"Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study.^{*}

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Summary

Objective: To evaluate the 16- and 52-week effectiveness of add-on omalizumab treatment under real-life heterogeneity in patients, settings, and physicians in an open-label, multi-center, pharmaco-epidemiologic study of patients with severe persistent allergic asthma in Belgium.

Methods: Effectiveness outcomes included improvement in 2005 global initiative for asthma (GINA) classification, physician-rated global evaluation of treatment effectiveness (GETE), quality of life (Juniper asthma-related quality of life (AQLQ) and European quality of life questionnaire 5 dimensions (EQ-5D)), and severe asthma exacerbations. Patients studied included both intent-to-treat and per-protocol populations.

Results: The sample (n = 158) had a mean age of 48.17 ± 17.18 years, and a slight majority were female (53.8%). Despite being treated with high-dose inhaled corticosteroids and long-acting β 2-agonists, all patients experienced frequent symptoms and had exacerbations in the past year. At 16 weeks, >82% had good/excellent GETE (*P* values <0.001), >82% had an improvement in total AQLQ scores of \geq 0.5 points (*P* < 0.001), and >91% were severe exacerbation-free (*P* <0.001). At 52 weeks, >72% had a good/excellent GETE rating (*P* <0.001), >84% had improvements in total AQLQ score of \geq 0.5 points (*P* <0.001), >56% had minimally important improvements in EQ-5D utility scores (*P* = 0.012), and >65% were severe exacerbation-free (*P*< 0.001). Significant reductions in healthcare utilization compared to the one year prior to treatment were noted.

Conclusion: The PERSIST study shows better physician-rated effectiveness, greater improvements in quality of life, greater reductions in exacerbation rates, and greater reductions in healthcare utilization than previously reported in efficacy studies. Under real-life conditions, omalizumab is effective as add-on therapy in the treatment of patients with persistent severe allergic asthma.

Keywords: Asthma ; allergic asthma ; severe asthma ; omalizumab

Introduction

Over the past four decades, the prevalence of and morbidity and mortality associated with asthma has increased substantially.¹ As there is no cure for asthma, the goal of treatment is aimed at controlling the clinical aspects of the disease.² Despite established guidelines for the evaluation, classification and treatment of asthma, the

Statement of originality: In the PERSIST study, we observed better physician-rated effectiveness, greater improvements in quality of life, greater reductions in rates of severe exacerbations, and greater reductions in healthcare utilization than previously reported in efficacy studies involving omalizumab in the treatment of severe persistent allergic asthma. Thus, under "real-life" heterogeneity in patients, clinical settings, and physician practices, omalizumab is effective as add-on therapy in the treatment of patients with persistent severe allergic asthma.

majority of patients are controlled sub-optimally, especially those with severe asthma.^{3,4} Omalizumab is a recombinant monoclonal antibody designed to treat immunoglobulin E (IgE)-mediated disease by inhibiting the binding of IgE to high-affinity receptors on pro-inflammatory cells. Omalizumab as add-on to previously initiated inhaled corticosteroids (ICS) and long-acting β 2-agonist (LABA) treatment represents a new therapeutic approach for severe persistent allergic asthma.

The safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of omalizumab have been studied in more than 4600 patients. In phase III trials of patients with allergic asthma, perennial allergic rhinitis, and seasonal allergic rhinitis, omalizumab compared to placebo has been shown to reduce the number of asthma exacerbations,⁵ lower concomitant medication burden,⁶ improve symptom severity, and enhance quality of life (QoL).^{7,8} In the INNOVATE trial,⁵ now commonly used as an omalizumab efficacy benchmark study, treatment efficacy was rated as good/ excellent in 60.5% of patients, and 60.8% had clinically meaningful improvements in asthma-related QoL after 28 weeks of treatment.⁵ Moreover, omalizumab decreased clinically significant exacerbation rates by 26%, and severe exacerbation rates by 50%.⁵ Similar omalizumab treatment effectiveness has been observed in recent open-label studies.^{9,10}

As with all asthma treatments,¹¹ there is some heterogeneity in response to treatment with omalizumab. Omalizumab treatment efficacy is often evaluated at 16 weeks, with a response to treatment rate close to 61% as measured by the global evaluation of treatment effectiveness (GETE).⁵ In many patients, however, continued, long-term treatments are essential to improve respiratory outcomes, reduce exacerbations and associated healthcare resource utilization, and enhance QoL.⁷ Despite the efficacy evidence from controlled trials and the emerging effectiveness findings, the outcomes of omalizumab treatment for persistent severe allergic asthma under real-life variability in patients, settings, and physicians remain poorly documented. This was the purpose of the present study.

