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Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: An open-label study

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Summary
Background: In a 1-year, randomized, open-label study in patients with moderate-to-severe allergic (immunoglobulin E (IgE)-mediated) asthma, adding omalizumab to best standard care (BSC) significantly improved efficacy outcomes compared with BSC alone (control). We assessed the efficacy of omalizumab in the subgroup of patients with inadequately controlled severe persistent allergic asthma despite high-dose inhaled corticosteroids (ICS) plus a long-acting β_2-agonist (LABA), which reflects the European Union (EU) label population.
Methods: Efficacy outcomes included annual asthma exacerbation rate, annual asthma deterioration-related incident (ADRI) rate, % predicted forced expiratory volume in 1 s (FEV_1), asthma symptoms (Wasserfallen score) and quality of life (Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)), which were compared in the omalizumab and control groups. Outcomes were also determined for omalizumab-treated patients judged to have responded to therapy ($\geq$0.5-point improvement in Mini-AQLQ overall score at 27 weeks).
Results: In total, 164 patients (omalizumab, $n = 115$; control, $n = 49$) were receiving high-dose ICS plus a LABA. Annual asthma exacerbation rate was significantly reduced by 59% in the omalizumab group vs. control (1.26 vs. 3.06; $P < 0.001$). ADRI rate was significantly reduced by 40% in the omalizumab group compared with control (5.61 vs. 9.40; $P < 0.05$). Significant improvements were also seen in % predicted FEV_1 (71% vs. 60%; $P < 0.001$), change from baseline in asthma symptom scores (−6.7 vs. 0.5; $P < 0.05$) and Mini-AQLQ overall score (1.32 vs. 0.17; $P < 0.001$).

In omalizumab-treated patients, 71/102 (70%) were judged to have responded to therapy. In these Mini-AQLQ-assessed responders, exacerbation rate was reduced by 64% vs. control (1.12 vs. 3.06; $P < 0.001$), ADRI rate was reduced by 50% vs. control (4.71 vs. 9.40; $P < 0.01$). Percent predicted FEV_1 (73% vs. 60%; $P < 0.001$), change from baseline in asthma symptom scores

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(−8.1 vs. 0.5; $P < 0.001$) and Mini-AQLQ overall score (1.81 vs. 0.17; $P < 0.001$) were also further significantly improved vs. control.
Conclusions: Adding omalizumab to BSC is efficacious in patients with inadequately controlled severe persistent allergic asthma despite high-dose ICS plus a LABA (EU label population), with further efficacy observed in patients judged to have responded to therapy which may more accurately illustrate the actual benefit of omalizumab therapy in clinical practice. The naturalistic setting of this study confirms the benefits observed in double-blind randomized clinical trials.

Introduction

Asthma is the cause of a significant health, economic and societal burden, which increases with increasing asthma severity. Patients with severe asthma are at high risk of asthma-related hospitalization or death,[1–6] suffer significant impairment to their quality of life (QoL),[7–10] and account for the majority of asthma-related costs incurred.[11–14] The Global Initiative for Asthma (GINA) guidelines 2006 state that the goal of asthma treatment should be to achieve and maintain control of symptoms for long periods with due regard to safety, adverse effects and costs.[15] The guidelines recommend a stepwise approach to asthma control, with treatment being stepped up until control is achieved and can be maintained. At GINA step 4, medium- or high-dose inhaled corticosteroids (ICS) plus a long-acting β_2-agonist (LABA), plus additional controller medications are indicated. However, even with ICS plus a LABA, asthma remains inadequately controlled in many patients.[16,17] For patients whose asthma remains uncontrolled at this step, GINA recommends adding anti-immunoglobulin E (IgE) treatment with omalizumab or oral corticosteroids (OCS).

