Respiratory Medicine (2013) **107**, 1141–1151

Available online at www.sciencedirect.com

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The eXpeRience registry: The 'real-world' effectiveness of omalizumab in allergic asthma

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Received 30 January 2013; accepted 25 April 2013
Available online 28 May 2013

KEYWORDS
Allergic asthma;
Anti-immunoglobulin E;
Asthma control;
Exacerbations;
Symptoms

Summary
Omalizumab has demonstrated therapeutic benefits in controlled clinical trials. Evaluation of outcomes in real-world clinical practice is needed to provide a complete understanding of the benefits of omalizumab treatment.

eXpeRience was a 2-year, international, single-arm, open-label, observational registry that evaluated real-world effectiveness, safety and use of omalizumab therapy in 943 patients with uncontrolled persistent allergic asthma. Effectiveness variables (physician's Global Evaluation of Treatment Effectiveness [GETE], and change from baseline in exacerbation rate, symptoms, rescue medication use, and oral corticosteroid [OCS] use) were evaluated at pre-specified time-points. Safety data were also recorded.

By physician's GETE, 69.9% of patients were responders to omalizumab after 16 (±1) weeks. The proportion of patients with no clinically significant exacerbations increased from 6.8% during the 12-month pre-treatment period to 54.1% and 67.3% at Months 12 and 24, respectively. Symptoms and rescue medication use at Month 24 were reduced by >50% from baseline. Maintenance OCS use was lower at Month 24 (14.2%) compared with Month 12 (16.1%) and baseline (28.6%). Overall, omalizumab had an acceptable safety profile.

The results from eXpeRience indicate that omalizumab was associated with improvements in outcomes in patients with uncontrolled persistent allergic asthma; these improvements were consistent with the results of clinical trials.

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http://dx.doi.org/10.1016/j.rmed.2013.04.017

Introduction

Omalizumab is a humanised anti-immunoglobulin E (IgE) monoclonal antibody licensed in the European Union for patients aged ≥6 yrs with severe allergic asthma that is inadequately controlled with inhaled corticosteroids (ICSs) and long-acting β_2-agonists (LABAs); and in the United States for patients aged ≥12 yrs with moderate-to-severe allergic asthma inadequately controlled with ICSs. Patients for whom omalizumab is indicated typically have a high frequency of asthma symptoms and exacerbations, impaired lung function and reduced quality of life.[1] Although persistent asthma can often be controlled using ICSs and LABAs, many patients with severe asthma remain uncontrolled despite these therapies.[1] Although asthma control is often achieved in clinical trials, this is frequently not the case in everyday clinical practice.[2] Non-adherence to treatment and poor inhaler technique are the main factors that affect asthma control in real-world settings.[3,4] Evaluation of outcomes in real-world clinical practice is therefore necessary to supplement information from clinical trials and to provide a more complete understanding of the value of treatments for patients with asthma.

Numerous randomised clinical trials have shown that adding omalizumab to current asthma therapy is effective and well tolerated.[5–14] Data from these clinical studies have shown that add-on therapy with omalizumab significantly reduces asthma exacerbations, ICS requirements and emergency room (ER)/hospital visits *versus* placebo in patients with uncontrolled moderate-to-severe and severe allergic asthma.[5–14] To complement the efficacy and safety data from these clinical trials, a 2-year, global, post-marketing observational registry (eXpeRience) was initiated. Its main purpose was to evaluate outcomes in patients receiving omalizumab for uncontrolled persistent allergic asthma in 'real-world' clinical practice, and, additionally, to review the nature and frequency of serious adverse events (SAEs).

Methods

The eXpeRience registry was an international, single-arm, open-label, observational registry set up to facilitate the collection of data from patients receiving omalizumab for uncontrolled persistent allergic (IgE-mediated) asthma. Patients from 14 countries in Europe, the Americas and Asia were enrolled. The registry was not designed to test a formal hypothesis. Treatment and follow-up of patients was at the discretion of treating physicians, who followed local medical practice and labelling/reimbursement guidelines. The registry design was reviewed by independent ethics committees or institutional review boards at each centre, and the registry itself was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent to participate.

The enrolment target of 1300 patients was flexible and could vary, as no formal global sample size was specified, and participating countries were permitted to enrol patients to meet local needs for information. However, an interim review concluded that a minimum of 900 patients would be sufficient to draw meaningful conclusions from the registry. Recruitment was therefore stopped in October 2009 when 943 patients had been enrolled.

Patients were eligible for inclusion if they met the local labelling requirements for omalizumab use and had commenced omalizumab within the previous 15 weeks. Enrolment took place over an approximately 2.5-year period, beginning in May 2006, and participants were followed for up to 2 yrs after treatment initiation. Patients were excluded if they were currently enrolled and receiving treatment in a clinical trial of omalizumab or another asthma medication, or if they had received omalizumab in the past 18 months. The protocol was amended for Canada to allow 20 participants from a prospective study of patients treated under real-world conditions (the XCEED study)[15] to be enrolled in the eXpeRience registry, despite the fact that they may have started omalizumab more than 15 weeks before enrolment.

