

Short communication

Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma

Background: Omalizumab is efficacious in the treatment of moderate-to-severe and severe persistent allergic (immunoglobulin E-mediated) asthma, reducing exacerbations, emergency visits and improving quality of life (QoL). However, as exacerbations are relatively infrequent, assessment of efficacy on day-to-day symptoms is warranted.

Aims: To investigate the effect of add-on omalizumab on day-to-day symptoms, and how they correlate with QoL in severe persistent asthma.

Methods: The correlation between asthma symptom scores and QoL [Asthma Quality of Life Questionnaire (AQLQ)] was assessed. Symptom-free days (total symptom score = 0) and symptom-controlled days (definition 1: total symptom score ≤ 1 ; and definition 2: morning peak expiratory flow $\geq 90\%$ of baseline, daytime asthma score ≤ 1 and night-time asthma score = 0) were compared between the omalizumab-treated group, omalizumab responders and placebo.

Results: Four hundred and nineteen patients (omalizumab, $n = 209$; placebo, $n = 210$) were included in the efficacy analyses, and 61% (118/195) of patients with response data were classified as responders. Total symptom score strongly correlated with AQLQ overall and symptom scores and individual domains. AQLQ overall score correlated well with symptom scores. Responders had significantly more symptom-free days than the omalizumab-treated and placebo groups (45.8%, 37.2% and 22.6% respectively), and more symptom-controlled days (definition 1: 56.1%, 47.9% and 35.3%, respectively, and definition 2: 50.8%, 43.9% and 28.0%, respectively).

Conclusions: In patients with inadequately controlled severe persistent asthma, day-to-day symptoms correlate well with QoL. Add-on omalizumab significantly improves day-to-day symptoms compared with placebo. Further improvement in responders confirms the physician's assessment as a response measure.

M. Humbert¹, W. Berger², G. Rapatz³, F. Turk⁴

¹Université Paris-Sud 11, Service de Pneumologie, Hôpital Antoine Bécclère, Clamart, France; ²Allergy and Asthma Associates, Mission Viejo, CA, USA;

³Novartis Pharma AG, Basel, Switzerland; ⁴Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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Prof. M. Humbert
Service de Pneumologie et Réanimation
Respiratoire
Hôpital Antoine Bécclère
Assistance Publique Hôpitaux de Paris
Université Paris-Sud 11
157, rue de la Porte de Trivaux
92140 Clamart
France

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Severe asthma is associated with a high risk of asthma-related hospitalization and mortality (1, 2) and significantly impairs patients' quality of life (QoL) (3). The economic burden of asthma is the greatest in patients with inadequately controlled severe persistent asthma (4). Although treatments are available for severe persistent asthma, many patients remain inadequately controlled. For example, the INSPIRE study reported that 52% of patients were classified by the Asthma Control Questionnaire as having uncontrolled asthma and 74% of patients used short-acting β_2 -agonists daily despite regular maintenance therapy with inhaled corticosteroids (ICS) or ICS plus a long-acting β_2 -agonist (LABA) (5).

Adding omalizumab, an anti-immunoglobulin (Ig) E antibody, to standard asthma therapies (ICS with or without an LABA and additional controller medications as needed) has proven efficacy in the treatment of severe persistent allergic (IgE-mediated) asthma, reducing

exacerbations, emergency visits for asthma and improving QoL (6).

Analyses of clinical trial data (6) and pooled data (7–11) have found the physician's overall assessment – a composite measure including patient interview, review of medical notes, spirometry and symptom diaries, rescue medication use and peak expiratory flow (PEF) – to be the most meaningful measure of response to omalizumab therapy (12). Graded in a five-level evaluation of asthma control (complete control; marked improvement in control; discernible but limited control; no appreciable change; worsening in control), those with marked improvement or complete control are defined as responders (12). In this responder group, clinical outcomes were further improved compared with the overall omalizumab-treated population (12). In order to target those patients who will benefit most from omalizumab, thereby minimizing unnecessary drug exposure and healthcare costs,

the omalizumab European Union (EU) label states that treatment response should be assessed at 16 weeks by the physician and treatment discontinued in those judged not to respond.