Add-on omalizumab, an anti-IgE antibody, has proven efficacy in the treatment of moderate-to-severe and severe persistent allergic (IgE-mediated) asthma, reducing the rate of exacerbations and emergency visits for asthma, and improving QoL.[18–26] In the European Union (EU), omalizumab is indicated for the treatment of inadequately controlled severe persistent allergic (IgE-mediated) asthma despite treatment with high-dose ICS plus a LABA. The efficacy of omalizumab in this patient population was demonstrated in a randomized, double-blind, placebo-controlled study (INNOVATE).[18] In the INNOVATE study, adding omalizumab to high-dose ICS plus a LABA significantly reduced asthma exacerbation and total emergency visit rates and significantly improved lung function, asthma symptoms and QoL. Confirmatory evidence was obtained in a pooled analysis of seven randomized controlled trials in patients with predominately severe persistent asthma.[26]

In the double-blind, placebo-controlled INNOVATE study, efficacy in omalizumab-treated patients was notably improved across a range of outcome measures in patients who were judged to have responded to therapy using the physician's overall assessment, a composite measure that encompasses multiple aspects of response based on clinical assessments, including patient interview, review of medical notes, spirometry and symptom diaries, rescue medication use, and peak expiratory flow.[27] According to the EU label, the response to omalizumab should be assessed by a physician after 16 weeks of therapy, and treatment continued only if the patient has achieved complete or a marked improvement in asthma control.

A 1-year randomized, open-label study[19] in patients with inadequately controlled moderate-to-severe allergic (IgE-mediated) asthma with many similarities to the INNOVATE study[18] has also been conducted, however in a naturalistic setting. Consistent with data reported in the INNOVATE study, omalizumab significantly reduced asthma exacerbation rates, significantly improved lung function and asthma symptoms, and was shown to be safe and well tolerated.[19] The aim of this post-hoc analysis was to extend the findings of this open-label study[19] with an assessment of the effectiveness of omalizumab in a subgroup of patients with inadequately controlled severe persistent allergic (IgE-mediated) asthma despite receiving high-dose ICS plus a LABA. This subgroup corresponds to the highly targeted EU label patient population in which health-economic analyses have shown omalizumab to be cost-effective.[28,29] In addition, efficacy was assessed in patients judged to have responded to omalizumab therapy, reflecting the EU label. Targeting patients in whom benefits are apparent will most closely reflect the benefits that might be expected when omalizumab is used in accordance with the EU label, particularly when non-responders are excluded.

Methods

Study design

This post-hoc subgroup analysis was conducted on efficacy results of a large, 1-year, randomized, open-label, parallel-group study conducted at 49 centers in five European countries (France, $n = 10$; Germany, $n = 9$; Spain, $n = 7$; Switzerland, $n = 3$; United Kingdom, $n = 20$).[19] Further details of the original study have been reported previously.[19] Briefly, patients were randomized (2:1) to receive best standard care (BSC) with or without subcutaneous omalizumab for 12 months. BSC was defined by the National Heart, Lung and Blood Institute (NHLBI) guidelines.[30] Patients were using medium- or high-dose ICS with or without a LABA. Use of salbutamol pressurized metered dose inhaler as rescue medication was permitted throughout the study. Omalizumab was administered every 2 or 4 weeks based on baseline total IgE and bodyweight using a dosing table. Patients had inadequately controlled asthma, defined as $\geq$1 emergency room visit or hospitalization and $\geq$1 additional course of OCS because of asthma in the previous year.

The subgroup analysis reported here included only patients with inadequately controlled severe persistent allergic (IgE-mediated) asthma who were receiving high-dose ICS (>1000 μg/day beclometasone equivalent) plus a LABA.

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 center.

Efficacy assessments

Efficacy outcomes were evaluated for control patients and omalizumab-treated patients. Additionally, in order to reflect the EU label, outcomes were evaluated in those omalizumab-treated patients who were considered to have responded to therapy. A previous analysis has identified the physician's overall assessment as the most reliable method of evaluating response to omalizumab therapy,[27] but among other measures of asthma control assessed in the same study, ≥0.5-point improvement in the 32-item Asthma Quality of Life Questionnaire (AQLQ) showed similar properties[27] to the physician's overall assessment in its utility in evaluating response. As the physician's overall assessment was not an outcome measured in the original study,[19] ≥0.5-point improvement in the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)[31] overall score was used as a measure to identify responders. The 27-week assessment was the first assessment performed after 16 weeks of therapy, which is the time specified for evaluating response to omalizumab treatment in the EU label. Thus, in this analysis, responders were defined as achieving ≥0.5-point improvement in the Mini-AQLQ overall score at 27 weeks (further details of QoL assessments are provided below).

