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ORIGINAL ARTICLE

Improvement in quality of life with omalizumab in patients with severe allergic asthma

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ABSTRACT

Background: Patients with severe persistent asthma experience daily symptoms and frequent serious exacerbations that contribute to a significant impairment of health-related quality of life (QoL).

Methods: A pooled analysis was completed of six controlled clinical trials that evaluated the effect of add-on omalizumab on asthma-related QoL in patients with severe persistent allergic (IgE-mediated) asthma. Asthma-related QoL was assessed at baseline and treatment endpoint using the well-validated Juniper Asthma Quality of Life Questionnaire (AQLQ). Change from baseline in AQLQ total score was compared between treatments using analysis of covariance methods. The percentage of patients who achieved a clinically meaningful (≥ 0.5-point) improvement in AQLQ total score was compared using the Mantel–Haenszel Chi-square test.

Results: The pooled patient population comprised 2548 patients (omalizumab, $n = 1342$; control, $n = 1206$), of whom 96% had severe persistent asthma according to the GINA 2002 classification. Omalizumab produced significantly greater improvements in AQLQ total score vs the control group (mean increases of 1.01 and 0.61 points, respectively; $p < 0.001$). In addition, significantly more omalizumab-treated patients achieved a clinically meaningful improvement in AQLQ total score than patients in the control group (66.3% vs 52.4%; $p < 0.001$).

Conclusions: Add-on therapy with omalizumab improves QoL to a significant and clinically meaningful level in patients with severe persistent allergic asthma.

Introduction

It is well recognised that, despite the use of inhaled corticosteroids (ICS) and other standard asthma medications, patients with severe persistent asthma are often inadequately controlled and remain at increased risk of frequent, potentially fatal, exacerbations[1,2]. In turn, the physical, emotional and social aspect of the daily lives of such patients is significantly impaired[3,4], the burden on quality of life (QoL) being much greater than that of patients with milder, well-controlled disease[5]. The Global Initiative for Asthma (GINA) 2005 report notes that asthma can severely restrict the physical, emotional and social aspects of the lives

of patients and may have an impact on their careers, especially if symptoms are not adequately controlled[6]. To date, however, relatively few studies have examined whether tangible QoL benefits could be achieved in patients with severe persistent asthma through improved disease control. This paucity of information most likely reflects the limited treatment options available for such patients.

Omalizumab (Xolair*) is a recombinant humanised monoclonal anti-immunoglobulin E (IgE) antibody that has demonstrated significant clinical efficacy in patients with moderate-to-severe and severe allergic (IgE-mediated) asthma, reducing exacerbation rates and improving disease control in a number of placebo-controlled studies[7–13] and an open-label controlled study[14].

In a recent pooled analysis of seven controlled studies with omalizumab, in which 93% of patients met the GINA 2002 criteria for severe persistent asthma (based on clinical features and asthma therapy), omalizumab significantly reduced asthma exacerbations and emergency visit rate[15]. Six of these studies also collected QoL data and, as part of this pooled analysis, we sought to determine whether the clinical benefits of omalizumab are paralleled by improvements in asthma-related QoL for patients with severe persistent allergic asthma.

Methods

Study design and patients

This was a pooled analysis of data from six controlled trials that investigated the effects of add-on omalizumab compared with add-on placebo or current asthma therapy alone on the health-related QoL of patients aged ≥ 12 years with severe persistent allergic (IgE-mediated) asthma. Details of the studies included in the analysis are shown in Table 1.

Five of the studies were randomised, double-blind studies in which patients received subcutaneous injections of omalizumab or placebo. The remaining study was a randomised, open-label investigation of add-on therapy with omalizumab vs current asthma therapy alone.

Allergic asthma was confirmed in all patients using either a skin-prick test or a radioallergosorbent (RAST) test for perennial allergens. Omalizumab was administered by subcutaneous injection every 2 or 4 weeks as add-on therapy to concomitant asthma treatment. A dosing table, based on patients' baseline IgE levels and bodyweight, was used to determine omalizumab dose[16].

