = 2533)	0.978	1.595	0.617	0.613 (0.520–0.723)	<0.0001
Baseline FEV ₁ (% predicted)					
<60 (n = 1136)	1.129	2.232	1.103	0.506 (0.412–0.621)	<0.0001
60 to <80 (n = 1853)	0.863	1.266	0.403	0.681 (0.566–0.820)	<0.003
≥80 (n = 1282)	0.716	1.043	0.327	0.687 (0.538–0.877)	0.0003
Baseline serum IgE					
<median (n = 2076)	0.938	1.323	0.385	0.708 (0.587–0.855)	<0.0001
≥median (n = 2091)	0.741	1.367	0.626	0.542 (0.455–0.646)	<0.0001
Dosing schedule					
4-weekly (n = 2060)	0.960	1.442	0.482	0.665 (0.554–0.799)	<0.0001
2-weekly (n = 1516)	0.893	1.593	0.700	0.561 (0.462–0.681)	<0.0001

FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E; CI, confidence interval.

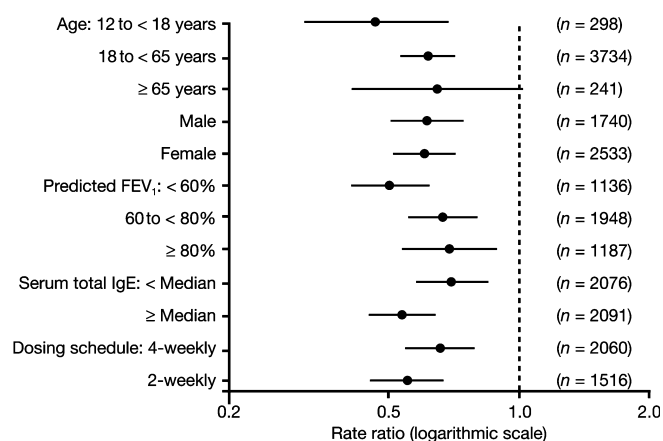


Figure 1. Relative rates of asthma exacerbations across subgroups in pooled studies [intention-to-treat (ITT) population with imputation]. Point estimates and 95% confidence intervals for asthma exacerbation rate ratio (omalizumab : control) from Poisson regression models are plotted.

Effect of baseline factors

Estimates with 95% confidence intervals for the asthma exacerbation rate ratio (omalizumab : control) by demographic subgroup for the pooled controlled studies are summarized in Table 6 and displayed graphically in Fig. 1. The rate of asthma exacerbations was statistically significantly less for the omalizumab group compared with control groups for all age subgroups except for older patients (≥65 years of age). However, patients ≥65 years of age represented the smallest demographic subgroup evaluated and the rate ratios of asthma exacerbations approached that of the 18 to <65 year group. The rate of asthma exacerbations was also statistically significantly

less for omalizumab patients compared with control patients for both males and females, for patients with a percentage predicted FEV₁ of <60%, between 60 and 80%, and 80% or greater, for both patients with baseline IgE levels above or below the median level (148 IU/ml), and for patients on both 2- and 4-weekly dosing schedules. However, there is some suggestion of a trend of greater relative improvement in patients with worse lung function as shown by baseline percentage predicted FEV₁.

Discussion

These data from controlled clinical studies in patients with severe persistent asthma show that omalizumab is highly efficacious as add-on treatment to concomitant asthma therapy, as shown by the consistent reduction in asthma exacerbation rates compared with control-treated patients. Overall, exacerbations were significantly reduced ($P < 0.0001$) by 38.3% (annualized rate: 0.910 vs 1.474) with omalizumab compared with the control group. Thus, it is not surprising that omalizumab significantly reduced the rate of emergency visits for asthma care by 47% compared with control therapy ($P < 0.0001$). Hospital admissions were reduced by 52% ($P = 0.041$), emergency room visits by 61% ($P = 0.013$) and unscheduled doctor visits by 47% ($P = 0.0003$).