Efficacy variables assessed in this subgroup analysis were the annual rate of clinically significant asthma exacerbations (asthma worsening requiring treatment with systemic corticosteroids) and the annual rate of asthma deterioration-related incidents (ADRIs) (defined as ≥1 of the following events due to asthma: course of systemic corticosteroids or antibiotics for ≥2 days, ≥2 missed school/work days (or significantly reduced performance for non-working adult patients, as judged by the patient), unscheduled physician visit, or hospitalization/emergency room visit).[32]

Other efficacy variables assessed were lung function analyzed as percentage of predicted forced expiratory volume in 1 s (FEV_1) (% predicted FEV_1) and change in absolute FEV_1 at 1 year, the Wasserfallen asthma symptom score[33] and QoL (Mini-AQLQ).[31] The Mini-AQLQ comprises 15 questions on symptoms (five items), activity limitations (four items), emotional function (three items) and environmental stimuli (three items). Mini-AQLQ overall and individual domain scores were recorded. In addition, the percentage of patients with clinically meaningful (≥0.5), moderate (≥1.0-point) and large (≥1.5) improvements in Mini-AQLQ overall score at 52 weeks was calculated.

Statistical analysis

For the rate of exacerbations and ADRIs, an imputation method was applied to account for patients who were withdrawn prematurely from the study. Between-group differences were analyzed using Poisson regression. The effect of add-on therapy with omalizumab on lung function parameters (% predicted FEV_1) and change from baseline in symptom scores were analyzed using an analysis of variance (ANOVA) model. Between-group effects on Mini-AQLQ scores were assessed using an analysis of covariance (ANCOVA) model and the percentage of patients with ≥0.5 and ≥1.5-point improvements in overall Mini-AQLQ scores was compared using the Fisher exact permutation test.

Results

Baseline demographics and clinical characteristics

Of the 312 patients (omalizumab, $n = 206$; control, $n = 106$) included in the original study,[19] 164 patients (omalizumab, $n = 115$; control, $n = 49$) were receiving high-dose ICS plus a LABA and were included in this analysis. Patients' asthma was inadequately controlled. All omalizumab-treated patients and all but one of the control patients had taken courses of OCS in the previous year. In addition, 105 (91.3%) omalizumab-treated patients and 46 (93.9%) control patients had attended an emergency room and 54 (47%) omalizumab-treated patients and 23 (46.9%) control patients had been hospitalized in the previous year. Other baseline demographic and clinical characteristics of the omalizumab and control (BSC alone) groups were also similar and are shown in Table 1. All patients were at step 4 of GINA 2002 treatment guidelines. Despite receiving high-dose ICS plus a LABA, and additional controller medication in many cases, healthcare utilization, OCS use and days of work/school missed in the past year were high in both treatment groups (Table 1).

Exacerbation rates and ADRIs

The annual rate of asthma exacerbations was significantly lower in the omalizumab group compared with control (1.26 vs. 3.06; $P < 0.001$, Fig. 1). The rate ratio [95% CI] for omalizumab:control was 0.410 [0.288, 0.583], which equates to a 59% reduction with omalizumab.

The annual ADRI rate was also significantly lower in the omalizumab group than control (5.61 vs. 9.40). The rate ratio [95% CI] for omalizumab:control was 0.597 [0.380, 0.938] ($P < 0.05$), which equates to a 40% reduction in ADRIs with omalizumab. The individual events that comprised ADRIs during the study are summarized in Table 2. Overall, the omalizumab group had fewer occurrences and shorter durations of all individual ADRI events compared with control although, as the study was not powered to show differences in individual events, these were not statistically significant.

