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Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO

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ABSTRACT

Background: Patients included in clinical trials do not necessarily reflect the real-world population.

Objective: To understand the characteristics, including disease and comorbidity burden, of patients with asthma receiving omalizumab in a real-world setting.

Methods: The Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) was a US-based, multicenter, single-arm, and prospective study. Patients (≥ 12 years of age) with allergic asthma initiating omalizumab treatment based on physician-assessed need were included and followed for 12 months. Exacerbations, health care use, adverse events, and Asthma Control Test (ACT) scores were assessed monthly. Biomarkers (blood eosinophils, fractional exhaled nitric oxide, and periostin) were evaluated and patient-reported outcomes (Asthma Quality of Life Questionnaire for 12 Years and Older [AQLQ+12] and Work Productivity and Activity Impairment: Asthma questionnaire [WPAI:Asthma]) were completed at baseline and months 6 and 12. The Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) was completed at baseline and 12 months.

Results: Most of the 806 enrollees (91.4%) were adults (mean age 47.3 years, SD 17.4), white (70.3%), and female (63.5%). Allergic comorbidity was frequently reported (84.2%), as were hypertension (35.5%) and depression (22.1%). In the 12 months before study entry, 22.1% of patients reported at least 1 asthma-related hospitalization, 60.7% reported at least 2 exacerbations, and 83.3% reported ACT scores no higher than 19 (uncontrolled asthma). Most patients had low biomarker levels based on prespecified cut-points. Baseline mean patient-reported outcome scores were 4.0 (SD 1.4) for AQLQ+12, 2.7 (SD 1.4) for MiniRQLQ, and 47.7 (SD 28.9) for WPAI:Asthma percentage of activity impairment and 33.5 (SD 28.7) for percentage of overall work impairment.

Conclusion: The population initiating omalizumab in PROSPERO reported poorly controlled asthma and a substantial disease burden.

Trial Registration: ClinicalTrials.gov Identifier: NCT01922037.

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Introduction

Asthma is recognized as a heterogeneous inflammatory disease of the airways,¹ and new data enhance the understanding of asthma phenotypes. Type 2 asthma biomarkers, including peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO), serum periostin, and immunoglobulin E (IgE), have been evaluated in the context of identifying patients likely to respond to new and emerging asthma biologics.^{2–11} However, the applicability of these biomarkers in a real-world setting is unknown. Despite the availability of new biologic therapies for patients with uncontrolled persistent asthma, the population of patients who could benefit from a given therapy remains unclear, especially because different patient populations were enrolled in the pivotal trials investigating each biologic.^{4,10,12,13} In addition, at the time of the design and conduct of the omalizumab pivotal studies,^{14,15} type 2 biomarkers were not yet identified or applied to the identification of asthma phenotypes. Limited data are currently available on type 2 biomarker profiles of patients eligible for omalizumab treatment.¹⁶

Omalizumab is indicated for patients at least 6 years of age with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS).¹⁷ It was the first monoclonal antibody approved for the treatment of asthma in the United States and more than 14 years of patient data are available from a large number of randomized controlled clinical trials looking at different end points.^{14,15,18,19} Although these studies have contributed significantly to our understanding of the efficacy and safety of omalizumab, the strict predefined inclusion and exclusion criteria required of such trials mean participants might not reflect real-world patients who often have significant comorbidities and different levels of disease severity that would have excluded them from trial participation. As a result, data on the real-world effectiveness of omalizumab are limited.

The Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) was designed to improve understanding of the safety and efficacy of omalizumab in a real-world setting and to determine whether baseline clinical characteristics, including biomarkers, are associated with different individual and composite clinical outcomes. It had 2 goals to address known knowledge gaps in patients with asthma: (1) to understand the types of patients who initiate omalizumab in a real-world setting, including identifying patient characteristics, unmet needs, disease burden, and disease phenotypes from an omalizumab-eligible patient population—knowledge that cannot be obtained outside a study such as the present one; and (2) to understand how reported clinical parameters might be associated with distinct outcomes.

The focus of the present analyses is on the first goal; we describe the design of PROSPERO and the clinical characteristics, including asthma burden, comorbidities, and biomarker profiles, of patients with asthma who were enrolled. Because entry into the study was based on physician assessment of need and access to omalizumab, it was assumed that the patients enrolled would likely reflect the type of patients who initiate omalizumab in the real-world setting. Data related to the second goal will be published separately. The goal of this publication is to present data that enhance the understanding of the types of patients who initiate omalizumab in a real-world setting, including identifying unmet needs, disease burden, and asthma phenotypes.