Upon enrolment, medical records were used to provide baseline information on patients' asthma status, asthma control and healthcare utilisation during the year before omalizumab initiation. No diagnostic or monitoring procedures were applied. After entry into the registry, data on clinical symptoms, asthma control, lung function, exacerbations, concomitant medication and status of comorbidities were collected prospectively at approximately 16 weeks and at 8, 12, 18 and 24 months after initiation of omalizumab treatment, with a minimum requirement of two data collections per year. Patients were removed from the registry if they withdrew consent, if data collection was no longer possible due to the patient not returning or being lost to follow-up, or if the patient enrolled in a clinical study. Patients who discontinued omalizumab remained in the registry and were followed up, wherever possible, for up to 2 yrs after treatment initiation.

Registry assessments

Response to omalizumab was assessed using the physician's Global Evaluation of Treatment Effectiveness (GETE), an overall clinical evaluation of asthma control at 16 weeks, based on all available information: patient interview and physical examination, and review of patient notes and diary (if used). Following the Week 16 assessment, GETE was not collected for the duration of the registry.[16] Investigators also assessed symptom control and performed spirometry measurements before rating the effect of omalizumab on a five-point scale, where 1 = excellent (complete control of asthma), 2 = good (marked improvement), 3 = moderate (discernible, but limited improvement), 4 = poor (no appreciable change) and 5 = worsening. Patients with an 'excellent' or 'good' response were considered to be responders.

Numbers of clinically significant and severe clinically significant asthma exacerbations were recorded. Global Initiative for Asthma (GINA) definitions were used[17]: clinically significant exacerbations were defined as any worsening of asthma considered by the treating physician to require systemic corticosteroids, and were regarded as severe if there was a reduction in peak expiratory flow

(PEF) to <60% of the patient's predicted or personal best. Data on exacerbations were annualised; that is, for Month 12, rates were derived from Week 16, Month 8 and Month 12 data; for Month 24, rates were derived from data collected at Months 18 and 24.

Investigators were provided with the Asthma Control Test™ [ACT™] and/or asthma control questionnaire (ACQ), but were not required to use them. Where used, the ACT and ACQ were generally routinely administered throughout the evaluation period. The ACT assesses interference with activities, shortness of breath, nocturnal symptoms, rescue medication use, and self-rating of asthma control.[18,19] The overall score for each patient is the total of the responses to the 5 questions, and ranges from 5 (poorly controlled asthma) to 25 (well-controlled asthma). The minimum important difference for the ACT has been defined as ≥3 points.[19] The ACQ includes both patient-reported symptoms and physician-determined forced expiratory volume in 1 s (FEV_1).[20] In eXpeRience, the overall ACQ score was calculated as the sum of individual item scores divided by the number of questions answered at each time-point, provided at least four questions were answered; otherwise, no value was entered for that time-point. ACQ scores range from 0 (completely controlled) to 6 (extremely poorly controlled). A decrease in ACQ score of ≥0.5 points is considered to be the minimal clinically important improvement.[21]

Investigators were also provided with (but not obliged to use) the standard 32-item Asthma Quality-of-Life Questionnaire (AQLQ) or the 15-item version (mini-AQLQ), both of which are validated measures of functional impairment in adults with asthma.[22,23] An increase in AQLQ or mini-AQLQ score of ≥0.5 points is considered to be the minimal clinically important improvement.[22,24]

Other assessments included symptoms, use of rescue medication, lung function (FEV_1 and PEF), asthma-related healthcare utilisation (hospitalisations, ER visits and unscheduled doctor visits), days of missed work or school, and oral corticosteroid (OCS) use.

Data on serious adverse events (SAEs) were collected during the registry. SAEs were defined as events that were fatal or life-threatening, resulted in persistent or significant disability/incapacity, or required inpatient hospitalisation or prolongation of existing hospitalisation. Information on SAEs, regardless of suspected causality, was collected and reported within 24 h of the event's occurrence. All SAEs were followed until resolution.

Statistical analysis

The primary effectiveness analysis was performed on the intent-to-treat (ITT) population, which comprised all enrolled patients who received at least one dose of omalizumab and had at least one post-baseline effectiveness assessment. Efficacy tables were also created for the per-protocol (PP) population to assess the impact on the results of patients with at least one major protocol deviation. The safety population comprised all patients who were enrolled in the registry, received at least one dose of omalizumab and had at least one post-baseline safety assessment.

Table 1 Baseline demographics and clinical characteristics (safety population).

Variable	Value (N = 925)
Age group, *n* (%)	
<12 yrs	2 (0.2)
12–17 yrs	51 (5.5)
18–64 yrs	796 (86.1)
≥65 yrs	76 (8.2)
Age, yrs	
Mean (SD)	45 (15.0)
Gender, *n* (%)	
Male	325 (35.1)
Female	600 (64.9)
Race, *n* (%)	
Caucasian	855 (92.4)
Asian	32 (3.5)
Black	21 (2.3)
Native American	2 (0.2)
Other	15 (1.6)
Body weight, kg[a]	
Mean (SD)	75.5 (17.7)
Baseline IgE level, IU/mL[a]	
Mean (SD)	323.1 (460.9)
Range	8–7670[f]
Duration of allergic asthma, yrs[b]	
Mean (SD)	19.4 (13.6)
Median	16.0
Positive skin-prick test/RAST for perennial aeroallergens, *n* (%)[a]	816 (88.2)
Specification[c]	
Dust mites	698 (75.5)
Cat dander	327 (35.4)
Dog dander	300 (32.4)
Cockroaches	110 (11.9)
Other	103 (11.1)
History of allergy to seasonal aeroallergens present, *n* (%)[a]	587 (63.5)
Smoking history, *n* (%)[d]	
Never smoked	719 (77.7)
Ex-smoker	173 (18.7)
Current smoker	30 (3.2)
Asthma clinical symptoms (n = 916)	
Daytime asthma symptoms, *n* (%)	829 (90.5)
Limitations of activities, *n* (%)	788 (86.0)
Nocturnal symptoms/ awakenings, *n* (%)	729 (79.6)
Asthma control[e] (n = 916)	
Controlled, *n* (%)	13 (1.4)
Partly controlled, *n* (%)	209 (22.8)
Uncontrolled, *n* (%)	690 (75.3)
Unknown, *n* (%)	3 (0.3)
Missing, *n* (%)	1 (0.1)