Other outcome variables

Compared with control, patients treated with omalizumab showed a significant improvement in % predicted FEV_1 throughout the 1-year treatment period (Fig. 2). Absolute mean [SD] FEV_1 values at baseline were similar in the omalizumab group (2.09 L [0.792]) and control (2.08 L [0.713]).

Table 1 Baseline demographic and clinical characteristics

	Omalizumab ($n = 115$)	Control ($n = 49$)
Age (years)		
Mean (SD)	38.7 (15.52)	39.3 (13.39)
Median (range)	37.0 (12.0–73.0)	40.0 (15.0–71.0)
Sex, *n* (%)		
Male	29 (25.2)	15 (30.6)
Female	86 (74.8)	34 (69.4)
Equivalent BDP dose, μg/day		
Mean (SD)	2803.0 (1436.16)	2969.4 (1433.99)
Median (range)	2000.0 (1250.0–10000.0)	2000.0 (1500.0–8000.0)
Asthma medication, *n* (%)[a]		
Anti-cholinergics	14 (12.2)	10 (20.4)
Anti-histamines	4 (3.5)	3 (6.1)
Anti-leukotrienes	40 (34.8)	20 (40.8)
Inhaled corticosteroids	115 (100)	49 (100)
Long-acting β_2-agonists	112 (97.4)	49 (100)
Short-acting β_2-agonists	113 (98.7)	46 (93.9)
Xanthines and xanthine derivatives	33 (28.7)	11 (22.4)
FEV_1 (% of predicted), mean (SD)	65.6 (20.45)	64.1 (19.17)
Wasserfallen asthma symptom score, mean (SD)	19.1 (10.2)	17.5 (9.44)
GINA (2002) asthma severity step 4, *n* (%)	115 (100)	49 (100)
GINA asthma treatment step 4, *n* (%)	115 (100)	49 (100)
Profile of poor asthma control in last year		
Patients with ≥1 emergency room visit, *n* (%)	105 (91.3)	46 (93.9)
Patients with ≥1 hospitalization, *n* (%)	54 (47.0)	23 (46.9)
Patients taking courses of OCS, *n* (%)	115 (100)	48 (98)
Number of OCS courses, mean (SD)	4.1 (3.49)	4.0 (4.06)
Number of days of school/work missed, mean (SD)	47.0 (76.62)	57.0 (94.79)

BDP, beclometasone dipropionate; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; OCS, oral corticosteroids; SD, standard deviation.

[a] In the 14 days prior to the baseline visit.

At 1 year, they were 2.25 L [0.829] in the omalizumab group and 1.93 L [0.644] in the control group ($P < 0.05$) representing a between-group difference of 320 mL.

At 1 year, asthma symptom score was significantly improved (lower) in the omalizumab group compared with control (12.0 vs. 17.1, $P < 0.05$). Analysis of change from baseline in asthma symptom score showed significant improvements over control throughout the treatment period (Fig. 3).

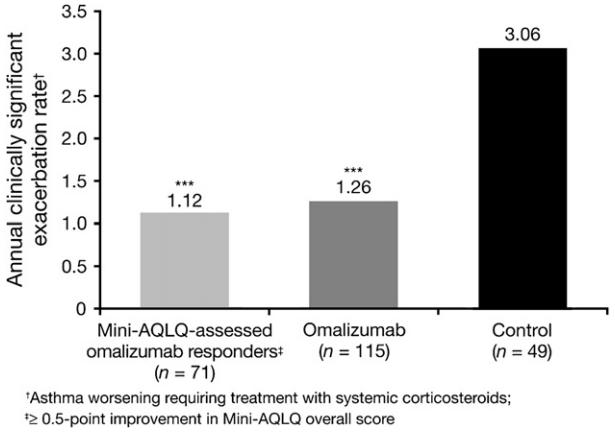

Figure 1 Effect of omalizumab on the rate of clinically significant exacerbations. ***$P < 0.001$ vs. control.