Asthma exacerbations and exacerbation-related health-care resource use are strong indicators of lack of asthma control, but can occur relatively infrequently in many patients. Day-to-day asthma symptoms are also of major relevance to patients, and therefore may be useful in demonstrating the efficacy of a given treatment.

The aims of this study were to investigate the correlation between day-to-day asthma symptoms and asthma-related QoL, and to evaluate the effect of add-on omalizumab on day-to-day control of asthma symptoms in patients with severe persistent asthma. Results in omalizumab responders were also examined.

Material and methods

Study design

This *post hoc* analysis was conducted on efficacy results of a large, randomized, double-blind, placebo-controlled trial (INNOVATE study) (5). All patients included in the INNOVATE study had symptoms that remained inadequately controlled despite Global Initiative for Asthma (GINA) 2002 step 4 therapy (high-dose ICS plus a LABA with additional controller medication as necessary) (13). All patients received omalizumab or placebo in addition to their current asthma therapy for 28 weeks. Omalizumab was administered subcutaneously for every 2 or 4 weeks according to the patients' body weight and baseline IgE levels. Further details of the INNOVATE study had been reported previously (5).

Data analysis

Correlation between day-to-day asthma symptoms and QoL at baseline. The Asthma Quality of Life Questionnaire (AQLQ) is a broad measure of patient-related outcomes, and a correlation between this and asthma symptom scores may indicate the importance of asthma symptoms in the disease burden of asthma experienced by patients. Questions in the AQLQ relate to the previous 2 weeks. Therefore average asthma symptom scores (night, day, morning and total) over the 2 weeks prior to randomization (weeks -2 to 0) were determined so that they related to the same time period. The correlation between average asthma symptom scores and AQLQ scores (overall and individual domains) taken at baseline was then assessed using Pearson's correlation coefficients. The assessment was performed on baseline data pooled from all treatment groups in order to show any correlation irrespective of treatment.

Symptom-free days and symptom-controlled days. Between-group data for symptom-free and symptom-controlled days were compared in the omalizumab-treated group, omalizumab-responder subgroup (as judged by the physician's overall assessment) and the placebo group.

Symptom-free days were defined as a total symptom score of 0 (no symptoms) during the day that measurements were taken. The total symptom score is the sum of the daytime (range 0–4), night-time (range 0–4) and morning (range 0–1) scores, with a score of 0 signifying no symptoms (9).

Symptom-controlled days were defined as follows: definition 1: minor symptoms (total symptom score ≤ 1); and definition 2: a day on which the morning PEF rate was $\geq 90\%$ of baseline, daytime asthma score was ≤ 1 and night-time asthma score was 0.

Symptom-free and symptom-controlled days were determined at 2-weekly intervals from baseline (taken as being the first 2 intervals recorded, i.e. weeks -4 to -2 and weeks -2 to 0) to endpoint (weeks 26–28). The percentage of symptom-free days (total symptom score of 0) and symptom-controlled days were compared at the last observed interval (weeks 26–28) between treatment groups using chi-square test.

Results

Baseline demographics and clinical characteristics

The baseline demographics and clinical characteristics of the omalizumab-treated group, omalizumab-responder subgroup and placebo group were similar and are shown in Table 1. Of the 419 patients (omalizumab $n = 209$; placebo $n = 210$) included in efficacy analyses of the INNOVATE study (18), response data (i.e. responder or non-responder) were available for 396 patients (omalizumab $n = 195$; placebo $n = 201$), and of the omalizumab-treated patients, 61% (118/195) were classified as responders using the physician's overall assessment.