Assessment of asthma-related QoL

Asthma-related QoL was assessed at baseline and treatment endpoint using the Juniper Asthma Quality of Life Questionnaire (AQLQ)[17], a disease-specific instrument that has good reliability and responsiveness with excellent cross-sectional and longitudinal validity[18]. This questionnaire comprises 32 questions (or 'items') grouped into four domains: activity limitations (11 items), emotions (five items), symptoms (12 items), and exposure to environmental stimuli (four items). In brief, each question was answered by the patient on a 7-point scale, with a score of 7 representing no impairment and a score of 1 representing the greatest impairment. Lower AQLQ scores therefore represent greater QoL impairment. Findings are shown

Table 1. *Details of the controlled studies included in the pooled analysis*

Study	Patient population (*n*)	Patients with severe persistent asthma*, *n* (%)	Treatment arms	Duration (weeks)
1. INNOVATE: Humbert *et al.*[10]	Inadequately controlled severe asthma (419)	419 (100)	Omalizumab + CAT vs placebo + CAT	28
2. ETOPA: Ayres *et al.*[14]	Inadequately controlled moderate-to-severe asthma (312)	294 (94.2)	Omalizumab + CAT vs CAT alone	52
3. SOLAR: Vignola *et al.*[12]	Co-morbid moderate-to-severe asthma and rhinitis (405)	364 (89.9)	Omalizumab + CAT vs placebo+ CAT	28
4. Busse *et al.*[8]	Severe asthma (525)	523 (99.6)	Omalizumab + CAT vs placebo + CAT	28
5. Solèr *et al.*[12]	Moderate-to-severe asthma (546)	537 (98.4)	Omalizumab + CAT vs placebo + CAT	28
6. Holgate *et al.*[9]	Severe asthma dependent on high-dose ICS (341)	315 (92.4)	Omalizumab + CAT vs placebo + CAT	32

n: number of patients; CAT: current asthma therapy; ICS: inhaled corticosteroids
*GINA 2002 classification

* Xolair is a registered trademark of Novartis Pharma AG, Basel, Switzerland

as the mean score for each domain, along with a mean total score. The percentage of patients achieving a clinically meaningful improvement in QoL, defined as an increase in AQLQ total score of ≥ 0.5 from baseline was also calculated, along with the percentage of patients with a 'moderate' or 'large' improvement in QoL (≥ 1.0 or ≥ 1.5 point increase, respectively) from baseline[19].

Statistical analysis

The between-group difference for change from baseline in AQLQ total score was analysed using an analysis of covariance (ANCOVA) method, while the percentage of patients who achieved clinically meaningful, moderate or large improvements in QoL (AQLQ total score) was compared between treatments using the Mantel–Haenszel Chi-square test.

Results

There were no clinically relevant differences in baseline demographics, clinical characteristics and QoL scores between the omalizumab (n = 1342) and control groups (n = 1206) (Table 2).

On the basis of clinical features and asthma therapy, 96% of patients met the criteria for the GINA (2002) classification of severe persistent asthma. Mean AQLQ scores were consistent with marked impairment of QoL.

Asthma-related QoL

The effect of omalizumab on QoL (least squares mean change from baseline in AQLQ total score) in the individual studies and the pooled analysis is shown in Table 3.

Table 2. *Demographic and clinical characteristics at baseline: pooled population*

Characteristic	Omalizumab (n = 1342)	Control (n = 1206)
Females, n (%)	808 (60.2)	714 (59.2)
Mean age, years (range)	40.1 (12–79)	40.1 (12–74)
Mean serum total IgE, IU/mL (SD)	211.6 (166.9)	210.8 (165.2)
Mean ICS dose, μg/day (SD)*	1534 (1191)	1463 (1070)
LABA use, n (%)	543 (40.5)	433 (35.9)
Mean FEV_1, % predicted (SD)	69.5 (17.3)	70.2 (17.2)
Severe persistent asthma, n (%)†	1287 (95.9)	1165 (96.6)
Mean duration of asthma, years (range)	21.0 (1–72)	21.3 (1–66)
Mean AQLQ domain scores (SD)		
Activities	4.2 (1.2)	4.2 (1.1)
Emotions	4.3 (1.4)	4.3 (1.5)
Symptoms	4.2 (1.1)	4.2 (1.1)
Environmental exposure	4.0 (1.4)	4.0 (1.4)
Total score	4.2 (1.1)	4.2 (1.1)