QoL significantly improved in patients treated with omalizumab compared with control, with significant improvements seen in all individual domains and overall score at 52 weeks (Table 3). A significantly greater proportion of the omalizumab group achieved a clinically meaningful (≥0.5-point) improvement from baseline in Mini-AQLQ overall score (76.5 vs. 41.7%, $P < 0.001$) at 52 weeks compared with control. Similarly, a significantly greater proportion of omalizumab-treated patients achieved a moderate (≥1.0-point) improvement (55.1 vs. 25.0%, $P = 0.003$) or large (≥1.5-point) improvement in overall score (45.9 vs. 13.9%, $P < 0.001$) at 52 weeks compared with control.

Responder identification (using Mini-AQLQ) and outcomes

Data were available for 102 omalizumab-treated patients in the Mini-AQLQ-assessed responder analysis. In total, 71/102 omalizumab-treated patients (70%) were classified as responders (≥0.5-point improvement in Mini-AQLQ overall score at 27 weeks). It is also worth noting that 56 (54%) achieved a moderate (≥1.0-point) improvement and 39 (38%) had a large (≥1.5-point) improvement. The baseline

Table 2 Use of systemic corticosteroids, antibiotics, medical resource utilization and absenteeism due to asthma

	Omalizumab ($n = 115$)	Omalizumab responders ($n = 71$)	Control ($n = 49$)
Use of systemic corticosteroids, *n* (%)	69 (64.5)	45 (64.3)	32 (80.0)
Median number of days of systemic corticosteroids use (range)[a]	34.0 (1–365)	36.0 (1–364)	43.0 (1–370)
Use of antibiotics, *n* (%)	42 (39.3)	28 (40.0)	22 (55.0)
Median number of days of antibiotics use (range)[a]	12.5 (2–108)	14.0 (3–93)	15.0 (3–56)
Unscheduled physician visits, *n* (%)	43 (40.2)	28 (40.0)	21 (52.5)
Median number of days with unscheduled physician visits (range)[a]	2.0 (1–12)	2.0 (1–12)	3.0 (1–19)
ER visits, *n* (%)	18 (16.8)	9 (12.9)	10 (25.0)
Median number of days with ER visits (range)[a]	1.0 (1–46)	1.0 (1–4)	1.5 (1–11)
Hospitalizations, *n* (%)	12 (11.2)	6 (8.6)	5 (12.5)
Median number of days of hospitalization (range)[a]	8.0 (1–53)	13.0 (1–45)	11.0 (2–21)
Absenteeism, *n* (%)[b]	56 (52.3)	40 (57.1)	27 (67.5)
Median number of days of absenteeism (range)[a]	15.5 (1–365)	15.5 (1–257)	46.0 (3–186)

[a] For patients experiencing this outcome.
[b] Or significantly reduced performance in non-working patients.

demographic and clinical characteristics of omalizumab-treated responders and non-responders were similar (data not shown).

In Mini-AQLQ-assessed responders, the annual exacerbation rate (1.12) was significantly reduced by 64% compared with control (rate ratio [95% CI]: 0.365 [0.244, 0.546]; $P < 0.001$, Fig. 1). The annual ADRI rate (4.71) was significantly reduced by 50% compared with control (rate ratio [95% CI]: 0.505 [0.310, 0.821]; $P < 0.01$). The individual events that comprised ADRIs during the study in the Mini-AQLQ-assessed responder group are summarized in Table 2. Responders had fewer occurrences and shorter durations of all individual ADRI events compared with control (although not statistically significant). However, compared with the omalizumab group outcomes in responders were broadly similar, with slight reductions seen in ER visits and hospitalizations, and slight increases in duration of antibiotic use, duration of hospitalization and absenteeism (none of which were statistically significant).

Significant improvement in % predicted FEV_1 was seen in the Mini-AQLQ-assessed responders, compared with control (Fig. 2). Absolute FEV_1 was also further improved in responders compared with control. At baseline, absolute mean [SD] FEV_1 was 2.10 L [0.737] in responders and increased to 2.29 L [0.80] at 1 year, representing a difference of 360 mL compared with control. Mean [SD] baseline symptom score was similar in responders and control (19.1 [9.80] and 17.5 [9.44] respectively). Significant improvements were seen in mean [SD] symptom score at 1 year compared with control (11.0 [10.27] vs. 17.1 [10.65], $P < 0.001$), and in change from baseline in symptom score throughout the treatment period (Fig. 3).