Correlation between day-to-day symptoms and QoL

Average total symptom score was strongly correlated with AQLQ overall score ($r = -0.503$) and AQLQ symptoms score ($r = -0.601$) and also correlated with each individual AQLQ domain score (Table 2). Of the components of average total asthma symptom score, daytime symptom score ($r = -0.517$) was the most strongly correlated with AQLQ overall score followed by night-time symptom score ($r = -0.508$) and morning symptom score ($r = -0.368$).

Symptom-free days and symptom-controlled days

The percentage of symptom-free days for the last observed interval (weeks 26–28) was significantly ($P < 0.001$) greater in the omalizumab-responder subgroup (45.8%) than in the omalizumab-treated group (37.2%) and placebo group (22.6%, Fig. 1A). Significant ($P < 0.001$) improvements were observed for total, morning, daytime and night-time symptoms (Fig. 1B–D). Graphical comparisons of the number of symptom-free days (symptom score = 0) from baseline to weeks 26–28 are shown alongside symptom-free morning, daytime and night-time periods (Fig. 1A–D).

Graphical comparisons of the number of symptom-controlled days (definitions 1 and 2) are shown in Fig. 2A,B respectively. The percentage of symptom-controlled days (definitions 1 and 2) was significantly ($P < 0.001$) greater in omalizumab-responder subgroup (definition 1: 56.1%, definition 2: 50.8%) than in the

Table 1. Baseline demographics and clinical characteristics

	Placebo (<i>n</i> = 210)	Omalizumab-treated population (<i>n</i> = 209)	Omalizumab responder population (<i>n</i> = 118)
Age (years), mean (SD)	43.3 (13.49)	43.4 (13.29)	44.1 (13.58)
Sex, <i>n</i> (%)			
Male	72 (34.3)	68 (32.5)	40 (33.9)
Female	138 (65.7)	141 (67.5)	78 (66.1)
Race, <i>n</i> (%)			
Caucasian	164 (78.1)	163 (78.0)	93 (78.8)
Black	14 (6.7)	14 (6.7)	6 (5.1)
Oriental	3 (1.4)	2 (1.0)	1 (0.8)
Other	29 (13.8)	30 (14.4)	18 (15.3)
Weight (kg), mean (SD)	79.2 (17.48)	81.2 (19.75)	78.7 (18.14)
Smoking history, <i>n</i> (%)			
Never smoked	162 (77.1)	157 (75.1)	85 (72.0)
Ex-smoker	48 (22.9)	52 (24.9)	33 (28.0)
FEV ₁ (% of predicted), mean (SD)	61.6 (13.83)	61.0 (14.42)	63.5 (13.73)
Reversibility (%), mean (SD)	24.5 (23.27)	28.9 (23.27)	27.2 (20.85)
AQLQ overall score, mean (SD)	3.9 (1.12)	3.9 (1.05)	3.8 (0.98)
Serum total IgE (IU/ml), mean (SD)	189.6 (153.14)	197.6 (145.18)	222 (153.11)
Duration of allergic asthma (years), mean (SD)	22.7 (14.72)	23.3 (15.23)	23.2 (14.82)
ICS dose* (µg/day), mean (SD)	2300.9 (978.3)	2359.1 (1210.2)	2232.9 (1049.5)
Patients at baseline receiving, <i>n</i> (%) [†]			
ICS plus LABA	210 (100)	209 (100)	118 (100)
Anti-leukotrienes	72 (34.3)	74 (35.4)	43 (36.4)
Theophyllines	51 (24.3)	64 (30.6)	38 (32.2)
Maintenance OCS	42 (20.0)	49 (23.4)	23 (19.5)
Oral β ₂ -agonists	3 (1.4)	1 (0.5)	0 (0)

FEV₁, forced expiratory volume in 1 s; AQLQ, Asthma Quality of Life Questionnaire; IgE, immunoglobulin E; ICS, inhaled corticosteroids; LABA, long-acting β₂-agonist; OCS, oral corticosteroids; SD, standard deviation.

*Beclometasone dipropionate (BDP) equivalent.

