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Original article

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE

Background: Patients with severe persistent asthma who are inadequately controlled despite Global Initiative for Asthma (GINA) 2002 step 4 therapy are a challenging population with significant unmet medical need. We determined the effect of omalizumab on clinically significant asthma exacerbations (requiring systemic corticosteroids) in the first omalizumab study to exclusively enrol patients from this difficult-to-treat patient population.
Methods: Following a run-in phase, patients (12–75 years) inadequately controlled despite therapy with high-dose inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) with reduced lung function and a recent history of clinically significant exacerbations were randomized to receive omalizumab or placebo for 28 weeks in a double-blind, parallel-group, multicentre study.
Results: A total of 419 patients were included in the efficacy analyses. The clinically significant asthma exacerbation rate (primary efficacy variable), adjusted for an observed relevant imbalance in history of clinically significant asthma exacerbations, was 0.68 with omalizumab and 0.91 with placebo (26% reduction) during the 28-week treatment phase ($P = 0.042$). Without adjustment, a similar magnitude of effect was seen (19% reduction), but this did not reach statistical significance. Omalizumab significantly reduced severe asthma exacerbation rate (0.24 *vs* 0.48, $P = 0.002$) and emergency visit rate (0.24 *vs* 0.43, $P = 0.038$). Omalizumab significantly improved asthma-related quality of life, morning peak expiratory flow and asthma symptom scores. The incidence of adverse events was similar between treatment groups.
Conclusions: In patients with inadequately controlled severe persistent asthma, despite high-dose ICS and LABA therapy, and often additional therapy, omalizumab significantly reduced the rate of clinically significant asthma exacerbations, severe exacerbations and emergency visits. Omalizumab is effective and should be considered as add-on therapy for patients with inadequately controlled severe persistent asthma who have a significant unmet need despite best available therapy.

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Key words: anti-immunoglobulin E; exacerbations; Global Initiative for Asthma 2002 step 4 therapy; omalizumab; severe persistent asthma.

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Approximately 5% of asthma patients have severe asthma, which is often inadequately controlled by inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) (1, 2). Global Initiative for Asthma (GINA) guidelines recommend an approach of aiming for best possible results in terms of symptoms, rescue medication use and lung function (2). These patients are at high risk of severe exacerbations and death (3, 4) and have few therapeutic options available. Oral corticosteroids are effective in some patients, but are associated with significant side-effects (5). Experimental drugs, including methotrexate, cyclosporin, gold salts or troleandomycin, have failed to demonstrate an acceptable risk : benefit ratio (6–9). Patients with severe asthma have the greatest medical need among the asthmatic population today and represent the greatest economic cost (>50% of total asthma-related health care costs) (10–12).

Omalizumab, a monoclonal anti-immunoglobulin (Ig)E antibody, has been extensively evaluated in allergic respiratory disease. In patients with allergic asthma, omalizumab significantly reduced asthma exacerbations and use of inhaled ICS (13–16). Benefits were also reported in patients with concomitant asthma and perennial allergic rhinitis (17). Asthma-related quality of life (QoL) was improved (18) and omalizumab was well-tolerated during long-term use (19, 20). Most patients (>90%) in these

studies met the GINA (2002) definition of severe persistent asthma. Subgroup analyses showed that omalizumab was particularly effective in reducing exacerbations in patients at high risk of death as indicated by previous intubation or recent hospitalization/emergency treatment (21). Furthermore, across a range of patients, omalizumab was effective in reducing exacerbation rates resulting in hospitalization, emergency treatment or unscheduled doctor visits (22). Factors increasing the likelihood of responding to omalizumab compared with placebo are those that reflect more severe asthma (23).

The primary objective of the INNOVATE study was to evaluate the effect of add-on omalizumab on asthma exacerbations in patients with severe persistent asthma who were inadequately controlled despite GINA step 4 therapy, which comprises high-dose ICS plus LABA and additional controller medication if required (2). Other indicators of asthma control were collected as secondary variables, and safety and tolerability were assessed.

Methods

Details of the study methodology described below include changes made following a protocol amendment. The amendment followed scientific advice from the European Union Committee on Proprietary Medicinal Products (CPMP) and reflected the updated GINA guidelines (2). The main differences prior to amendment were: patients were recruited immediately after hospitalization; changes in dosage of asthma medications (including ICS and LABA) were permitted; no baseline period was enforced; and high-dose ICS was defined as ≥800 μg/day beclomethasone dipropionate (BDP) or ≥400 μg/day fluticasone propionate.