Methods

Study design

PERSIST was a prospective, open-label, observational, multicenter study in patients with severe persistent allergic asthma treated with omalizumab. The primary objectives of PERSIST were to: 1) describe the patients who, in their treating physician's best clinical judgment, were being treated with omalizumab, 2) determine the 16- and 52-week effectiveness of omalizumab as add-on therapy, 3) describe treatment patterns involving add-on omalizumab treatment, and 4) describe the safety and tolerability of treatment with omalizumab when used in a pragmatic trial. As a secondary objective, patients' healthcare resource utilization patterns over the 52-week treatment period were assessed and compared to the one year prior to starting omalizumab.

All visits in PERSIST coincided with visits required by the Belgian authorities for the reimbursement of omalizumab and as such integrated into routine practice. During the baseline patient assessment, data on healthcare utilization visits in the one year prior to starting omalizumab were collected historically. Approximately 16 weeks after the first treatment with omalizumab, the treating physician determined whether to continue omalizumab therapy in accordance with the scientific leaflet and the Belgian reimbursement criteria. Treatment was continued if the patient showed response to treatment at 16 weeks; any such patient was followed for the remainder of the study (approximately 52 weeks). Patients who discontinued omalizumab therapy were asked to remain in the study (Fig. 1).

The PERSIST study included patients for whom the treating physician decided, in his/her best clinical judgment, to prescribe omalizumab, in accordance with the scientific leaflet and the Belgian reimbursement criteria. Physicians were approached for participation in PERSIST based on their potential use of omalizumab in patients with severe persistent allergic asthma seen in their practice. Participating physicians enrolled all patients treated with omalizumab in their practice who met inclusion criteria if they provided written informed consent during the 24 month enrollment period from September 2006 to September 2008. Study eligible patients were at least 12 years of age, had poorly controlled severe persistent allergic asthma despite taking at least an ICS and a LABA according to the 2005 global initiative for asthma (GINA) guidelines, and had given written informed consent prior to inclusion in the study. Patients were excluded from participation if they were pregnant or nursing. As per Belgian reimbursement criteria, eligible patients had a baseline IgE \geq 76 IU/mL, a positive radioallergosorbent test, percentage of predicted forced expiratory volume in 1 sec (FEV₁) <80%, regularly occurring day or nighttime asthma symptoms, and at least two documented asthma exacerbations requiring systemic corticosteroids, emergency services, or hospitalization during the previous two years. A total of 183 patients were screened for inclusion in PERSIST; 160 patients were enrolled, and 158 met inclusion criteria and

had effectiveness data collected. Human subjects approval for the study was granted by the Ethical Committee of the University of Ghent. The Ethical Committee of each center approved the study for local participation.





Measurement of effectiveness

Prescribing physicians were asked to judge if there was an improvement in 2005 GINA asthma classification (based on asthma symptoms and lung function) at 16 and 52 weeks. During the conduct of the study, GINA classification of asthma changed considerably.² Thus, the frequency of daytime and nocturnal asthma symptoms and FEV_1 were also recorded.

Prescribing physicians were asked to rate the effectiveness of omalizumab at 16 and 52 weeks using the global evaluation of treatment effectiveness (GETE) scale. In the GETE scale the treating physician judges whether the patient's overall response to treatment is excellent, good, moderate, poor, or if the patient's condition is worsening.

Subjective asthma-related QoL was assessed at baseline and at 16 and 52 weeks, using the Juniper asthmarelated QoL questionnaire (AQLQ).¹² A change of ≥ 0.5 on the 7-point AQLQ scale represents a clinically meaningful improvement in asthma-related QoL. In addition, generic QoL was assessed using the European quality of life questionnaire 5 dimensions (EQ-5D) at baseline and 52 weeks.

According to established guidelines, EQ-5D utility data were calculated using Belgian population norms.¹³ Taken from established utilities from a broad range of chronic conditions, a minimally important improvement in EQ-5D was defined as an absolute increase of ≥ 0.074 .¹⁴ Both the AQLQ and EQ-5D are widely used in clinical research.

PERSIST severe exacerbations were those that met the following criteria: the patient required a systemic corticosteroid, or the patient required an emergency room visit or hospitalization for the exacerbation. The incidences of PERSIST severe exacerbations were assessed at 16 and 52 weeks.

Note that prescribers are required to report GINA classification, GETE rating, and AQLQ total and subscores to qualify patients for omalizumab reimbursement in Belgium. Hence these data are recorded in routine clinical practice and do not constitute additional burden on either patient or physician.

Statistical methods

Data were analyzed using SPSS v15.0 (Chicago, Illinois, USA), and Stata MP v10.0 (College Station, Texas, USA). The level of statistical significance was set at 0.05. Data are presented for both the intent-to-treat (ITT) - all patients with visit data available - and the per-protocol (PP) - all patients remaining on omalizumab - populations. Data were summarized with respect to background and demographic characteristics, effectiveness measurements, as well as safety observations using descriptive statistics of frequency, central tendency, and dispersion under consideration of applicable levels of measurement. As appropriate, paired t-tests or Wilcoxon Signed Ranks tests were used to describe observed trends.