IgE = immunoglobulin E; RAST = radioallergosorbent test; SD = standard deviation.
[a] Data missing for one patient.
[b] Data missing for 13 patients.
[c] Multiple entries possible.
[d] Data missing for three patients.
[e] Investigator's assessment.
[f] Confirmed by the investigator.

Background and demographic variables were summarised using mean and standard deviation (SD), and frequencies for discrete variables. Descriptive summaries are presented for physician's GETE, clinically significant asthma exacerbations, FEV_1 and PEF, ACT, ACQ, AQLQ and mini-AQLQ scores, healthcare utilisation, and OCS use.

Results

Baseline demographics and clinical characteristics are shown in Table 1. Nine hundred and forty-three patients were enrolled in the eXpeRience registry, of whom 694 (73.6%) completed 2 yrs of follow up (Fig. 1, patient disposition). The ITT population comprised 916 patients; 27 patients were excluded due to absence of post-baseline assessments. Major protocol deviations were recorded in 706 patients in the ITT population, giving a PP population of 210 patients. Despite this large discrepancy in sample size, similar results were seen in both populations for efficacy outcomes (Novartis data on file). The safety population comprised 925 patients. Enrolment by country was as follows: Argentina, 22 patients; Bulgaria, 12; Canada, 95; Cyprus, 20; Czech Republic, 114; Hungary, 60; The Netherlands, 156; Philippines, 1; Portugal, 62; Russia, 65; Slovakia, 204; Slovenia, 11; Spain, 101; and Taiwan, 20.

Five patients (0.5%) had previously been treated with omalizumab (mean time to restarting treatment 33.86 months). Maintenance therapy at baseline consisted of OCS monotherapy (28.4%), ICS monotherapy (26.5%), LABA monotherapy (16.4%), ICS/LABA fixed-dose combination therapy (82.1%), short-acting β_2-agonist (SABA) monotherapy (5.1%), LAMA monotherapy (20.3%), SABA/LAMA fixed-dose combination therapy (3.4%), leukotriene inhibitors (61.4%) and other monotherapies (26.5%). Mean total daily doses at baseline were 15.49 mg prednisolone equivalent for OCS monotherapy and 1675 μg beclomethasone dipropionate equivalent for ICS (monotherapy or combination therapy).

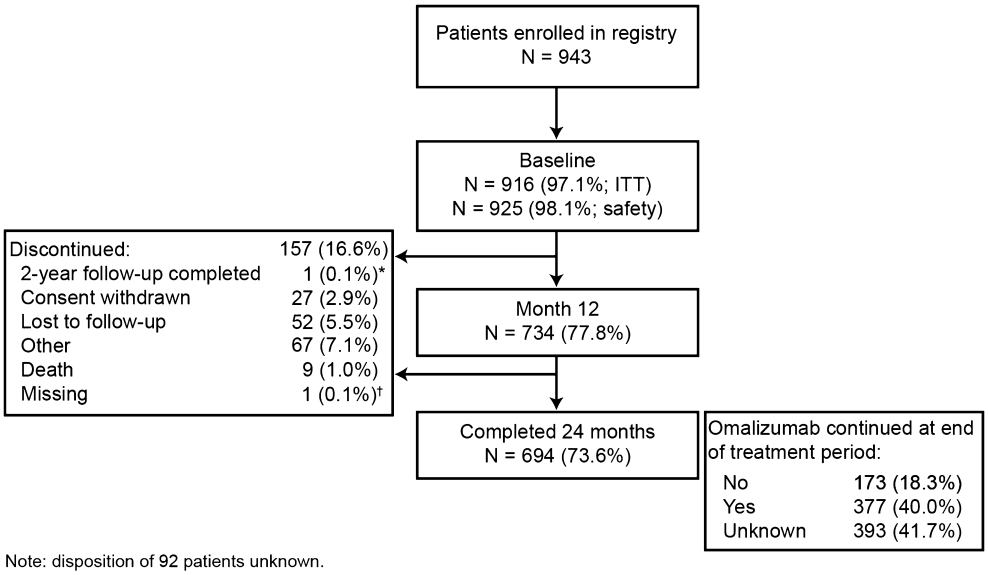
The individual last time-point (ILT; the time-point at which the patient was last recorded as being on treatment) was up to 24 months. Most (70.2%) of the ITT population had an ILT at Month 24; 5.2%, 5.0%, 7.9%, 8.5% and 3.2% had an ILT at 18 months, 12 months, 8 months, 16 weeks and at baseline, respectively.