Overall, data pooling for subgroup analysis demonstrated a consistent benefit of omalizumab in terms of reduction in exacerbation rate regardless of disease severity (defined by lung function), duration of disease, age or gender. The loss of statistical significance in patients aged ≥65 years old may predominantly be due to the small number of patients in this age cohort, although the magnitude of effect suggests that IgE remains an

important factor in asthma in the elderly despite the likelihood of more frequent confounding comorbidity in that age group. Considering baseline FEV₁ as a marker of disease severity, the treatment difference in favour of omalizumab was largest in patients with the lowest FEV₁ (a reduction of 49% in exacerbation rate in patients with FEV₁ <60% predicted; $P < 0.0001$). Smaller relative reductions, although still statistically significant *vs* control therapy, were seen in patients with FEV₁ 60 to <80% predicted (33%; $P < 0.0001$) and those with FEV₁ ≥80% predicted (30%; $P = 0.003$). This finding is supported by an earlier report (20) showing that baseline factors predictive of a greater response to omalizumab therapy were those reflecting more severe asthma: FEV₁ ≤65% predicted, beclomethasone dipropionate (BDP) dose ≥800 µg/day, and history of emergency asthma treatment in the past year. The likelihood of response increased further in the presence of two or more of these high-severity factors.

Patients with a history of emergency asthma treatment are at the greatest risk of asthma-related morbidity and death, and present the greatest concern to treating doctors (10). A previous history of life-threatening exacerbations, hospitalization within the previous year, and a history of intubation for asthma are all specific factors associated with an increased risk of asthma mortality (6). Data from three of the studies discussed in this report were previously subjected to a meta-analysis (18) of asthma exacerbation rates in a group of 254 adult and adolescent patients who were defined as high risk on the basis of an overnight hospitalization, an intensive care unit stay or an emergency room visit in the past year, or any prior intubation. In this small but important high-risk population, omalizumab reduced the rate of asthma exacerbations by 55% ($P < 0.0004$ *vs* placebo). Again, the reduction appeared to be most marked in patients with more severe asthma, with ratios of treatment effect (omalizumab : placebo) of 0.340, 0.501 and 0.722 in subjects whose FEV₁ values were ≤60%, >60% to ≤80% and >80% predicted, respectively. A previous meta-analysis of data from 1405 patients from two of the studies included in this report (11, 12) and a further study in children with less severe asthma (24) demonstrated that omalizumab therapy significantly reduced the rate of serious asthma exacerbations resulting in unscheduled outpatient visits, emergency room treatment and hospitalization (19). The results from these two previous meta-analyses are confirmed by the present analysis from a body of data that is larger and more representative of the likely clinical use of omalizumab, since the present results were obtained in patients older than 12 years with severe

persistent asthma, including 731 patients with inadequately controlled asthma despite high-dose ICS use.

The decreases in the rates of asthma exacerbations and those requiring emergency care, are highly relevant to the management of patients with severe asthma. Severe exacerbations are responsible for the mortality associated with asthma, and contribute heavily to the morbidity and costs of the disease. Indeed, the 5–10% of asthma patients with the most severe form of the disease contribute some 50% of the total costs associated with asthma (25). Decreasing the rate of exacerbations in patients with severe asthma is likely to be associated with improvements in quality of life and decrease burdens on patients and health care systems, as well as potentially saving lives.

Omalizumab is administered every 2 or 4 weeks by a doctor. For patients with severe persistent asthma, this schedule may have advantages in providing regular monitoring, helping to improve adherence and not adding further to the complexity of self-administered multiple drug regimens that these patients often require. It is also important that a new treatment should not add to the burden of tolerability for the patient. Individual publications of the studies included in the present analysis, including three studies of 1 year's duration, report excellent tolerability (11–15, 22, 23).

Currently, experts acknowledge that achieving disease control in patients with severe persistent asthma may not be possible (10). These patients experience highly variable but continuous symptoms despite the use of high-dose ICS and LABAs, and are at higher risk of exacerbation, hospitalization and even death than other patients with asthma. These patients may receive treatment with leukotriene antagonists or theophylline in addition to their primary therapy. If their asthma still remains inadequately controlled, they currently have very limited therapeutic options. The fact that medications such as oral corticosteroids, cyclosporin, methotrexate and oral gold are used in this population reflects that even modest improvements in symptoms are considered clinically meaningful despite the risk of significant side-effects.

As an add-on to current asthma therapy, omalizumab significantly improved disease control in terms of decreasing the rate of exacerbations, with a pronounced reduction in the rate of asthma-related emergency medical consultations. This demonstration of clinically relevant efficacy in such a difficult-to-treat population is an important finding. Omalizumab should be considered as add-on treatment for patients with severe persistent asthma who continue to suffer with inadequately controlled asthma despite best available therapy.

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