For measures of omalizumab treatment effectiveness, the binomial test was used to test the null hypothesis that the proportion of patients responding to treatment with omalizumab at 16 weeks was 0.605. This referent proportion was derived from the INNOVATE study.⁵ The proportion of patients with a) improvement in 2005 GINA classification, b) GETE rating of good/excellent, c) improvement in AQLQ total or subscales of \geq 0.5 points, and d) the proportion that was exacerbations-free at 16 weeks were tested. The binomial test was also used to test the null hypothesis that the proportion of patients responding to treatment with omalizumab at 52 weeks was 0.605 adjusted for a persistence failure of 0.30, therefore a proportion of 0.424. The proportion of patients with a) improvement in 2005 GINA classification, b) GETE rating of good/excellent, c) improvement in AQLQ total or subscales of \geq 0.5 points, d) improvement in EQ-5D utility score of \geq 0.074, and e) the proportion that was exacerbation-free were tested.

Currently, the commonly accepted clinical criteria for omalizumab treatment response is the GETE; patients with a GETE of good or excellent are considered responders.¹⁵

Results

The baseline evaluable sample consisted of 158 patients with severe persistent asthma enrolled from 35 participating centers. Patients ranged in age from 12 to 83 years (Table 1). Almost 54% were female and 94.9% of patients were Caucasian. Mean IgE at baseline was high and ranged widely (median 317, inter-quartile range = 142.5-661.0 lU/mL). Baseline generic and asthma-related QoL were both in the low range (mean AQLQ total score: 3.24; mean EQ-5D VAS: 52.29; mean EQ-5D utility score: 0.54). All patients had poorly controlled asthma despite treatment with high-dose ICS and a LABA (Table 2). In addition, 63.3% were on oral corticosteroids. The majority of patients (70.9%) experienced daily asthma symptoms, and a slight majority (57%) experienced nocturnal symptoms weekly.

During the 12 months preceding enrollment 69 patients had asthma-related general practitioner visits (mean[SD] 5.13[4.77], annual rate 2.44), 149 had specialist visits (4.38[2.98] visits, annual rate 4.18), 22 had emergency room visits (1.35[0.89] visits, annual rate 0.22), and 64 required hospitalization (1.44[0.89] hospitalizations, annual rate 0.60). In the preceding 12 months, patients had on average 2.67[1.28] PERSIST severe exacerbations.

Baseline characteristics	n = 158		
Age (years)			
Mean (SD)	48.17 (17.18)		
Median (range)	49.50 (12-83)		
Gender <i>n</i> (%)			
Male	73 (46.2%)		
Female	85 (53.8%)		
Race <i>n</i> (%)			

 Table 1. Baseline characteristics of patients treated with omalizumab.

Caucasian	150 (94.9%)
Other	8 (5.1%)
Weight (kg)	
Mean (SD)	71.46 (16.53)
Median (range)	72.00 (32-118)
Smoking history	
Current smoker	16 (10.1%)
Former smoker	33 (20.9%)
Never smoked	109 (69%)
FEV ₁ (% of predicted)	
Mean (SD)	56.54 (14.72)
Median (range)	57.50 (22-92)
IgE (IU/mL)	
Mean (SD)	613.89 (860.19)
Median (range)	317.00 (40-5152)
AQLQ total score ($n = 157$)	
Mean (SD)	3.24 (1.21)
Median (range)	3.00 (1-6.3)
EQ-5D VAS ($n = 124$)	
Mean (SD)	52.29 (17.34)
Median (range)	53.50 (8-90)
EQ-5D index/utility ($n = 126$)	
Mean (SD)	0.54 (0.24)
Median (range)	0.58 (-0.16-1.00)

Abbreviations: AQLQ = Juniper asthma-related quality of life, EQ-5D = European quality of life questionnaire 5 dimensions, $FEV_1 = forced$ expiratory volume at 1 s (% predicted), IgE = immunoglobulin E, IU = international units, kg = kilograms, SD = standard deviation, VAS = visual analogue scale.