n: number of patients; IgE: immunoglobulin E; SD: standard deviation; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; AQLQ: Asthma Quality of Life Questionnaire

*Beclometasone dipropionate equivalent

†According to the GINA (2002) classification based both on clinical features and asthma therapy

Table 3. *Omalizumab significantly improved AQLQ scores*

Study	Change from baseline in total AQLQ score, least squares mean (n)		p
	Omalizumab	Control	
1. INNOVATE: Humbert *et al.*[10]	0.94 (204)	0.49 (205)	< 0.001
2. ETOPA: Ayres *et al.*[14]	1.19 (188)	0.26 (88)	< 0.001
3. SOLAR: Vignola *et al.*[13]	1.39 (208)	1.12 (192)	0.010
4. Busse *et al.*[8]	0.93 (256)	0.61 (246)	< 0.001
5. Solèr *et al.*[12]	1.02 (244)	0.64 (235)	< 0.001
6. Holgate *et al.*[9]	0.46 (158)	0.18 (152)	0.011
Pooled	1.01 (1258)	0.61 (1118)	< 0.001

n: number of patients. Patient numbers signify those who fully completed QoL assessments. These values are slightly lower than the total number of patients in each study

Compared with control, significantly greater improvements in QoL were observed with omalizumab across all studies. Pooled analysis showed that omalizumab recipients had a mean increase in AQLQ total score of 1.01 points, compared with 0.61 in the control group ($p < 0.001$) (Figure 1), with significantly greater improvements in mean AQLQ score with omalizumab for all individual domains (activities, emotions, symptoms and environment).

Further analysis showed that treatment with omalizumab resulted in a greater proportion of patients achieving a clinically meaningful (≥ 0.5-point) improvement in QoL compared with control in each of the individual studies (Table 4).

Thus, for the pooled population, significantly more omalizumab-treated patients achieved a clinically meaningful improvement in QoL than in the control group (66.3% [834/1258] and 52.4% (586/1118) respectively; $p < 0.0001$) (Figure 2). Patients receiving omalizumab were also more likely to have a clinically significant improvement in each of the individual domains of the AQLQ than control patients (Figure 2).

Patients receiving omalizumab were more likely to have moderate or large improvements (≥ 1.0 or 1.5 points) in AQLQ scores than control patients in each of the individual studies and in the pooled analysis (Table 4). Omalizumab-treated patients were also more likely to have clinically meaningful, moderate or large improvements in each of the individual domains of the AQLQ (activities, emotions, symptoms and environment) than control patients (Figures 2 and 3).

Discussion

Severe persistent asthma is characterised by daily symptoms, frequent exacerbations and nocturnal asthma symptoms, and significant airflow obstruction[6]. However, measurement of clinical variables such as symptoms, exacerbations and lung function does not provide a complete picture of the impact of severe asthma on the health status of patients. Juniper *et al*. showed that health status in patients with asthma is associated with four distinct components (asthma-specific QoL, airway calibre, night-time clinical problems and daytime clinical problems) and tends to be more severely impaired in patients with severe asthma than in those with milder disease[5]. Patients with severe asthma have few therapeutic options available to reduce the impact of asthma and improve well being. In addition, the high doses of ICS required to treat severe asthma have the potential to cause adverse effects similar to those of oral corticosteroids, including increased bone turnover[20].