At 52 weeks, 91.2% of the Mini-AQLQ-assessed responders identified at 26 weeks continued to show ≥0.5-point improvement from baseline in Mini-AQLQ overall score, 73.5% achieved a moderate (≥1.0-point) improvement and 60.3% achieved a large (≥1.5-point) improvement. The mean scores for individual domains and overall

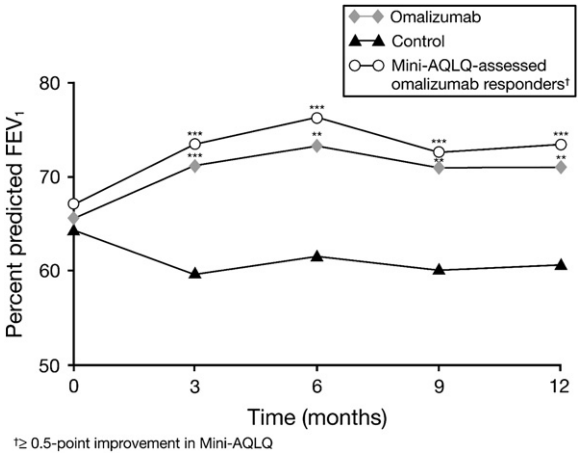

Figure 2 Effect of omalizumab on % predicted FEV_1. $^{**}P < 0.01$ vs. control; $^{***}P < 0.001$ vs. control.

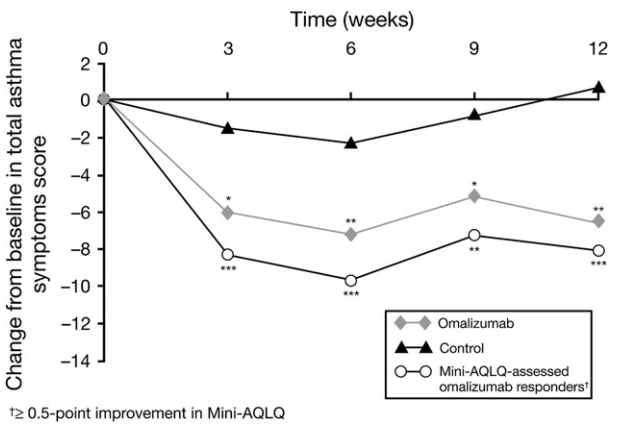

Figure 3 Effect of omalizumab on asthma symptom score. $^{*}P < 0.05$ vs. control; $^{**}P < 0.01$ vs. control; $^{***}P < 0.001$ vs. control.

Table 3 Change from baseline in Mini-AQLQ scores in the omalizumab and control groups

Domain, mean	3 months		6 months		9 months		12 months	
	OMA ($n = 104$)	Control ($n = 40$)	OMA ($n = 102$)	Control ($n = 39$)	OMA ($n = 102$)	Control ($n = 38$)	OMA ($n = 99$)	Control ($n = 37$)
Symptoms	1.05*	0.48	1.20**	0.47	1.10**	0.39	1.31***	0.19
Activities	1.16*	0.66	1.11**	0.45	1.09*	0.49	1.38***	0.29
Environment	0.80	0.42	0.99*	0.44	1.03***	0.11	1.19***	−0.03
Emotions	1.02	0.36	1.24*	0.50	1.32**	0.29	1.37***	0.09
Overall	1.03*	0.50	1.14**	0.48	1.14***	0.36	1.32***	0.17

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. control. OMA, omalizumab.

Mini-AQLQ score for omalizumab-treated responders and control groups are presented in Table 4.

Discussion

In this post-hoc subgroup analysis of data from a randomized open-label study, adding omalizumab to high-dose ICS plus a LABA significantly reduced clinically significant exacerbation rates and ADRI rates. Lung function, asthma symptom scores and QoL were also significantly improved in the overall omalizumab-treated population of patients with inadequately controlled severe persistent allergic asthma, compared with control. Despite the relatively small patient numbers, statistical significance was achieved for all endpoints evaluated.