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

Table 2. Correlation between Asthma Quality of Life Questionnaire (AQLQ) overall score and individual domain scores with day-to-day asthma symptoms

Variable	<i>r</i>				
	AQLQ overall score	AQLQ symptoms score	AQLQ activities score	AQLQ emotions score	AQLQ environment score
Average morning symptom score	−0.368	−0.469	−0.227	−0.273	−0.207
Average day symptom score	−0.517	−0.598	−0.411	−0.366	−0.285
Average night symptom score	−0.508	−0.602	−0.377	−0.374	−0.281
Average total symptom score	−0.503	−0.601	−0.379	−0.345	−0.291

omalizumab-treated group (definition 1: 47.9%, definition 2: 43.9%) and placebo group (definition 1: 35.3%, definition 2: 28.0%, Fig. 2A,B).

Discussion

Our results show a correlation between day-to-day asthma symptom scores (morning, day, night and total) and the AQLQ across all domains in patients with inadequately controlled severe persistent allergic asthma despite GINA 2002 step 4 therapy. Day, night and total asthma symptom scores were strongly correlated with AQLQ overall and symptoms domains, particularly daytime symptoms. This confirms that day-to-day asthma

symptom scores provide a measure of asthma control that is highly relevant to patients, and are an important component of assessments of asthma control in addition to asthma exacerbations (14). Indeed, the characteristics listed in the GINA 2006 guidelines indicating controlled asthma include the absence of daytime and nocturnal symptoms (15).

Baseline clinical characteristics, AQLQ score and additional controller medication usage were similar in all groups. All patients had inadequately controlled severe persistent asthma, high medication use and healthcare utilization, and had experienced continuing uncontrolled asthma symptoms despite GINA 2002 step 4 therapy (13). The similar baseline clinical characteristics between the omalizumab-treated group and the