Patients

Inclusion criteria were very strict in order to enrol the most severe patients with persistent allergic asthma (12–75 years):

- Positive skin prick test to ≥1 perennial aeroallergen, to which they were likely to be exposed during the study, and total serum IgE level of ≥30 to ≤700 IU/ml.
- Severe persistent asthma requiring regular treatment with >1000 μg/day BDP or equivalent and LABA (GINA step 4 treatment).
- Forced expiratory volume in 1 s (FEV_1) ≥40 to <80% of predicted normal value and continuing asthma symptoms.
- FEV_1 reversibility ≥12% from baseline within 30 min of inhaled (up to 400 μg) or nebulized (up to 5 mg) salbutamol.
- Despite high-dose ICS and LABA use at least two asthma exacerbations requiring systemic corticosteroids, or one severe exacerbation [peak expiratory flow (PEF)/FEV_1 <60% of personal best, requiring systemic corticosteroids] resulting in hospitalization or emergency room treatment, in the past 12 months.
- Additional asthma medications, taken regularly from >4 weeks prior to randomization were permitted, including theophyllines, oral β_2-agonists and antileukotrienes.
- Maintenance oral corticosteroids (maximum 20 mg/day) were permitted providing at least one of the exacerbations in the previous 12 months had occurred while on this therapy.

Exclusion criteria included:

- Smokers or smoking history of ≥10 pack-years.
- Treatment for an exacerbation within 4 weeks of randomization (the run-in could be extended if necessary).
- Use of methotrexate, gold salts, troleandomycin or cyclosporin within 3 months of the first visit.
- Prior omalizumab treatment.

The study was performed with International Review Board approval and in accordance with good clinical practice and the Declaration of Helsinki.

Study design and assessments

This was a randomized, placebo-controlled, double-blind study with a 28-week treatment phase to determine the efficacy, safety and tolerability of omalizumab. Patients were recruited at 108 centres in 14 countries. The study comprised four phases: a 7-day screening period (for evaluating eligibility), an 8-week run-in phase, the 28-week drug add-on treatment phase and a 16-week follow-up phase (not reported here). During the first 4 weeks of the run-in period, each subject's asthma management was reviewed to include advice on allergen avoidance, theophylline monitoring if applicable and inhaler technique. Asthma medication could be adjusted to achieve the best control, but no further adjustments were permitted in the last 4 weeks of the run-in prior to randomization.

Patients made study visits at screening, every 2 weeks during the run-in, at weeks 0, 1, 2, 4, 12, 20 and 28 of the treatment phase, and at weeks 4 and 16 of the follow-up. The primary efficacy variable was the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids) during the 28-week double-blind treatment phase. Hospitalization, emergency visit and unscheduled doctor's visits for exacerbations were also recorded. Diary cards were used to record the clinical symptom score, PEF and use of rescue medication (14). QoL was assessed using the Juniper Adult Asthma Quality of Life Questionnaire (AQLQ) (24) at weeks 0, 12 and 28 of the treatment phase. Patients and investigators made evaluations of treatment effectiveness at treatment end. Spirometry was performed at each visit apart from treatment week 1. Adverse events were recorded at each visit and samples were collected for haematological assessment, blood chemistry and urine at screening, at weeks 0, 12 and 28 of treatment and during follow-up. All visits (apart from treatment week 1) included assessment of vital signs and physical examination.

To minimize a potential treatment group imbalance of clinical asthma management practice and concomitant asthma medication use, randomization was stratified by country group and by concomitant asthma medication (in addition to ICS and LABA) use at baseline: (i) patients not receiving theophylline, oral β_2-agonists, antileukotrienes or maintenance oral steroids; (ii) patients receiving one or more from theophylline, oral β_2-agonists and antileukotrienes, but not receiving maintenance oral steroids; (iii) patients receiving maintenance oral steroids. Patients were randomized (1 : 1) to receive omalizumab or matching placebo by subcutaneous injection. Investigators and personnel involved in monitoring the study remained blinded throughout all study periods. Omalizumab dose was based on the patient's bodyweight and total serum IgE level at screening and was administered every 2 or 4 weeks to provide a dose of at least 0.016 mg/kg per IU/ml of IgE, as previously described (25). Patients visited the clinic for study drug administration every 2 or 4 weeks according to dosing schedule. The doses of ICS and LABA (taken separately or as a fixed combination) and other concomitant asthma medications were kept constant during

the last 4 weeks of the run-in period and maintained during the treatment period. Patients were permitted short-acting β_2-agonist rescue medication as required.