<i>Table 2.</i> malles of poor asimila control prior to omalizanab	Table	2.	Indices	of poor	asthma	control	prior to	omalizumab
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Indices of poor asthma control	n (%)
Concomitant medications	
ICS plus LABA	158 (100)
Oral corticosteroid use	
Intermittent	55 (34.8)
Daily	45 (28.5)
Leucotriene antagonists	102 (64.6)
Anticholinergics	63 (39.9)
Theophylline/derivatives	61 (38.6)
Antihistamines	45 (28.5)
Daytime symptoms	
<once td="" week<=""><td>5 (3.2)</td></once>	5 (3.2)
>Once/week	41 (25.9)
Daily	112 (70.9)
Nighttime symptoms	
<2 Times/month	35 (22.2)
>2 Times/month	33 (20.9)
Weekly	90 (57.0)
Asthma-related healthcare visits in past year	
≥ 1 General practitioner visit	69 (43.7)
≥1 Specialist visit	149 (94.3)
≥1 Emergency room visit	22 (13.9)
≥ 1 Hospitalization	64 (40.5)
Asthma exacerbations in past year	
≥1 PERSIST severe exacerbation	155 (98.1)

Abbreviations: ICS = inhaled corticosteroid, LABA = long-acting beta agonist.

16-Week treatment effectiveness

At 16 weeks, the ITT sample included 153 and the PP sample 146 patients. Using the 0.605 INNOVATE responder proportion, this sample size permitted detection of such proportion and associated 95% confidence interval (CI) with precision of ± 0.077 .

16-Week 2005 GINA classification, asthma symptoms and lung function

Over a mean[SD] study duration of 15.92[9.77] weeks, 37.9% of the ITT population (P < 0.001), and 38.4% of the PP population (P < 0.001) were judged to have an improvement in 2005 GINA classification (Table 3). Reduction in the frequency of daytime symptoms was observed in 60.8% of the ITT population (P = non-significant (ns)), and 62.3% of the PP population (P = ns). Reduction in the frequency of nocturnal symptoms was observed in 52.9% of the ITT population (P = no.34) and 54.1% of the PP population (P = ns). FEV₁ data were available on 87.5% (n = 134) of the ITT population and 89% (n = 130) of the PP population. FEV| improved significantly from baseline in both the ITT (mean[SD] improvement 12.20[19.41]%) and PP populations (11.70[18.00]%) (both P < 0.001).

Population	п	16-Week effectiveness	P value
		% Improving in 2005 GINA classification	
ITT	153	37.9%	< 0.001
PP	146	38.4%	< 0.001
		% With good or excellent GETE rating	
ITT	153	82.4%	< 0.001
PP	146	83.8%	< 0.001
		% Improving in AQLQ total score ≥ 0.5	
ITT	147	82.3%	< 0.001
PP	142	83.8%	< 0.001
		% PERSIST severe exacerbation-free	
ITT	132	90.9%	< 0.001
PP	125	91.2%	< 0.001

Table 3. 16-Week omalizumab treatment effectiveness (Visit 2).

Tested against the null of 60.5% effectiveness. Abbreviations: AQLQ = Juniper asthma-related quality of life, GETE = physician-rated global evaluation of treatment effectiveness, GINA = 2005 Global Initiative for Asthma, ITT = intent-to-treat population, PP = per-protocol population.

16-Week physician-rated GETE

82.4% of the ITT and 83.6% of the PP population had good/ excellent GETE ratings (both P < 0.001).

16-Week quality of life

82.3% of the ITT population had an improvement of total AQLQ scores of ≥ 0.5 points (P < 0.001). There was a moderate improvement in total AQLQ (≥ 1.0 points)⁹ in 67.8% of the ITT population, and a large improvement in AQLQ (≥ 1.5 points)⁹ in 36.7% of the ITT population. The mean[SD] 16-week improvement in total AQLQ score was 1.37[1.09] for the ITT population. 83.8% of the PP population had an improvement in total AQLQ scores of at least 0.5 points (P < 0.001). Similar results were observed for all four AQLQ subscales.

Exacerbations at 16 weeks

During the first 16 weeks of treatment with omalizumab, 12 patients (9.1%) in the ITT population had at least one PERSIST severe exacerbation (range 1-2). 90.9% of the ITT population were PERSIST severe exacerbation-free (P < 0.001). In the PP population, 11 patients (8.8%) had at least one PERSIST severe exacerbation. 91.2% of the PP population were PERSIST severe exacerbation-free (P < 0.001) after 16 weeks of treatment.

52-Week treatment effectiveness

At 52 weeks, the ITT sample included 130 patients and the PP sample 105 patients. Using the 0.605 INNOVATE responder proportion adjusted for persistent failure (0.424), this sample size permitted detection of

such proportion and associated 95% CI with precision of ± 0.107 .

52-Week 2005 GINA classification, symptoms and lung function

Over a mean[SD] study duration of 56.43[11.03] weeks, 31% of the ITT population was judged to have an improvement in 2005 GINA classification (P = 0.005), as was 35.2% of the PP population (P = ns) (Table 4). Compared to baseline, daytime symptoms were reduced in 63.8% of the ITT population (P < 0.001), and in 72.4% of the PP population (P < 0.001). Nocturnal symptoms were reduced in 49.2% of the ITT population (P = ns), and in 54.3% of the PP population (P = 0.009). FEV₁ improved significantly compared to baseline in both the ITT (mean[SD] improvement 12.23[24.18]%) and PP populations (12.72[25.39]%) (both P < 0.001).