The findings of the present pooled analysis in patients with severe persistent allergic asthma demonstrate that add-on anti-IgE therapy with omalizumab provides significant and clinically meaningful improvements in health-related QoL. These improvements parallel the previously reported reduction in asthma exacerbations and emergency medical consultations[15] and represent an important achievement for this difficult-to-treat population who remain inadequately controlled despite best available therapy. Add-on therapy with omalizumab led to a highly significant increase in mean AQLQ total score of 1.01 points vs 0.61 points in the control group ($p < 0.001$) and 66.3% of patients achieved a clinically meaningful (≥ 0.5-point) improvement in QoL (vs 52.4% of patients in the control group; $p < 0.001$). As AQLQ comprehensively assesses asthma-related QoL through evaluation of different components or domains, the results of this pooled analysis demonstrate a consistent and significant improvement in QoL with omalizumab across all domains. In three of the studies[8,9,12], the improvements in QoL with omalizumab occurred despite reductions in ICS doses.

A number of potential limitations of our analyses should be noted. In particular, the inclusion of an open-label study in the pooled analysis raises the possibility of bias. While the difference in change from baseline in AQLQ score between omalizumab and control was larger in the open-label study, the differences in the

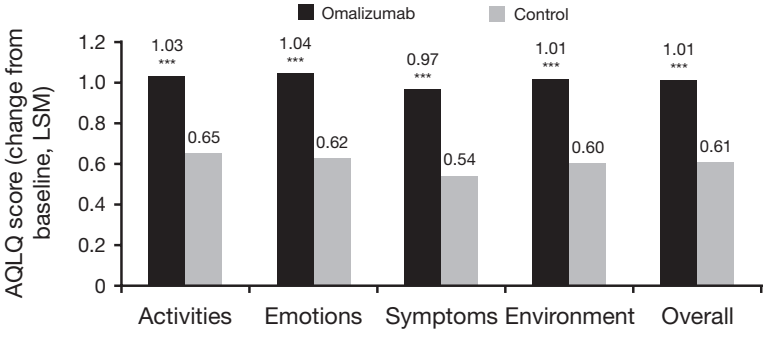

Figure 1. *Least squares mean (LSM) change from baseline in AQLQ total score during treatment with either omalizumab plus current asthma therapy or current asthma therapy alone (control).* ***p < 0.001 *vs control*

Table 4. *Percentage of patients achieving clinically meaningful, moderate and large improvements in AQLQ total score*

Study	≥ 0.5-point improvement			≥ 1.0-point improvement			≥ 1.5-point improvement		
	Omalizumab, *n* (%)	Control, *n* (%)	*p*-value	Omalizumab, *n* (%)	Control, *n* (%)	*p*-value	Omalizumab, *n* (%)	Control, *n* (%)	*p*-value
1. INNOVATE: Humbert *et al.*[10]	124 (60.8)	98 (47.8)	0.008	92 (45.1)	51 (24.9)	< 0.001	56 (27.5)	35 (17.1)	0.012
2. ETOPA: Ayres *et al.*[14]	136 (72.3)	38 (43.2)	< 0.001	96 (51.1)	23 (26.1)	< 0.001	77 (41.0)	15 (17.0)	< 0.001
3. SOLAR: Vignola *et al.*[13]	164 (78.8)	134 (69.8)	0.039	140 (67.3)	96 (50.0)	< 0.001	100 (48.1)	64 (33.3)	0.003
4. Busse *et al.*[8]	169 (66.0)	126 (51.2)	< 0.001	125 (48.8)	78 (31.7)	< 0.001	84 (32.8)	41 (16.7)	< 0.001
5. Solèr *et al.*[12]	161 (66.0)	135 (57.4)	0.054	112 (45.9)	79 (33.6)	0.006	69 (28.3)	39 (16.6)	0.002
6. Holgate *et al.*[9]	80 (50.6)	55 (36.2)	0.012	52 (32.9)	22 (14.5)	< 0.001	26 (16.5)	10 (6.6)	0.007
Pooled	834 (66.3)	586 (52.4)	< 0.001	617 (49.0)	349 (31.2)	< 0.001	412 (32.8)	204 (18.2)	< 0.001

n: number of patients

double-blind studies were also statistically significant and clinically meaningful. The open-label study was a randomised controlled study designed to closely resemble clinical practice and, therefore, provides a valuable illustration of the results that could be expected during the routine use of omalizumab. In addition, the patient population and methodology of the open-label trial were similar to those in the placebo-controlled trials.