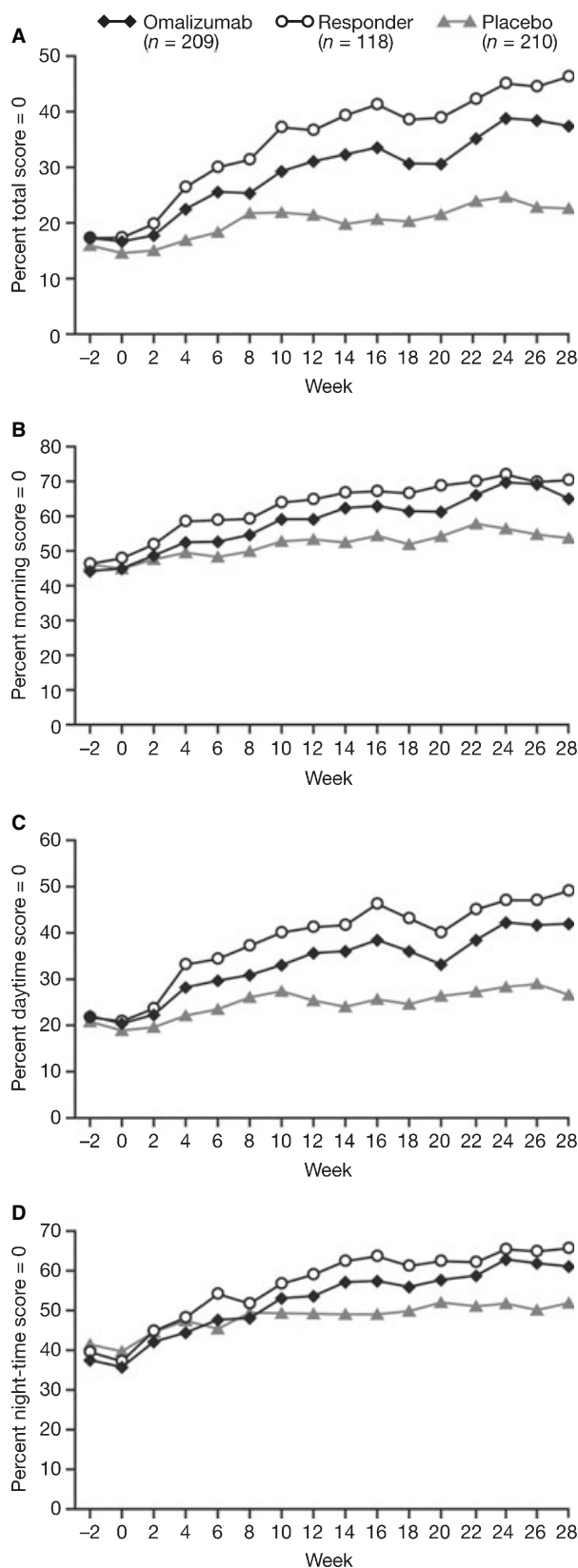
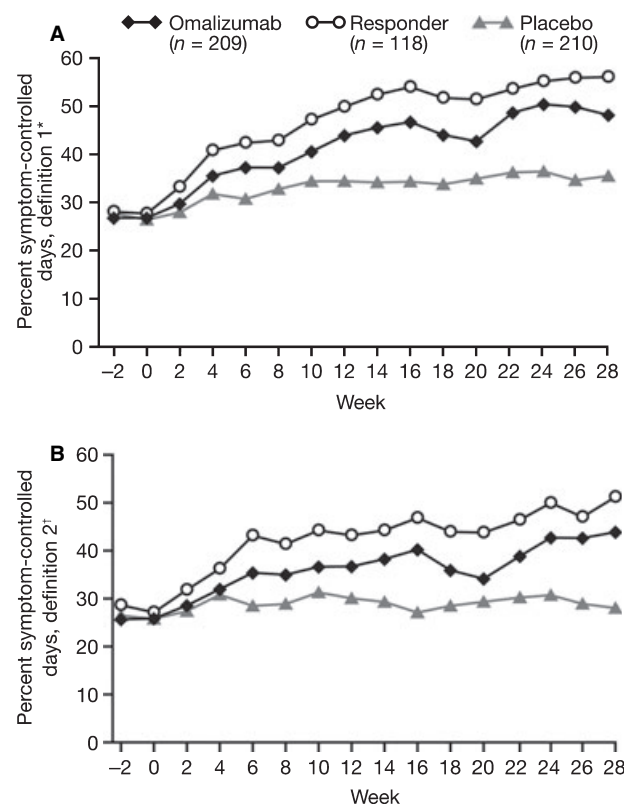


Figure 1. Total symptom-free days (A), morning period (B), daytime period (C) and night-time period (D) from baseline to the last observed interval (weeks 26–28).



*Definition 1: total score ≤ 1

†Definition 2: morning peak expiratory flow $\geq 90\%$ of baseline, daytime score ≥ 1 and night-time score = 0

Figure 2. Symptom-controlled days for definition 1 (A) and definition 2 (B) from baseline to the last observed interval (weeks 26–28).

omalizumab-responder subgroup provide further evidence of the difficulty in predicting which patients might achieve the greatest benefit with omalizumab, and the value of assessing response after 16 weeks of treatment.

Our results show that add-on omalizumab significantly increases the number of symptom-free days, symptom-controlled days and improves day-to-day symptoms compared with add-on placebo in patients with inadequately controlled severe persistent allergic asthma despite GINA 2002 step 4 therapy. The assessment of the effectiveness of omalizumab in patients who respond to omalizumab therapy was an important feature of this study. In the omalizumab-responder population, further improvements were seen over the omalizumab-treated population in all outcomes. Assessment of this subgroup may reflect treatment outcomes seen in clinical practice after omalizumab therapy is continued only in those judged by a physician to have responded to omalizumab after 16 weeks of treatment, as stated in the EU label.

In conclusion, day-to-day asthma symptoms correlate well with improved QoL and provide an important

additional simple measure of asthma control. Add-on omalizumab improves day-to-day symptoms in patients with inadequately controlled severe persistent allergic asthma. This study also illustrates the value of assessing treatment response to omalizumab after 16 weeks.

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