Physician's Global Evaluation of Treatment Effectiveness

For various reasons, including local label specifications, GETE was not collected at the pre-specified Week 16 time-point in all patients, but was collected at an earlier or later time-point. Five hundred and eighty-four patients had a GETE assessment at Week 16 (±1 week); of these patients, 69.9% were considered responders (excellent/good response) and 30.1% were non-responders (moderate/poor response, or worsening asthma; Fig. 2a). At this time-point, 16 (1.7%) patients stopped treatment because they were identified as non-responders by the physician. Data on GETE evaluated at any time-point during the study were available for 915 patients (Fig. 2b). Of these, 64.2% were classified as responders, 30.7% were non-responders and 5.1% had no GETE assessment. Asthma was considered to have worsened in five patients (0.5%). Of the 210 patients in the PP population, 64.8% were responders on GETE evaluated at any time-point during the study.

Exacerbations

The proportions of patients with no clinically significant or severe clinically significant asthma exacerbations were markedly higher at Months 12 and 24 than during the



Note: disposition of 92 patients unknown.
*Patient discontinued at Month 18 – reason given was '2-year follow-up completed'.
†Patient discontinued at Month 24 without providing primary reason for discontinuation.
ITT = intent-to-treat

Figure 1 Patient disposition at Month 24 (end of registry).

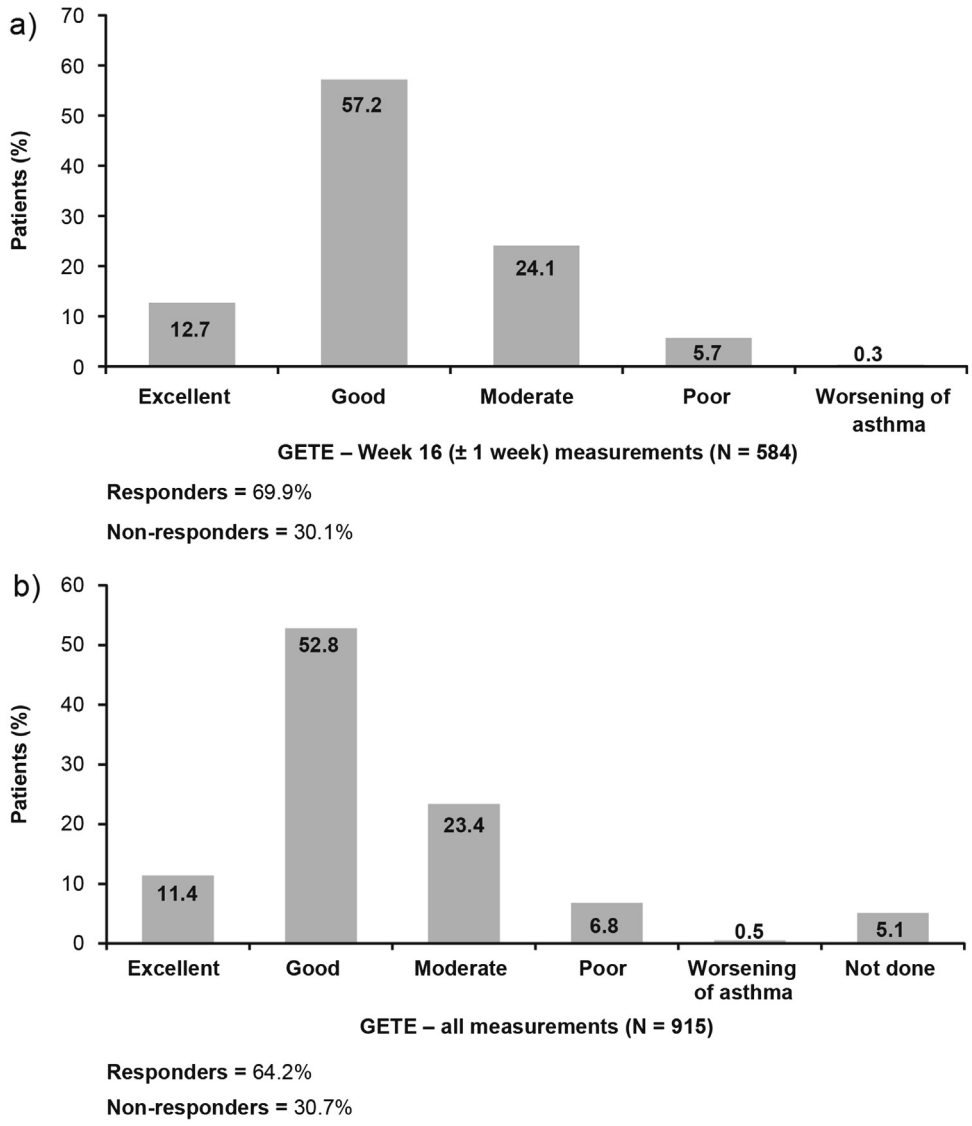
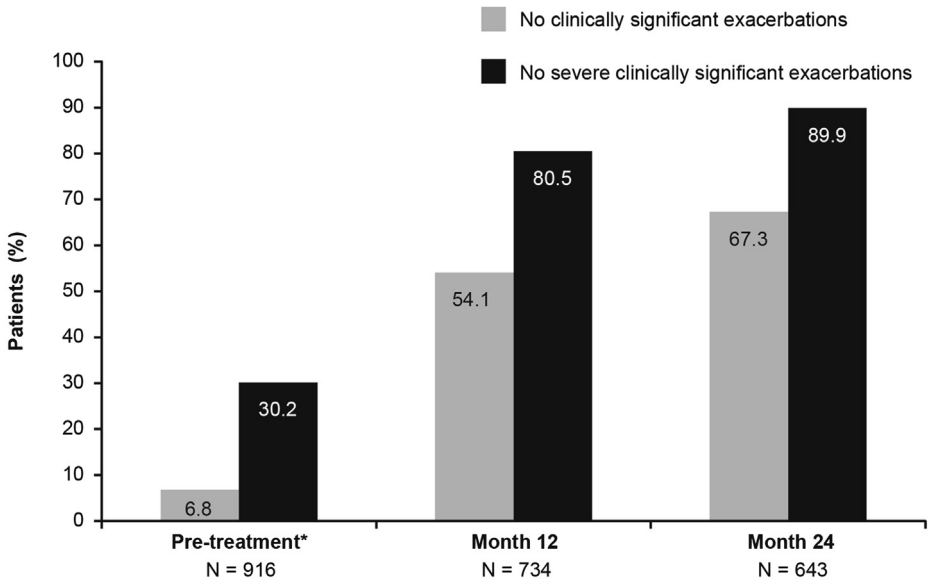