The magnitude of the benefits in the omalizumab-treated population was similar to those seen in the original study in patients with moderate-to-severe asthma.[19] Most importantly, these data also confirm the efficacy of omalizumab in a naturalistic setting in a patient population that reflects the EU label for omalizumab (inadequately controlled severe persistent allergic asthma despite high-dose ICS plus a LABA) previously demonstrated in a randomized, placebo-controlled study.[18] Inadequate control of asthma in the present study was clearly demonstrated by the impaired lung function, high symptoms scores and emergency medical interventions prior to the study. More than 90% of patients required an emergency room visit, almost 50% required hospitalization, and almost all patients required short courses of OCS (approximately four per patient) in the previous year. In addition, a remarkably high average of around 50 school/work days had been lost due to asthma in the previous year.

The clinical benefits of omalizumab in responders are of particular importance as only patients who are judged by a physician to have responded to therapy at 16 weeks should continue to receive omalizumab (EU label), thereby improving overall effectiveness, preventing unwarranted drug exposure and improving cost-effectiveness.

An analysis by Bousquet et al. (2007)[27] found that a physician's overall assessment was the most useful and reliable method of evaluating response to omalizumab therapy. In their analysis, the physician's overall assessment identified 61% of omalizumab-treated patients as responders who experienced marked reductions in the rate of clinically significant and severe exacerbations, along with a number of additional measures of asthma control. As the physician's overall assessment was not an outcome measure in the current analysis, we selected ≥0.5-point improvement in Mini-AQLQ overall score to identify responders. This selection was based on the findings of Bousquet et al. (2007),[27] which showed that broad measures such as improvements in QoL are the most appropriate for evaluating response to omalizumab therapy. In their analysis, QoL also correlated very strongly with physician and patient overall evaluation of treatment effectiveness. Using a threshold of ≥0.5-point improvement in the 32-item AQLQ showed similar (if somewhat less discriminatory) properties to the physician's overall assessment.

As mentioned previously, response to therapy was assessed at 27 weeks as this was the first assessment performed after 16 weeks of therapy (the time specified for evaluating response to omalizumab treatment in the EU label). In patients who were judged to have responded to omalizumab (≥0.5-point improvement in Mini-AQLQ overall score at 27 weeks) efficacy was further enhanced for all

Table 4 Change from baseline in Mini-AQLQ scores in the Mini-AQLQ-assessed omalizumab responders and control groups

Domain, mean	3 months		6 months		9 months		12 months	
	OMA-R ($n = 70$)	Control ($n = 40$)	OMA-R ($n = 71$)	Control ($n = 39$)	OMA-R ($n = 70$)	Control ($n = 38$)	OMA-R ($n = 68$)	Control ($n = 36$)
Symptoms	1.5	0.48	1.79	0.47	1.59	0.39	1.73	0.19
Activities	1.53	0.66	1.65	0.45	1.54	0.49	1.84	0.29
Environment	1.21	0.42	1.64	0.44	1.65	0.11	1.65	−0.03
Emotions	1.69	0.36	1.95	0.50	1.97	0.29	1.99	0.09
Overall	1.49	0.50	1.76	0.48	1.67	0.36	1.81	0.17

OMA-R, Mini-AQLQ-assessed omalizumab responder (≥0.5-point improvement in Mini-AQLQ).

endpoints evaluated including asthma exacerbation rates, ADRI rates, lung function, and asthma symptoms.

Additionally, the improvement of 1.64 in change from baseline in overall Mini-AQLQ score after 1 year compared with control describes a high level of persistency of response. Further reassurance that improvements in QoL following treatment with omalizumab reflect a true pharmacological effect rather than background disease variability is provided by the much higher Mini-AQLQ responder persistency (between 26 and 52 weeks) observed in the omalizumab compared to control group. This confirms the persistency of benefit after 52 weeks of omalizumab therapy.