There were large improvements in QoL from baseline in the control groups in all of the studies included in our analyses. This is not unexpected as subjective measures (such as QoL) may be particularly influenced by a placebo effect[21]. A number of hypotheses could be advanced to explain the improvements in the control groups, such as improved background therapy, enhanced adherence to treatment and the nature of treatment administration (clinic-based subcutaneous injection). However, testing these hypotheses is beyond the scope of the current analysis. Importantly, in all of the individual studies (as well as the pooled analysis) the improvements in the omalizumab-treated patients were significantly greater than in the control groups despite this.

It has been suggested[22] that the threshold for detecting clinically important differences in the domains of the AQLQ is higher than the 0.5-point threshold described by Juniper *et al.*[19] and used in the present analyses. However, our analyses of AQLQ outcomes showed that omalizumab was also associated with significantly greater percentages of patients achieving moderate (≥ 1 point) or large (≥ 1.5 point) improvements in AQLQ scores. In the pooled analysis, 49.0% of patients receiving omalizumab had moderate improvements and 32.8% had large improvements, compared with 31.2% and 18.2%, respectively, in the control group: overall, a significantly greater proportion of patients experienced clinically significant, moderate and large improvements in AQLQ scores ($p < 0.001$ vs control), despite a large placebo effect.

The patients enrolled in the studies included in our analyses were all classified as having moderate-to-severe or severe persistent asthma despite asthma therapy. Although previous studies have shown that patients are frequently misclassified as having severe persistent asthma due to alternative or additional diagnoses or non-adherence[23], the population enrolled in the studies of omalizumab are likely to reflect the characteristics of patients classified as having severe persistent asthma in clinical practice. Indeed, 96% of patients in this analysis met GINA criteria for severe persistent asthma based both on clinical features and current therapy.

Patients with severe persistent asthma account for more than 50% of the total asthma-related healthcare cost[24–26]. Treatments that reduce exacerbations (as

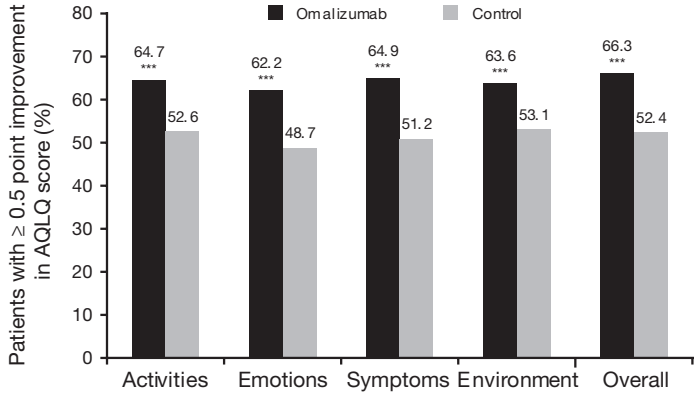

Figure 2. *Clinically meaningful improvements in QoL (≥ 0.5-point improvement in AQLQ score) during treatment with either omalizumab or control. ***p < 0.001 vs control*