Figure 2 Physician's Global Evaluation of Treatment Effectiveness (GETE): (a) Week 16 measurements (±1 week); (b) all measurements. *Patients with an 'excellent' or 'good' response were considered responders; those with a 'moderate' or 'poor' response, and those with worsening of asthma, were considered non-responders.

12-month pre-treatment period (Fig. 3). Among the subgroup of responders, the proportion of patients with no clinically significant or severe clinically significant asthma exacerbations was also markedly higher at Months 12 (82.4% and 95.8%, respectively) and 24 (81.9% and 95.6%, respectively) than during the 12-month pre-treatment period (4.9% and 27.4%, respectively). Although not as marked, similar findings were reported for severe clinically significant asthma exacerbations among non-responders; 68.0%, 68.2% and 35.6% of non-responding patients had no clinically significant asthma exacerbations at Month 12, Month 24 and during the 12-month pre-treatment period, respectively. Additionally, the mean annualised numbers of clinically significant and severe clinically significant exacerbations per patient in the ITT population were considerably lower at Months 12 and 24 than the numbers prior to treatment (Fig. 4).

Symptoms and rescue medication use

In the week prior to the Month 12 and 24 time-points, a lower proportion of patients had daytime symptoms, activity limitations or nocturnal symptoms or awakenings, or required rescue medication use, compared with baseline (Table 2). At the Month 24 time-point, the number of days in the previous week on which patients had experienced each of these endpoints was less than half of the corresponding baseline value. Similar results were seen in responders and non-responders, except for rescue medication



Values inside the bars refer to the percentage of patients.
* 'Pre-treatment' is for 12 months prior to the start of omalizumab treatment.
Annualised data are presented for 'Month 12' (combining Week 16, Month 8 and Month 12 time-points) and 'Month 24' (combining Month 18 and Month 24 time-points).
N = number of evaluable patients at baseline, Months 12 and 24, respectively.

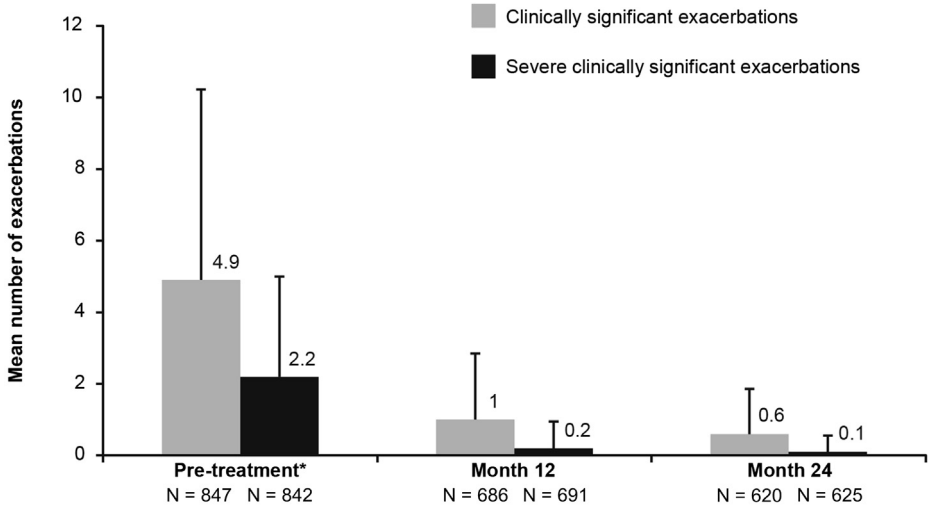
Figure 3 Percentage of patients with no exacerbations each time-point.

use in non-responders, which was reduced from a mean of 4.9 days at baseline to 2.5 days at Month 24.