Statistical analysis

The primary variable was analysed using Poisson regression via generalized estimating equations, with treatment, dosing schedule, country grouping and asthma medication strata included as parameters in the model. As a result of an unexpected between-group difference in pretreatment exacerbation history over the previous year that continued through the run-in, an adjustment was made to the primary efficacy variable to account for differences in pretreatment exacerbation history. This adjustment was in keeping with recent CPMP recommendations to adjust for baseline measures of the primary variable (26). Whilst CPMP recommends that adjustment is planned prospectively, *post hoc* adjustment was considered justified as exacerbation rate was the primary variable, and this was a clinically relevant imbalance observed over a meaningful time period. The history of exacerbations (number of exacerbations in the year prior to screening and the run-in) was therefore included as a covariate in the model. The distribution of patients with different number of prior exacerbations was analysed by the Cochran Mantel–Haenszel test stratified by asthma medication strata. Similar Poisson regression methods were used for severe exacerbations, hospitalizations and emergency room and doctor's visits, although no baseline adjustment was made.

Patients discontinuing prematurely were included in the analysis using an imputed number of clinically significant asthma exacerbations (imputation applied to neither severe exacerbations nor emergency visits). One exacerbation was added to the total for that patient (unless the patient had an exacerbation within 7 days of discontinuation), with a duration deemed as 0 days. Sensitivity analyses were performed to assess the impact of discontinuations and the imputation rule.

Secondary efficacy variables were analysed by ANCOVA with last observation carried forward (as applicable), with asthma medication strata, country grouping, dosing schedule and baseline as covariates.

The number needed-to-treat (NNT) to save one exacerbation was calculated as 1 divided by the difference between the annualized rate on placebo and the annualized rate on omalizumab, where the rates were determined by Poisson regression.

Following scientific advice from CPMP, efficacy analyses were performed on the patient population randomized after implementation of the protocol amendment described above. Patients randomized postamendment comprise the primary intent-to-treat (PITT) population (analysis of the entire ITT population produced similar results to the PITT population and will be reported separately). The safety population comprised all patients who received treatment.

All statistical tests were two-sided with significance set at the 5% level.

Results

Patients

A total of 482 patients were randomized, 10.8% (52 of 482) of patients discontinued treatment [30 patients (12.2%) and 22 patients (9.3%) in the omalizumab and placebo groups, respectively], 3.1% (15 of 482) because of an adverse event [11 patients (4.5%) and four patients (1.7%) in the omalizumab and placebo groups, respectively]. In total 419 patients (86.9%) were included in the efficacy analyses after protocol amendment (PITT population).

With the exception of prior exacerbation history, the demographics and background characteristics of the PITT population were similar (Table 1). Almost all patients (97%) had severe persistent asthma as defined by GINA 2002. All patients were receiving inhaled ICS and LABA, and two-thirds of patients were receiving additional controller medications (including 22% maintenance oral corticosteroids). The characteristics of the safety population ($n = 482$) did not differ in any important respects from the PITT population.

Patients had a mean FEV_1 of 61% of predicted and had experienced an average of 2.1 exacerbations per year requiring oral corticosteroid treatment and 67% were considered at high risk of asthma-related death. Exacerbation history recorded during the previous year and in run-in period is shown in Table 2. At baseline, patients who subsequently received omalizumab had experienced more frequent exacerbations and more multiple exacerbations than those in the placebo group. This difference was reflected in historical emergency room visit rates and higher number of patients with previous intubation.

Clinically significant asthma exacerbations

The primary efficacy variable analysis included a *post hoc* adjustment for baseline exacerbation history, as described above. After adjustment (PITT population), the clinically significant asthma exacerbation rate showed a statistically significant between-group difference ($P = 0.042$, Fig. 1A): 0.68 with omalizumab and 0.91 with placebo; rate ratio 0.738 (95% CI: 0.552–0.998). Although of similar magnitude, the treatment group difference (rate ratio 0.806, $P = 0.153$) failed to reach statistical significance in the primary analysis not accounting for previous exacerbations. The NNT for 1 year to save one clinically significant exacerbation was 2.2.