Population	n	52-Week effectiveness	P value
		% Improving in 2005 GINA classification	
ITT	130	31.0%	< 0.005
PP	105	35.2%	< 0.082
		% With good or excellent GETE rating	
ITT	130	72.3%	< 0.001
PP	105	80.9%	< 0.001
		% Improving in AQLQ Total Score ≥ 0.5	
ITT	122	84.4%	< 0.001
PP	100	89.0%	< 0.001
		% Improving in EQ-5D utility score ≥0.074 points	
ITT	67	56.7%	0.012
PP	54	57.6%	0.019
		% PERSIST severe exacerbation-free	
ITT	128	65.6%	< 0.001
PP	103	66.0%	< 0.001

Table 4. 52-Week omalizumab treatment effectiveness (Visi	it 3	;)).
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Tested against the null of 42.4% effectiveness. All results shown reflect full 52-week duration of the study. Abbreviations: AQLQ = Juniper asthma-related quality of life questionnaire, GETE = physician-rated global evaluation of treatment effectiveness, GINA = 2005 Global Initiative for Asthma, EQ-5D = European quality of life questionnaire 5 dimensions, ITT = intent-to-treat population, PP = per-protocol population.

52-Week physician-rated GETE

After 52 weeks of participation, 72.3% of the ITT population had a good/excellent GETE rating (P < 0.001). 80.9% of the PP population had a good/excellent GETE rating (P < 0.001) (Fig.2).

Figure 2. Omalizumab treatment effectiveness in the PERSIST study. Proportion of PERSIST populations with evidence of treatment effectiveness. % improvement in total AQLQ indicates an improvement in total AQLQ score ≥ 0.5 points, % PERSIST severe exacerbation-free indicates no evidence of a PERSIST severe exacerbation. ITT 16-week n = 153, 52-week n = 130. PP 16-week n = 146, 52-week n = 105. Abbreviations: AQLQ = asthma quality of life questionnaire, GETE = physician-rated Global Evaluation of Treatment Effectiveness, ITT = intent-to-treat population, PP = per-protocol population.



52-Week quality of life

Comparative AQLQ data were available on 122 (93.8%) of the ITT population. 84.4% of the ITT population had an improvement in total AQLQ score of ≥ 0.5 points (P < 0.001), 68.9% had an improvement of ≥ 1 point, and 53.3% had an increase in total AQLQ score of >1.5 points compared to baseline. The mean[SD] 52-week improvement in total AQLQ score was 1.79[1.13] for the ITT population (Fig. 3). Comparative AQLQ data were available on 100 (95.2%) of the PP population. 89% of the PP population had improvement in total AQLQ score of ≥ 0.5 points compared to baseline (P < 0.001). At 52 weeks, 76% of the PP population had an improvement in total AQLQ score of ≥ 1.0 point and 59% had an increase in total AQLQ score of ≥ 1.5 points compared to baseline. Similar results were observed with all four AQLQ subscales.

Comparative EQ-5D data were available on51.5% (n = 67) of the ITT population, and 51.4% (n = 54) of the PP population. General health, as estimated by the EQ-5D visual analogue scale, increased significantly in the ITT (mean[SD] difference 14.22[20.99]), and PP populations (15.82[20.41]) (both P < 0.001) (Fig. 4). EQ-5D utility scores also increased significantly in the ITT (mean[SD] improvement 0.14[0.23]), and PP populations (0.15[0.24]) (both P < 0.001). In addition, 56.7% of the ITT population (P = 0.012) and 57.6% of the PP population (P = 0.019) had minimally important improvements in EQ-5D utility (≥ 0.074).

Figure 3. Improvement in asthma-related quality of life during omalizumab treatment: Mean absolute change in AQLQ scores during treatment with omalizumab relative to baseline for the intent-to-treat population. Clinically meaningful improvement in AQLQ score (≥ 0.5 points) marked by dashed line. 16-week n = 147, 52-week n = 122. All P values <0.01 relative to baseline. Abbreviations: AQLQ = asthma quality of life questionnaire.



Figure 4. Improvements in EQ-5D utilities and general health during treatment with omalizumab. Changes in Belgian (Flemish) population norm-weighted EQ-5D utilities and general health (as measured by the VAS) for the intent-to-treat population (n = 67). Average change represented as mean (95% confidence interval). P value indicates significance of paired t-test. Abbreviations: EQ-5D = European quality of life questionnaire, VAS = visual analogue scale.