Lung function

Normal lung function (FEV_1 $\geq$80% predicted or personal best) was observed in 37.7% (n = 277/734) and 36.2% (233/643) of patients in the week prior to the Month 12 and Month 24 time-points, respectively, compared with 13.6% (125/916) in the week prior to baseline. Mean (SD) FEV_1 (% predicted) increased from baseline by 9.8% (18.1%) at Month 12 and by 8.7% (18.5%) at Month 24. Mean (SD) PEF increased from baseline by 40.4 (116.2) L/min at Month 12 and by 34.0 (132.2) L/min at Month 24.

Mean (SD) FEV_1 (% predicted) increased from baseline by 10.3% (18.5%) at Month 12 and by 9.9% (19.8%) at Month 24 among responders, and by 8.8% (16.7%) and 5.5% (15.1%), respectively, in non-responders. Mean (SD) PEF increased from baseline by 44.7 (122.0) L/min at Month 12 and by 37.3 (144.2) L/min at Month 24 among responders, and by



* 'Pre-treatment' is for 12 months prior to the start of omalizumab treatment.
Annualised data are presented for 'Month 12' (combining Week 16, Month 8 and Month 12 time-points) and 'Month 24' (combining Month 18 and Month 24 time-points).
N = number of evaluable patients at baseline, Months 12 and 24.

Figure 4 Mean number of clinically significant and severe clinically significant exacerbations. Error bars represent SD.

Table 2 Asthma symptoms, activity limitations, and rescue medication use. Except where otherwise stated, data relate to the week immediately prior to each of the stated time-points (ITT population).

	Baseline (N = 916)	Month 12 (N = 734)	Month 24 (N = 643)
Daytime symptoms			
Patients, *n* (%)	829 (90.5)	422 (57.5)	348 (54.1)
Number of days, mean (SD)	5.0 (2.28)	1.7 (2.14)	1.6 (2.20)
Change in number of days, mean (SD)	—	−3.3 (2.74)	−3.4 (2.76)
Limitations of activities			
Patients, *n* (%)	788 (86.0)	342 (46.6)	268 (41.7)
Number of days, mean (SD)	4.4 (2.44)	1.3 (1.94)	1.2 (1.96)
Change in number of days, mean (SD)	—	−3.1 (2.61)	−3.2 (2.71)
Nocturnal symptoms or awakenings			
Patients, *n* (%)	729 (79.6)	225 (30.7)	163 (25.3)
Number of days, mean (SD)	3.3 (2.37)	0.7 (1.41)	0.6 (1.43)
Change in number of days, mean (SD)	—	−2.6 (2.62)	−2.8 (2.47)
Rescue medication use			
Patients, *n* (%)	797 (87.0)	397 (54.1)	320 (49.8)
Number of days, mean (SD)	4.8 (2.49)	1.8 (2.35)	1.6 (2.31)
Change in number of days, mean (SD)	—	−3.0 (2.91)	−3.2 (2.85)

SD = standard deviation.

33.2 (96.6) L/min and 26.3 (102.0) L/min, respectively, in non-responders.

Asthma control and asthma-related quality of life

Based on investigator assessment, a higher percentage of patients had controlled or partly controlled asthma in the week prior to Months 12 and 24 than was noted at baseline (85.0% and 87.1%, respectively, *versus* 24.2%).

Asthma control, as measured by the ACT or ACQ, also improved post-treatment (Table 3). On average, a meaningful improvement in ACT score (i.e. an increase of ≥3 points *versus* baseline) was seen from baseline to Months 12 and 24 (change in score 6.1 and 6.2, respectively). Clinically relevant improvements (i.e. a decrease of ≥0.5 points *versus* baseline) of −0.83 and −0.80 were also seen in the ACQ score at Months 12 and 24, respectively. There was also a mean improvement from baseline in the AQLQ scores at Months 12 and 24 (Table 3), with clinically relevant (≥0.5 point) improvements seen in 67.2% of patients at Month 12 and 60.7% at Month 24. Similar findings were reported for mini-AQLQ scores.

Among the subgroup of responders, findings were similar to those reported for the whole ITT population. On average, among non-responders, a reduced but still meaningful improvement in ACT score was seen from baseline to Months 12 and 24 (change in score 4.9 and 5.2, respectively). A clinically relevant improvement of −0.66 was also seen in the ACQ score at Month 24. Of the patients who completed the AQLQ and mini-AQLQ at baseline, 12 months and 24 months, the majority had a clinically relevant improvement of ≥0.5 points.

Healthcare utilisation and missed work/school days

Healthcare utilisation and absences from work or school were reduced during omalizumab treatment. Mean (SD) annualised numbers of asthma-related medical healthcare uses (hospitalisations, ER visits and unscheduled doctor visits) per patient were 1.0 (1.96) at Month 12 and 0.5 (1.28) at Month 24, lower than during the 12-month pre-treatment period (6.2 [6.97]). The mean (SD) annualised numbers of days of missed work due to asthma were 3.5 (17.28) and 1.0 (4.66) at Months 12 and 24, respectively, substantially less than during the pre-treatment period (26.4 [49.61] days). Similarly, the mean (SD) numbers of days of missed school due to asthma at Months 12 and 24 were 1.6 (4.28) and 1.9 (5.46), respectively, compared with 20.7 (27.49) days during the pre-treatment period. Marked reductions in healthcare utilisation and numbers of days of missed work or school due to asthma were reported in both responders and non-responders.