Severe exacerbations

Severe exacerbation rate (PEF or FEV_1 $< 60\%$ of personal best, requiring treatment with systemic corticosteroids) was halved in the omalizumab group (0.24 *vs* 0.48, $P = 0.002$ *vs* placebo, Fig. 1B) with 49 severe exacerbations experienced by 16.8% (35 of 209) of patients. For the placebo group, there were 100 severe exacerbations among 26.2% (55 of 210) of patients. The NNT for 1 year to save one severe exacerbation was also 2.2.

Emergency visits for asthma

Rates were lower for omalizumab patients for each type of visit and statistically significantly lower for total emergency visits (0.24 *vs* 0.43, $P = 0.038$) (Table 3). The

Table 1. Demographic and background characteristics of the patients (PITT population)

	Omalizumab ($n = 209$)	Placebo ($n = 210$)
Age (years)		
Mean (SD)	43.4 (13.29)	43.3 (13.49)
Median (range)	44.0 (12–79)	44.0 (13–71)
Sex, *n* (%)		
Male	68 (32.5)	72 (34.3)
Female	141 (67.5)	138 (65.7)
Race, *n* (%)		
Caucasian	163 (78.0)	164 (78.1)
Black	14 (6.7)	14 (6.7)
Oriental	2 (1.0)	3 (1.4)
Other	30 (14.4)	29 (13.8)
Weight (kg)		
Mean (SD)	81.2 (19.75)	79.2 (17.48)
Smoking history, *n* (%)		
Never smoked	157 (75.1)	162 (77.1)
Ex-smoker	52 (24.9)	48 (22.9)
FEV_1 (% of predicted)		
Mean (SD)	61.0 (14.42)	61.6 (13.83)
Median (range)	62.2 (18–101)	61.9 (30–96)
Reversibility (%)		
Mean (SD)	28.9 (23.27)	24.5 (23.27)
Median (range)	21.5 (–20 to 158)	19.5 (–87 to 169)
Morning PEF		
Mean (SD)	299 (102.3)	311 (102.4)
Median (range)	298 (93–604)	298 (122–635)
Rescue medication (puffs/day)		
Mean (SD)	6.6 (7.24)	5.5 (5.86)
Median (range)	4.1 (0–46.1)	3.9 (0–34.7)
Total clinical symptom score		
Mean (SD)	3.2 (2.12)	3.3 (2.04)
Median (range)	3.0 (0–8.7)	3.2 (0–9.0)
Overall AQLQ score		
Mean (SD)	3.9 (1.05)	3.9 (1.12)
Median (range)	3.9 (1.2–6.4)	3.8 (1.4–6.7)
Serum total IgE (IU/ml)		
Mean (SD)	197.6 (145.2)	189.6 (153.1)
Median (range)	150 (21–607)	138.0 (22–632)
Duration of allergic asthma (years)		
Mean (SD)	23.3 (15.23)	22.7 (14.72)
Median (range)	20 (1–72)	20 (1–66)
Number of perennial allergies, *n* (%)		
1	18 (8.6)	9 (4.3)
2	46 (22.0)	37 (17.6)
3	39 (18.7)	43 (20.5)
≥4	106 (50.7)	120 (57.1)
≥1 mould allergies, *n* (%)	79 (37.8)	69 (32.9)
≥1 seasonal allergies, *n* (%)	120 (57.4)	111 (52.9)
≥1 food or drug allergies, *n* (%)	74 (35.4)	69 (32.9)
Inhaled corticosteroid dose* (μg/day)		
Mean (SD)	2359 (1210)	2301 (978)
Median (range)	2000 (900–8000)	2000 (1000–6000)
Patients at baseline receiving, *n* (%)†		
Inhaled corticosteroids plus LABA	209 (100)	210 (100)
Antileukotrienes	74 (35.4)	72 (34.3)
Theophyllines	64 (30.6)	51 (24.3)
Maintenance oral steroids	49 (23.4)	42 (20.0)
Oral β_2-agonists	1 (0.5)	3 (1.4)

AQLQ, Asthma Quality of Life Questionnaire; PITT, primary intent-to-treat; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; IgE, immunoglobulin E; LABA, long-acting β_2-agonists.

*Beclomethasone dipropionate (BDP) equivalent.

†To be maintained unchanged throughout the treatment phase of the study.

hospital admission rate equated to one admission per year of treatment for every four patients receiving placebo compared with every eight patients receiving omalizumab.