Exacerbations at 52 weeks

During the 12 month duration of the study, 44 (34.4%) in the ITT population had at least one PERSIST severe exacerbation. In the ITT population, 65.6% were PERSIST severe exacerbation-free during the 12 month

duration of the study (P < 0.001). During the duration of the study, 34 (33%) of the PP population had at least one PERSIST severe exacerbation. 66.0% of the PP population was PERSIST severe exacerbation-free during the 12 month duration of the study (P < 0.001). Compared to the one year prior to omalizumab treatment, exacerbation rates were substantially reduced during treatment (Fig. 5).

Figure 5. Comparison of annual severe exacerbation rates on omalizumab: Annual PERSIST severe exacerbation rates during the 52 weeks of treatment with omalizumab compared to annual severe exacerbation rates during the 52 weeks preceding treatment. ITT n = 130; PP n = 105. Abbreviations: ITT = intent-to-treat population, PP = per-protocol population.



Treatment patterns

62% of patients were started on omalizumab injections every 2 weeks (Q2W), while the remainder (38%) started on a 04W regimen. The mean[SD] Q2W dose was 314.54[63.4] mg, while the average 04W dose was 247.5[73.46] mg. The total average starting monthly dose was 484.18[215.58] mg. The modal regimen (29.1%) was 375 mg Q2W.

Deviations from recommended treatment

Potential under-prescribing occurred in 36 participants (22.8%); 30 study participants (18.9%) were started on omalizumab despite having a weight and/or IgE levels above the recommended range, and 6 study participants (3.8%) were started on a lower dose than recommended (including one who also was started at a lower frequency than recommended). The most common reasons for starting these patients on omalizumab were severity of disease or the prescribing physician's perceived therapeutic benefit. Potential over-prescribing occurred in four participants (2.5%); two had IgE levels lower than the reimbursement criterion (<76 IU/mL), one was started on a higher dose and one was started at a higher frequency than recommended. After 16 weeks of treatment, one patient was changed to 300 mg Q3W, and one to 450 mg Q2W. Both of these regimens differed from prescribing guidelines. Additionally, at 16 weeks, 27 patients (20.8%) were continued on baseline omalizumab dosing, despite baseline IgE and/or a 16-week weight above the dosing range. There was no significant difference in the change in GINA classification, GETE rating, indices of QoL, or frequency of exacerbations or healthcare visits comparing patients with IgE levels \leq 700 IU/mL and those with IgE levels >700 IU/mL at 16-weeks or 52-weeks of treatment (all *P* values >0.05) (data not shown).

Concomitant medication reduction

Over 52 weeks, 24 patients (18.45%) had methylpredniso-lone discontinued altogether and there was a 39.4% reduction in the average daily dose of methylprednisolone (7.31 [13.86] mg, P < 0.001). There was a 10.1% reduction in the average daily dose of budesonide (mean[SD] reduction 94.14[352.48] meg, P = 0.047), a 9.6% reduction in the average daily dose of formoterol (3.03[11.16] mg, P = 0.038). Additionally, leucotriene antagonists were discontinued in 9 (Wilcoxon signed ranks P = ns), anticholinergics in 11 (P = 0.013), antihistamines in 6 (P = ns), and theophylline/derivatives in 5 patients (P = ns).

Safety and tolerability

Overall, 55.6% (n = 89) of patients treated with omalizumab experienced at least one adverse event (AE). The majority of AEs reported were consistent with the omalizumab scientific leaflet. That is, nearly half of all AEs (46%) were respiratory disorders, especially asthma exacerbations and respiratory infections compatible with the course of the underlying disease or concurrent infections. Individual AEs with a frequency \geq 5% included cutaneous or subcutaneous disorders (not local), vascular disorders, headache, cough, immune disorders (facial edema, tight throat), tiredness, and gastrointestinal disorders. 39 patients (24.4%) experienced severe AEs mainly related to asthma exacerbations or other respiratory complications; 12 patients (7.5%) had severe AEs suspected to be related to omalizumab. There were 19 (12.0%) omalizumab discontinuations due to AEs (Table 5). Four patients died during the study periods; none of those deaths was attributed to omalizumab. One of them was discussed previously.¹⁶

Healthcare utilization

Overall, incidences of asthma-related healthcare utilization decreased during the 52 weeks of the study compared to the preceding year. 74 of 126 study participants (58.7%) had fewer healthcare visits (defined as general practitioner visits; specialist visits; emergency room visits; and hospitalizations) during the study than the previousyear. Over the 52-week treatment with omalizumab, there was a mean[SD] reduction of 1.49[7.56] healthcare visits (P = 0.028). There was a reduction in total healthcare utilization of 18.68% in the ITT population, and of 22.9% in the PP population. 47 study participants had seen general practitioners prior to and during the study. Over the course of the 52-week treatment with omalizumab, there was a mean[SD] reduction of 3.72[6.09] GP visits (P < 0.001). 117 participants had seen specialist prior to and during the study. There was a nonsignificant trend favoring a mean [SD] increase of 0.829[4.80] specialist visits (P = 0.064). Included in this analysis are all visits including appointments for omalizumab injections; thus, the increase in specialist visits can be explained, at least in part, by the way omalizumab is prepared and administered. There were decreasing trends observed in both emergency visits and hospitalizations, but neither reached statistical significance.