OCS use

The proportion of patients taking maintenance OCS therapy was lower at Month 24 (14.2%) than at Month 12 (16.1%) and baseline (28.6%). In addition, the mean (SD) total daily OCS dose (in prednisolone-equivalent mg) decreased markedly between baseline [15.5 (14.0) mg] and Month 12 [7.7 (10.9) mg], and was reduced further by Month 24 [5.8 (8.9) mg]. Similar findings were reported for the subgroup of responders: the proportion of patients taking maintenance OCS therapy was lower at Month 24 (12.1%) than at Month 12 (13.8%) and baseline (28.1%). Among non-responders, the proportion of patients taking maintenance OCS therapy was lower at Month 24 (17.9%) than at Month 12 (20.9%) and baseline (28.5%).

Among patients in the ITT population receiving OCS at baseline, there was a reduction in OCS dose or discontinuation of OCS treatment in 57.1% and 69.0% of patients at Months 12 and 24, respectively. A minority of patients at Month 12 (n = 5; 2.6%) at Month 24 (n = 4;

Table 3 Results for the Asthma Control Test™ (ACT), asthma control questionnaire (ACQ) and standard and abbreviated Asthma Quality-of-Life Questionnaires (AQLQ and mini-AQLQ, respectively) (ITT population).

Questionnaire	Baseline ($N = 916$)	Month 12 ($N = 734$)	Month 24 ($N = 643$)
ACT[a]			
Overall score			
n	496	417	361
Mean (SD)	13.0 (4.58)	19.1 (4.40)	19.7 (4.45)
Change from baseline			
n	—	342	292
Mean (SD)	—	6.1 (5.37)	6.2 (5.56)
ACQ[b]			
Overall score			
n	181	94	62
Mean (SD)	2.74 (0.97)	1.73 (1.12)	1.80 (1.07)
Change from baseline			
n	—	80	52
Mean (SD)	—	−0.83 (1.20)	−0.80 (1.19)
AQLQ[a]			
Overall score			
n	132	92	81
Mean (SD)	4.27 (1.27)	5.58 (1.06)	5.49 (1.30)
Change from baseline			
n	—	64	56
Mean (SD)	—	0.97 (0.97)	0.75 (1.09)
Mini-AQLQ[a]			
Overall score			
n	204	163	125
Mean (SD)	3.81 (1.19)	5.04 (1.33)	5.20 (1.30)
Change from baseline			
n	—	135	104
Mean (SD)	—	1.30 (1.43)	1.62 (1.40)

SD = standard deviation.
[a] Increase in score reflects an improvement.
[b] Decrease in score reflects an improvement.

2.4%) had increases in their OCS dose compared with baseline.

Serious adverse events

Nine deaths occurred during the registry, none of which were suspected to be related to omalizumab. There was one death each due to cardiac failure, malignant lung neoplasm, chronic obstructive pulmonary disease exacerbation, sudden death, cholestatic jaundice, progression of asthma and respiratory failure, and two deaths due to sepsis. One hundred and fifty SAEs were reported by 64 patients (6.9%; Table 4). The most common SAE was asthma (32 patients, 3.5%), followed by dyspnoea and pneumonia (each in 7 patients, 0.8%). Other SAEs were reported mostly for single patients, including one case of anaphylaxis suspected to be due to omalizumab. Thirty-eight patients discontinued omalizumab due to SAEs. Overall, 25 (16.7%) of the total 150 SAEs were suspected to be related to omalizumab, most commonly dyspnoea, sudden chest tightness and headache (3 events each). Of these, 14 SAEs (in five patients) led to permanent discontinuation of omalizumab and two SAEs led to temporary dosage interruption. For the remaining nine SAEs, no action was taken with regard to omalizumab treatment.

Discussion

The two-year eXpeRience registry enabled the collection and analysis of real-world data on outcomes in patients receiving omalizumab for uncontrolled allergic asthma. Baseline characteristics from 294 participants were reported previously[25] and highlighted the need for improved asthma control in this group of patients.

The results of this analysis indicate that a significant proportion of patients on omalizumab therapy responded well to treatment, with investigators rating the majority of patients (69.9%) as responders (16-week GETE assessment excellent/good). Similar results have been seen in clinical trials, in which 53%—60% of omalizumab-treated patients had an excellent/good response, compared with 33%—42% for placebo.[7,11] Real-world studies in smaller patient populations treated for shorter durations have reported excellent or good responses in 68%—89.1% of patients.[26—32] However, the eXpeRience registry is considerably larger,

Table 4 Serious adverse events (SAEs) in patients ($N = 925$)[a] receiving omalizumab therapy.