Asthma-related QoL

Omalizumab provided significantly greater improvements compared with placebo overall, and across all individual domains of the Juniper AQLQ instrument, with a significantly greater proportion of patients receiving omalizumab achieving a clinically meaningful ≥0.5-point improvement from baseline compared with those taking placebo (60.8% *vs* 47.8%, $P = 0.008$) (Table 4).

Symptoms, morning PEF, rescue medication use and FEV_1

Overall change from baseline in mean morning PEF was significantly greater for omalizumab patients than for placebo ($P = 0.042$). The FEV_1 (% predicted) was significantly improved with omalizumab compared with placebo at study completion ($P = 0.043$), with a difference of 2.8% predicted in favour of omalizumab at the study endpoint (improvements in FEV_1 were 190 ml and 96 ml in the omalizumab and placebo groups, respectively).

Mean change from baseline in total asthma symptom score was significantly greater with omalizumab compared with placebo during the overall treatment period ($P = 0.039$). Omalizumab patients used approximately 0.5 puffs/day less of rescue medication compared with placebo at study end (not statistically significant).

Global evaluations of treatment effectiveness

Omalizumab was evaluated more favourably than placebo to a similar degree by both patients and investigators, with a statistically significant ($P < 0.001$) overall difference for both evaluations (Fig. 2).

Safety and tolerability

The treatment groups had a similar overall incidence of adverse events (72.2% of omalizumab patients, 75.5% placebo); most were mild-or-moderate in severity. The most common adverse events (Table 5) were lower respiratory tract infections and nasopharyngitis. The only imbalance between groups in suspected drug-related events was in events classified as general and administration site conditions (4.9% omalizumab *vs* 1.7% placebo).

Table 2. Asthma history in previous year (primary intent-to-treat, PITT population)

	Omalizumab ($n = 209$)	Placebo ($n = 210$)
Admitted to hospital overnight for asthma, *n* (%)	83 (39.7)	79 (37.6)
Admitted to intensive care unit for asthma, *n* (%)	22 (10.5)	19 (9.0)
Admitted to an emergency room for asthma, *n* (%)	118 (56.5)	116 (55.2)
Ever had mechanical ventilator or throat tube for asthma, *n* (%)	29 (13.9)	13 (6.2)
Any of above (=high risk for asthma mortality), *n* (%)	143 (68.4)	136 (64.8)
Number of emergency room visits for asthma, mean (SD)	1.68 (2.61)	1.48 (2.47)
Number of urgent doctor office visits for asthma, mean (SD)	4.9 (5.66)	4.9 (6.11)
Number of work/school days missed due to asthma, mean (SD)	27.7 (48.59)	34.0 (58.53)
All exacerbations (previous 14 months), *n* (%)		
0	2 (1.0)	0
1	31 (14.8)	32 (15.2)
2	90 (43.1)	100 (47.6)
3	47 (22.5)	55 (26.2)
4	19 (9.1)	13 (6.2)
5	11 (5.3)	5 (2.4)
6	4 (1.9)	3 (1.4)
7	3 (1.4)	2 (1.0)
9	1 (0.5)	0
14	1 (0.5)	0
Mean (SD)	2.64 (1.56)	2.41 (1.09)

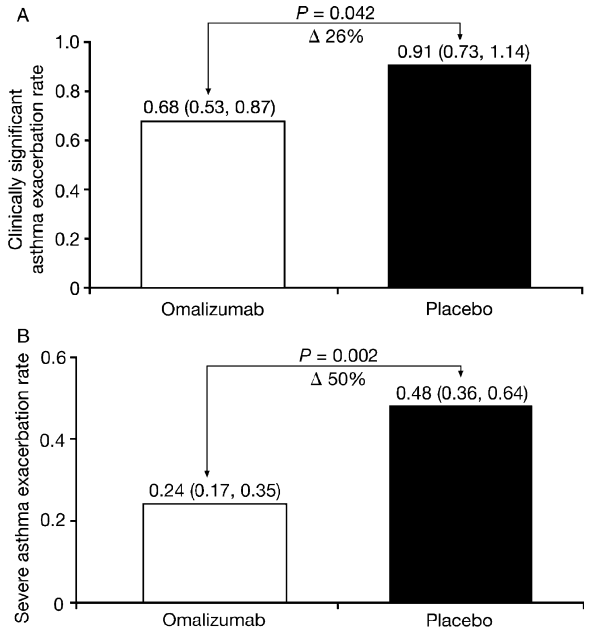

Figure 1. (A) Effect of omalizumab treatment on the rate of clinically significant asthma exacerbations (adjusted for baseline exacerbation history) during the 28-week treatment period (primary intent-to-treat, PITT population); mean (95% confidence interval). (B) Effect of omalizumab treatment on severe exacerbations [peak expiratory flow (PEF) or forced expiratory volume in 1 s (FEV_1) $<60\%$ of personal best] during the 28-week treatment period (PITT population).