Discussion

During the PERSIST study, we observed the therapeutic effectiveness of omalizumab prescribed as add-on therapy to treat severe persistent allergic asthma in routine medical practice in Belgium. During this study, physician-rated effectiveness was good or excellent in the vast majority of patients studied. In addition, we observed significant improvements in QoL and lung function, as well as significant reductions in severe asthma exacerbations and the frequency of daytime and nighttime symptoms. Moreover, there were reductions in incidence and rates of healthcare utilization in the majority of patients studied.

In most instances, the proportion of participants responding to treatment with omalizumab was greater than anticipated in reference to the results of large efficacy^{5,6,8} and open-label studies.^{9,10} Specifically, the PERSIST study shows better physician-rated effectiveness,^{5,8} greater improvements in OoL,^{5,9,15} and more pronounced reductions in exacerbation rates than previously reported.^{5,10,15,17} Further, reductions in healthcare utilization were superior than previously reported.^{5,10,17} These differences in effectiveness may be due, at least in part, to the fact that participants selected for treatment with omalizumab by their prescribing physician and included in this study presented with a greater asthma severity compared with the samples of other efficacy and other observational studies. For example, in comparison to INNOVATE⁵ and in part to an analysis of a merged sample of 2511 patients,¹⁷ subjects in PERSIST were older, had worse baseline pulmonary function, higher levels of IgE, and more were taking maintenance oral corticosteroids. Moreover, compared to the sample of a recent effectiveness study,⁹ participants in PERSIST were 10 years older on average, had a longer asthma duration and therefore had worse baseline pulmonary function. In general, our sample characteristics indicate a patient segment with more severe pathology compared to the samples of other studies of omalizumab perhaps leading to the possibility of greater improvements observed in this study.

The patients in PERSIST had a worse QoL at baseline compared to those in INNOVATE.⁵ In fact, baseline QoL (as assessed by both the AQLQ and EQ-5D) was comparable to that during an exacerbation requiring oral corticosteroids in a study of asthma patients from the United Kingdom.¹⁸ Perhaps the higher than expected effectiveness of omalizumab in this study reflects a sample of patients who had more therapeutic benefit to gain than those in prior efficacy and effectiveness studies. Higher levels of medication compliance with omalizumab injections (administered by medical providers) compared to other patient-administered asthma medication also may have been a factor in overall therapeutic effectiveness.

For most of the treating physicians, this study was their first experience with omalizumab outside of the confines of a clinical trial. Thus, participating physicians may have selected patients with more to gain from a new and effective severe asthma treatment. When omalizumab has been available for a longer period of time, the composition of participant characteristics will be interesting to trend. There were also several variations observed in omalizumab dosing, including several instances of IgE levels above and below the dosing guidelines, and failure to adjust per patient weight. But, these deviations in prescribing patterns likely reflect use of omalizumab in a naturalistic setting. Overall, the results reported herein suggest that omalizumab is effective in improving lung function and frequency of asthma symptoms, improving QoL, reducing exacerbations, reducing use of oral corticosteroids and reducing healthcare utilization under the conditions of real-life clinical practice and real-patient heterogeneity.

Study limitations and implications thereof PERSIST was an observational, open-label, pharmaco-epidemiologic study, not a randomized, controlled trial. Although in general, observational studies do not overestimate treatment effects,^{19,20} our study has limitations and revealed areas where more clarity is needed. For example, future research is needed to validate, if not extend, our findings regarding physician-rated effectiveness, as well as improvements in QoL, exacerbation rates and healthcare utilization that were greater in this heterogeneous population than reported in recent studies of omalizumab. However, it is likely that the reduction in healthcare utilization following omalizumab use has been underestimated due to the retrospective (as opposed to prospective) healthcare resources data collection for the one year period preceding omalizumab use. This study was conducted in one European country; thus, multi-national and multi-cultural follow-on studies are necessary. Further, this study, though adequately powered, was not a population-based study. Thus, despite efforts to ensure population representativeness, patient selection based on physician perceived benefit may have been a factor.

Conclusion

Patients selected to be treated with omalizumab by physicians under "real-life" treating conditions in Belgium had a longer asthma duration and presented with a greater asthma severity in comparison to patients of other trials/ studies. Significant improvements were observed in pulmonary function and the frequency of daytime and nocturnal symptom, physician-rated global effectiveness, QoL and rate of asthma exacerbation. Overall, the study results provide evidence that omalizumab is effective as add-on therapy in the management of severe persistent allergic asthma.