The data analyzed from the original study[19] were prespecified primary or secondary outcomes, and their use in this post-hoc analysis of clinical outcomes in the severe asthma subpopulation reflects the omalizumab EU label criteria, which were introduced after the original study. The post-hoc assessment of treatment efficacy in Mini-AQLQ-assessed responders in our analysis also examines the response assessment element of the EU label. This analysis required the use of a surrogate assessment of response instead of the validated physician's overall assessment as described by Bousquet et al.[27] While a good correlation between the AQLQ and the physician's overall assessment has been described,[27] differences in response assessment criteria should be borne in mind when evaluating the results in the responder group. As omalizumab responders represent a selected subgroup of the omalizumab group rather than an independent group, statistical comparison with the overall omalizumab group was not possible. The comparison of omalizumab responders with the control group should also be interpreted with caution as this will tend to overestimate the effect of omalizumab, although it serves to illustrate the expected real-world benefit of continuing therapy in only those who respond to treatment as specified in the EU label, and stopping therapy in those who do not show a response.

Although not as scientifically rigorous as randomized, double-blind placebo-controlled (RDBPC) trials, it remains important to understand how a therapy performs in a setting more reflective of the real world, thereby gaining insight into treatment benefits that might be expected for practicing physicians. Real-world effectiveness data are meaningful, but the limitations of such trial designs (e.g. the potential for bias to be introduced by patients and investigators in the assessment of outcomes and response assessment) should be considered when interpreting open-label data, which should be considered in the context of other RDBPC data.

Omalizumab RDBPC trials may have shown a particularly large placebo effect[34] due to the protocol requirements and method of administration (physician observed therapy every 2 or 4 weeks). This artificially increased contact with healthcare providers beyond the usual standard of care of patients may lead to an incremental placebo response resulting from earlier detection and treatment of loss of asthma control, increased compliance with asthma medications and iatrogenic influences. The visit schedule in this study, as distinct from the RDBPC INNOVATE study,[18] may reflect real-world outcomes in a severe population. Additionally, in the original study,[19] all patients received BSC as prescribed by the investigator. Wherever possible, concomitant medication was to be minimized, but increasing the dose of concomitant medications was permitted when required. Additional OCS and/or antibiotics were also permitted for severe exacerbations. This approach to concomitant medication reflects naturalistic practice. The 1-year duration of this study, compared with the 28-week duration of INNOVATE, also facilitates the examination of serious but relatively infrequent outcomes such as clinically significant asthma exacerbations.

In conclusion, this subgroup analysis of data from a 1-year, randomized, open-label study shows that adding omalizumab to high-dose ICS plus a LABA significantly improves asthma control. This is shown by reductions in exacerbation and ADRI rates, improvements in lung function, asthma symptoms and QoL in patients with inadequately controlled severe persistent allergic asthma compared with BSC alone. Patients classified as responders show greater improvement in outcomes than the omalizumab-treated group when compared with control, which may illustrate the actual benefit of omalizumab in clinical practice after response assessment at 16 weeks and continuing with therapy only in those patients who have responded to omalizumab as judged by the physician.

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Conflict of interest statement

RN has worked extensively with the pharmaceutical industry performing clinical trials with the following companies: GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Wyeth, Pharmaxis, Asthmatx. In the last 5 years RN has attended the following meetings internationally: ERS, ATS, AAAAI; and has received financial support to attend at one time or another from the following companies: GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Schering Plough, Ivax. RN is receiving a single-year unrestricted grant to support a specialist nurse clinical post part-time from Novartis. RN has lectured widely, in part sponsored by all the companies named above. RN has no stock interests or consultancy agreement with any of the above.

KFC has been remunerated for participation on advisory board meetings organized by AstraZeneca, Altana, Mundi-Pharma, Chiesi and Novartis and for lecturing at meetings sponsored by AstraZeneca, Altana, GSK and Novartis. He has been reimbursed by Boehringer Ingelheim, Merck and Novartis for traveling to international conferences. He has received a research grant from GSK and participated in clinical trials with Novartis and Asthmatx. He does not hold stocks and shares in pharmaceutical companies.

ZP, MB and GA are all employees of Novartis Pharmaceuticals.

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