Table 3. Frequency of emergency visits for asthma using Poisson regression (primary intent-to-treat, PITT population)

Type of visit	Statistic	Omalizumab ($n = 209$)	Placebo ($n = 210$)
Total emergency visits	Number	50	93
	Rate per treatment period	0.24	0.43
	Ratio of rates (95% CI)	0.561 (0.325–0.968)	
	P-value for ratio	0.038	
Hospital admissions	Number	13	25
	Rate per treatment period	0.06	0.12
	Ratio of rates (95% CI)	0.540 (0.250–1.166)	
	P-value for ratio	0.117	
Emergency room visits	Number	9	14
	Rate per treatment period	0.04	0.06
	Ratio of rates (95% CI)	0.659 (0.208–2.094)	
	P-value for ratio	0.480	
Unscheduled doctor visits	Number	28	54
	Rate per treatment period	0.13	0.24
	Ratio of rates (95% CI)	0.546 (0.271–1.100)	
	P-value for ratio	0.090	

Table 4. Effect of treatment (change from baseline) on Juniper AQLQ scores at endpoint (week 28 or discontinuation) in the PITT population

	Omalizumab ($n = 204$*) LSM	Placebo ($n = 205$) LSM	LSM difference	*P*-value
Activities domain	0.91	0.46	0.45	<0.001
Emotional domain	0.95	0.57	0.38	0.002
Symptoms domain	0.90	0.40	0.50	<0.001
Exposure domain	0.89	0.44	0.45	<0.001
Overall QoL	0.91	0.46	0.45	<0.001
Improvement from baseline, *n* (%)				
≥0.5	124 (60.8)	98 (47.8)		0.008
≥1.0	92 (45.1)	51 (24.9)		<0.001
≥1.5	56 (27.5)	35 (17.1)		0.011

LSM, least squares mean; AQLQ, Asthma Quality of Life Questionnaire; PITT, primary intent-to-treat; QoL, quality of life.
* Apart from exposure domain, where $n = 203$.

The total incidence of injection site reactions (a known effect of omalizumab therapy) was higher in the omalizumab group (5.3%) than the placebo group (1.3%). The only serious adverse events suspected to be drug-related were a case of pruritus, rash and petechiae in one omalizumab patient. There was no evidence of any clinically meaningful trends in laboratory tests or vital signs associated with omalizumab therapy.

Discussion

This study demonstrated the efficacy of omalizumab in patients with inadequately controlled severe persistent asthma, despite high-dose ICS and LABA therapy (GINA step 4 therapy), and is the first study to demonstrate efficacy exclusively in this difficult-to-treat population. Omalizumab significantly reduced the rate of

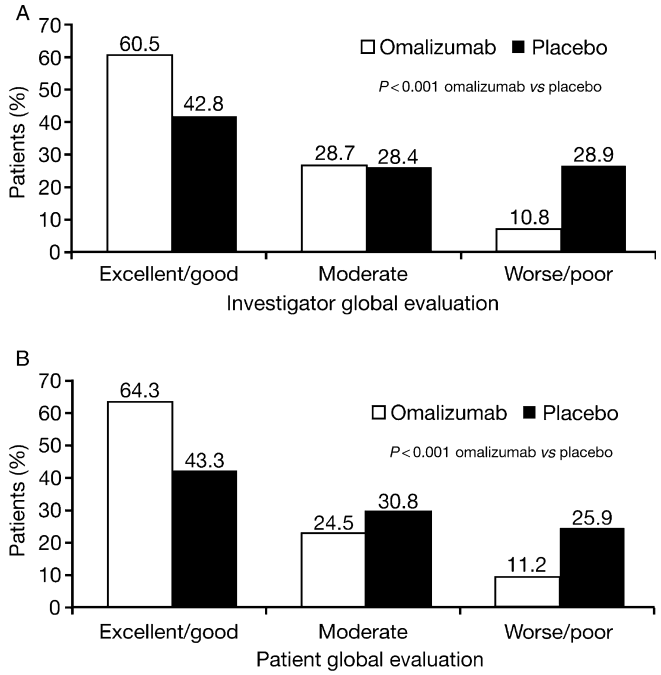

Figure 2. Investigators' (A) and patients' (B) global evaluations of treatment effectiveness recorded at study end (end of treatment or discontinuation) (primary intent-to-treat, PITT population).