Conflict of Interest Statement

Brusselle G. has, within the last 5 years, received honoraria for lectures from Astra-Zeneca, Boerhinger-Ingelheim, GlaxoSmithKline, MerckSharp and Dohme, Novartis, Pfizer and UCB; he is member of advisory boards for Astra-Zeneca, GlaxoSmithKline, Novartis and UCB. Michils A., Louis R. and Dupont L. are members of the advisory board of omalizumab for Novartis. Van de Maele B., Delobbe A., and Pilette C. do not have financial relationships with commercial entities that have an interest in the subject of this manuscript. Gurdain S., Vancayzeele S., Lecomte P., and Hermans C. are employees of Novartis Pharma. As employees of Matrix45 and The Epsilon Group prior to that, Abraham I., and MacDonald K., have consulted with, received research grants and contracts from, and/or served as a sponsored speaker for the following companies and, as applicable, their subsidiaries: Novartis, Johnson & Johnson (incl. Centocor, Ortho-Biotech, Janssen Pharmaceutica, Janssen-Cilag, Janssen-Ortho), Eli Lilly, Roche, Pfizer, Amgen, Merck, Bristol-Myers Squibb, Schering-Plough, Astra-Zeneca, Bayer, GlaxoSmithKline, Lundbeck, and Innogenetics (incl. Xcellentis). Lee C.S., and Song M. are employees of Matrix45. As per company policy, Matrix45 employees are barred from holding equity in any client companies and are subjected to internal and external review of their work to assure objectivity and transparency.

Role of the funding source

Funding: This study was supported by Novartis in the form of contracts to Matrix45 for: study design, protocol development, development of study materials, study implementation, data management, statistical analysis, interpretation of findings, manuscript preparation, and prior dissemination through abstracts and poster presentations. *Role of sponsor*. Omalizumab was approved for use in Belgium in October 2005, and reimbursement was granted in the second half of 2006 as a Class I medication. This requires the manufacturer to submit to health authorities follow-up pharmaco-epide-miologic, pharmacovigilance, and pharmacoeconomic data; based upon which further reimbursement decisions will be made. To this end, Novartis commissioned an independent third party (Matrix45) to design, implement, and analyze the PERSIST study reported here. The original study concept was presented to Sponsor by Abraham I. and MacDonald K. Sponsor had advisory input

in all subsequent stages of the study process; however any final decisions regarding design, statistical analysis, interpretation of findings, and dissemination were made by Brusselle G., Lee C.S., MacDonald K., and Abraham I. The role of sponsor-related authors was limited to critical review of the manuscript for intellectual content. Sponsor-related authors were entitled to review and comment only and refrained from any undue influence throughout the study. The manuscript was shared with other employees of Novartis for review and comment. All final content decisions were made by the external authors.

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References

1. Braman SS. The global burden of asthma. Chest 2006 Jul;130 (1 Suppl):4S-12S.

2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008 Jan;**31**(1):143-78.

3. Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007 Dec; **120**(6): 1360-7.

4. de Marco R, Cazzoletti L, Cerveri I, Corsico A, Bugiani M, Accordini S, et al. Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma. *Int Arch Allergy Immunol* 2005 Nov;**138**(3):225-34.

5. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005 Mar;**60**(3):309-16.

6. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-lgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001 Aug;**18**(2):254-61.

7. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-lgE antibody, in patients with allergic asthma. *Chest* 2004 Apr; **125**(4): 1378-86.

8. Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F, et al. The anti-lgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J* 2002 Nov;**20**(5):1088-94.

9. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respir Med* 2008 Oct;**102**(10):1371-8.

10. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med* 2008 Jan; **102**(1):71-6.

11. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004 Oct 15;**170**(8):836-44.

12. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992 Feb;**47**(2):76-83.

13. EQ-5D Value Sets. In: Szende A, Oppe M, Devlin N, editors. Inventory, comparative review and user guide. New York: Springer; 2007.

14. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005 Aug; **14**(6): 1523-32.

15. Price D. The use of omalizumab in asthma. Prim Care Respir J 2008 Jun;17(2):62-72.

16. Pilette C, Coppens N, Houssiau FA, Rodenstein DO. Severe serum sickness-like syndrome after omalizumab therapy for asthma. J Allergy Clin Immunol 2007 Oct;**120**(4):972-3.

17. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-lgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005 Mar;**60**(3):302-8.

18. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J* 2007 Feb; **16**(1): 22-7.

19. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000 Jun 22; **342**(25): 1878-86.

20. Concato J, Shah N, Horwitz Rl. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000 Jun 22;**342**(25):1887-92.