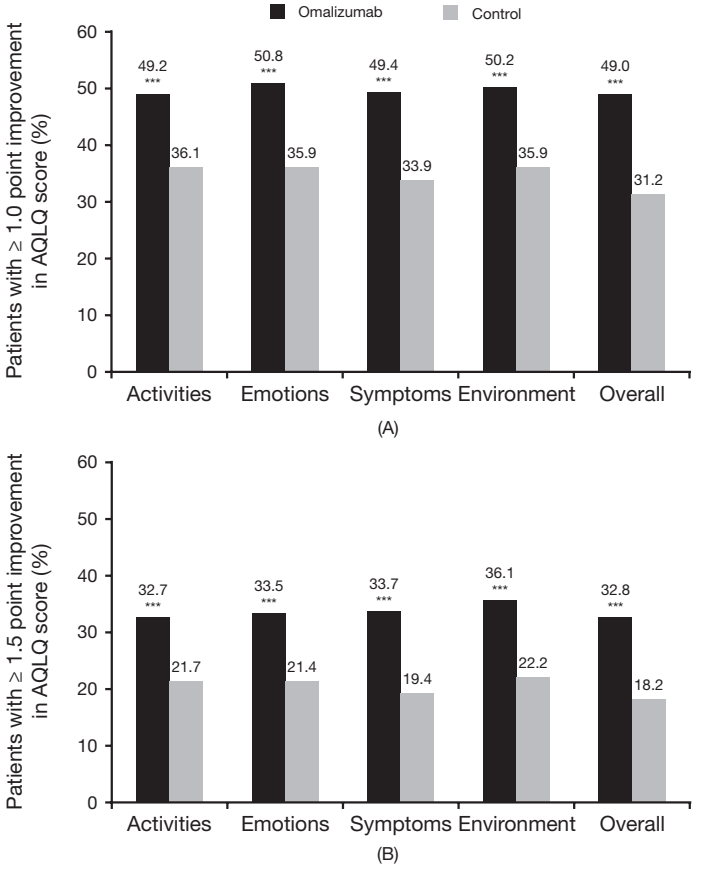

Figure 3. *Percentage of patients with moderate (a) or large (b) improvements in QoL (≥ 1.0 or ≥ 1.5-point improvement in AQLQ score) during treatment with either omalizumab or control. ***p < 0.001 vs control*

shown previously with omalizumab[15]) and improve QoL in this difficult-to-treat patient group, therefore, have the potential to reduce the burden of asthma in terms of both social costs and healthcare resource utilisation. For example, patients with severe persistent asthma have a four-fold greater risk of hospital admission and a two-fold greater risk of requiring an urgent care visit than patients with mild asthma[27]. Improving control of severe asthma might help to reduce this burden.

It is important to demonstrate that new treatment modalities improve patient well being using direct assessment of QoL, as measurements of symptoms or lung function are not necessarily accurate predictors of QoL outcomes[19]. Furthermore, patients and physicians tend to arrive at different conclusions regarding asthma severity[28], although introduction into clinical practice of an assessment that specifically measures QoL may facilitate the treatment decision-making process with less reliance on subjective opinion[29]. There is increasing evidence that broad measures of asthma control may be more useful than traditional single-item measures such as FEV_1[30–32]. An analysis of data from the five randomised,

placebo-controlled omalizumab trials[8–10,12,13] showed that patients categorised as responders (complete control or marked improvement in control) according to a physician's overall assessment had marked reductions in clinically significant exacerbations and other outcome measures including QoL compared with non-responders[33]. The use of broad measures of asthma control such as a physician's overall assessment or quality of life provides a more robust means of evaluating responses to omalizumab than use of single outcome measures and in accord with current treatment guidelines, which recognise the importance of defining asthma control in broad terms rather than solely according to single-item measures such as lung function[6]. Measurement of both QoL and clinical outcomes are necessary to describe the benefits of treatment on overall health status in patients with severe persistent asthma. The results of the present analyses of asthma-related QoL are, therefore, important in characterising the benefits of omalizumab and complement the evidence of reduced exacerbation rates, reduced emergency visit rates, improved symptoms and lung function reported previously in patients with severe persistent allergic asthma[7–14].

Conclusions

In addition to reducing asthma exacerbations and emergency medical consultations[15], add-on therapy with omalizumab improves health-related QoL to a significant and clinically meaningful level in patients with severe persistent allergic asthma. Concomitant anti-IgE therapy with omalizumab may, therefore, help to address the current unmet need of patients with severe asthma that is inadequately controlled despite best available therapy.

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