Table 5. Number (%) of patients with most frequently occurring adverse events (≥5% in either group)

	Omalizumab, *n* (%)	Placebo, *n* (%)
Total number of patients	245 (100)	237 (100)
Total number with an adverse event	177 (72.2)	179 (75.5)
Adverse events related to study medication	29 (11.8)	22 (9.3)
Serious adverse events	29 (11.8)	37 (15.6)
Lower RTI	27 (11.0)	24 (10.1)
Nasopharyngitis	24 (9.8)	22 (9.3)
Headache	17 (6.9)	22 (9.3)
Sinusitis	14 (5.7)	18 (7.6)
Influenza	11 (4.5)	13 (5.5)
Upper RTI	11 (4.5)	13 (5.5)
Cough	10 (4.1)	13 (5.5)
Upper RTI bacterial	4 (1.6)	13 (5.5)

RTI, respiratory tract infection.

clinically significant asthma exacerbations, adjusted for baseline exacerbation history, as well as severe exacerbation rate and the closely associated emergency visit rate. These findings indicate that omalizumab is an effective add-on therapy for these difficult-to-treat patients who have an important unmet medical need, and are consistent with previous studies with omalizumab [>90% severe persistent asthma (2)] (13–20).

In addition to high-dose ICS and LABA therapy, two-thirds of patients received additional controller medication (including 22% maintenance oral corticosteroids) in the current study. Despite best available therapy asthma was clearly inadequately controlled. In the previous year, more than half the patients required emergency room treatment, more than one-third were admitted to hospital, and 10% were admitted to an intensive care unit. Two-thirds of patients were considered at high risk of asthma-related death. Together with continuing symptoms, poor lung function and QoL measurements, these findings indicate an inadequately controlled population at high risk of major morbidity and mortality.

Adjusted for baseline exacerbation history, omalizumab add-on therapy decreased the clinically significant asthma exacerbation rate by 26% compared with placebo. Importantly, omalizumab halved the severe exacerbation rate (PEF or FEV_1 to <60% of personal best, defined in accordance with GINA 2002 guidelines). As a consequence, the emergency visit rate was reduced by 44% compared with placebo treatment and the hospital admission rate was halved. Omalizumab also significantly improved asthma-related QoL, lung function, asthma symptom scores, and patients' and investigators' global evaluation of treatment effectiveness.

The significance of the findings of this study can be interpreted in light of the association between poor asthma control, exacerbations, emergency medical interventions and a high risk of death as a result of asthma. Severe asthma itself is associated with an increased risk of hospitalization for asthma (27, 28), and patients with severe asthma account for the majority of asthma hospitalizations (29). Inadequate control of severe asthma is further associated with increased risk of hospitalization and asthma death (3, 4). Previous admission to hospital, emergency room or intensive care unit increases the risk of asthma mortality 10-fold (3, 30). While any patient with asthma may suffer a severe exacerbation, severe asthma is associated with an increased risk of fatal or life-threatening exacerbations (31, 32).

Omalizumab provided important benefits without adding unduly to the side-effects, which are commonly burdensome and may affect compliance at this treatment step. Omalizumab was generally well-tolerated by patients; the most common drug-related adverse event being local injection site reaction.

In conclusion, omalizumab significantly decreased asthma exacerbation rates in these difficult-to-treat patients with severe persistent asthma who were inadequately controlled despite high-dose ICS and concomitant LABA therapy as recommended according to GINA step 4. Omalizumab also significantly reduced the severe asthma exacerbation rate and the need for emergency medical interventions. Patients' QoL was improved, as were symptoms and lung function, and both patients and investigators considered omalizumab an effective treatment. Omalizumab was well-tolerated, with no evidence of clinically significant concerns of treatment. These clinically meaningful benefits demonstrate the usefulness of omalizumab as an add-on therapy

for patients with inadequately controlled severe persistent asthma who have a significant unmet medical need despite best available therapy.

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