Patients with any SAE(s) — *n* (%)	64 (6.9)
Total number of reported SAEs	150
Relationship to omalizumab (suspected) — *n* (%) of events	25 (16.7%)
No change in dosage	9 (36.0%)
Dosage temporarily interrupted	2 (8.0%)
Permanently discontinued	14 (56.0%)
Omalizumab-related SAEs (suspected) by primary system organ class and preferred term — *n* (%)	
Congenital, familial and genetic disorders	1 (4.0%)
Transposition of the great vessels	1 (4.0%)
Gastrointestinal disorders	1 (4.0%)
Dry mouth	1 (4.0%)
General disorders and administration side conditions	4 (16.0%)
Chest discomfort	3 (12.0%)
Oedema	1 (4.0%)
Immune system disorders	1 (4.0%)
Anaphylactic reaction	1 (4.0%)
Infections and infestations	1 (4.0%)
Sepsis	1 (4.0%)
Injury, poisoning and procedural complications	1 (4.0%)
Oxygen saturation decreased	1 (4.0%)
Nervous system disorders	5 (20.0%)
Dizziness	1 (4.0%)
Headache	3 (12.0%)
Tremor	1 (4.0%)
Pregnancy, puerperium and perinatal conditions	3 (12.0%)
Abortion missed	1 (4.0%)
Abortion spontaneous	1 (4.0%)
Intra-uterine death	1 (4.0%)
Respiratory, thoracic and mediastinal disorders	6 (24.0%)
Asthma	1 (4.0%)
Dyspnoea	3 (12.0%)
Dyspnoea at rest	1 (4.0%)
Pulmonary embolism	1 (4.0%)
Skin and subcutaneous tissue disorders	1 (4.0%)
Hyperhidrosis	1 (4.0%)
Vascular disorders	2 (8.0%)
Flushing	1 (4.0%)
Hypotension	1 (4.0%)

SAEs occurring at any time during the registry are presented.
[a] Represents safety population and includes all patients enrolled in the registry who received at least one dose of omalizumab and had at least one post-baseline safety assessment.

has a longer duration of follow-up and included more assessments than many of these previous studies. A 4-year omalizumab treatment real-world study has demonstrated significant improvements in lung function and other outcomes, but was conducted in a very small number of patients.[33]

In the present study, 1—2 yrs of treatment with omalizumab was associated with reductions in daytime symptoms, activity limitations, nocturnal symptoms/awakening, and rescue medication use. The overall frequencies of these outcomes were similar to those reported in a real-world study in Germany.[34] The eXpeRience registry also revealed substantial reductions in clinically significant asthma exacerbations, including those classified as severe, after 1 and 2 yrs of omalizumab treatment. Lung function (FEV_1 [% predicted] and PEF) improved at both time-points (Months 12 and 24) compared with pre-treatment values. Furthermore, omalizumab was associated with reductions in healthcare utilisation and in absence from work or school at all time-points *versus* baseline. These findings suggest that treatment with omalizumab may have a significant impact on the direct and indirect costs of illness in these patients. Improvements in asthma control (ACT and ACQ) and asthma-related quality of life (AQLQ and mini-AQLQ), as well as reductions in OCS use, were also observed.

Patients included in the eXpeRience registry were generally more heterogeneous (in terms of the frequency of asthma symptoms and exacerbations, lung function and frequent requirements for medical intervention) compared with subjects enrolled in controlled clinical trials. The difficulties of achieving control in asthma have been highlighted by the GOAL study,[35] in which approximately 30% of patients who received stepwise treatment with salmeterol/fluticasone for 1 yr (with or without prednisolone) did not achieve asthma control. Our results suggest that the addition of omalizumab to existing treatment may improve outcomes in this setting, and we propose that the findings of the eXpeRience registry are applicable to the general population of patients with uncontrolled persistent allergic asthma, despite following guideline-based background therapies.

In addition, our data are consistent with those from several pivotal clinical trials[5—14] and real-world studies[26—33] that predominantly enrolled populations with uncontrolled severe allergic asthma. Direct comparisons between our results and those of randomised controlled trials should be made with caution because of differences in trial design and duration, and in the definitions of some outcome measures.

No unexpected safety issues were identified during the eXpeRience registry. None of the nine deaths was suspected to be related to omalizumab, and the number of SAEs considered to be treatment-related was low. The frequency of SAEs in eXpeRience was comparable to that seen in controlled trials of omalizumab.[36]

As with all observational studies, the results should be interpreted with due consideration that factors other than the treatment of interest may have contributed to the findings. Other potential limitations include the fact that patient selection and continuation on omalizumab beyond 16 weeks was at the discretion of the treating physician, and that the indications for treatment vary between countries. A significant proportion of patients (16.6%) discontinued treatment, for various reasons, but this is likely to reflect the real-world situation. Finally, the relative infrequency of data collection introduces the potential for recall bias.

Despite these limitations, the concordance between our results and those of randomised controlled trials suggests

that the observed improvements in asthma control, number and severity of exacerbations, symptoms, lung function and healthcare utilisation were in all likelihood due to treatment with omalizumab.

In conclusion, results from the 2-year eXpeRience registry support findings from randomised trials that omalizumab significantly improves asthma control when added to current therapy in patients with uncontrolled persistent allergic asthma.

Conflict of interest statements

GJB has received grant/research support for consultations and/or speaking at conferences from Novartis, GSK, AstraZeneca and MSD.

CWC, RM, PG, GP, and JB are Novartis employees.

Acknowledgements

The registry was designed and sponsored by Novartis Pharma AG. The authors were assisted in the preparation of the manuscript by Dr Santosh Tiwari (Novartis). Writing support was funded by the registry sponsor.

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