Methods

PROSPERO was a US-based, multicenter, prospective, 12-month, treatment-based study that included patients at least 12 years of

age with asthma who initiated treatment with omalizumab prescribed by an allergist or a pulmonologist ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01922037) identifier NCT01922037). Patients were enrolled from 120 academic centers and community sites from June 2013 through March 2015. Patients were followed from study entry to a maximum of 12 months.

The primary objective of PROSPERO was to evaluate efficacy and safety outcomes of omalizumab treatment in a real-world setting and to identify clinical characteristics or biomarkers that could indicate treatment response.

During the 12 months of study, evaluation and treatment were dependent on the investigator's standard of practice and discretion. No treatment regimen was specified in the protocol.

All patients were required to sign institutional review board–approved informed consent. The study was conducted according to the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, US Food and Drug Administration regulations, and any applicable local, state, and national laws.

Eligibility

Enrollment in PROSPERO required physician identification of each patient as a candidate for treatment of allergic asthma with omalizumab. Minimal inclusion and exclusion criteria were by protocol defined to allow the physician to use clinical judgment to identify appropriate candidates for omalizumab treatment. Adolescents at least 12 years of age and adults with allergic asthma who initiated treatment with omalizumab and had not received omalizumab within the previous year were eligible for the study. Access to omalizumab through insurance or other funding was required. Patients who had a prior allergic reaction to omalizumab or who had received an experimental drug within 3 months of study enrollment were excluded.

Assessments

The study includes 3 main assessment points: baseline, 6 months, and end of study or early termination (eTable 1). Before the first dose of omalizumab, baseline demographics, medical history, current medication use, patient-reported outcomes (PROs), biomarker assessments, and pulmonary function test data were collected. Physician-assessed asthma severity (mild, moderate, or severe) was recorded at baseline. Prespecified or guideline criteria for these classifications were not provided to physicians to aid in their assessment.

Blood samples were drawn for complete blood cell count and differential, total and specific IgE, and periostin and sent to a designated central laboratory for analysis and/or storage. Periostin was measured using the Elecsys Periostin Immunoassay (Roche Diagnostics, Penzberg, Germany). Specific IgEs measured were *Alternaria tenuis*, *Aspergillus fumigatus*, cat dander, mountain cedar, American cockroach, dog dander, grass mix 2 (Bermuda grass, perennial rye grass, timothy grass, Kentucky blue grass, Johnson grass, Bahia grass), juniper mix (Berry, Rocky, Oneseed), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, mouse epithelium, ragweed, and staphylococcal enterotoxin.

Fractional exhaled nitric oxide was measured using a hand-held portable device (NIOX MINO; Aerocrine, Solna, Sweden) in accordance with American Thoracic Society and European Respiratory Society guidelines.²⁰ Spirometry evaluations were performed in accordance with American Thoracic Society guidelines.²¹ Three acceptable maneuvers were performed at each time point and the highest values were recorded in the electronic data capture system.

Patients reported their asthma-related quality of life using the Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ+12). The AQLQ+12 encompasses 4 domains: activity

limitations, symptoms, emotional function, and environmental stimuli.²² AQLQ+12 scoring ranges from 1 (severe impairment) to 7 (no impairment).²² The minimally important difference is 0.5.²³ The AQLQ+12 was completed at baseline, 6 months, and 12 months.

Patients reported asthma-related work productivity and activity impairment using the Work Productivity and Activity Impairment: Asthma questionnaire (WPAI:Asthma). The WPAI:Asthma describes percentage of impairment on a scale from 0% to 100%; high scores indicate high impairment.²⁴ The WPAI:Asthma was completed at baseline, 6 months, and 12 months.

The Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) assesses functional impairments that are troublesome to patients with seasonal or perennial rhinoconjunctivitis.²⁵ MiniRQLQ scores range from 0 (not troubled) to 6 (extremely troubled). The minimally important difference for the MiniRQLQ is 0.4.²⁶ MiniRQLQ was completed at baseline and month 12.

Patient asthma symptom control was assessed monthly using the Asthma Control Test (ACT), a 5-item questionnaire that assesses asthma impact on home and work activities, shortness of breath, symptoms, rescue medication usage, and overall asthma control.²⁷ In line with the National Heart, Lung, and Blood Institute terminology, ACT scores of at least 20 indicate well-controlled asthma, scores 16 to 19 suggest asthma is not well controlled, and scores no higher than 15 indicate asthma that is very poorly controlled.²⁸ The minimally important difference for the ACT is 3.²⁹ The ACT was completed monthly.

On a monthly basis, patients reported concomitant medications, exacerbations (worsening of asthma symptoms requiring the use of oral corticosteroids, an emergency department visit, or hospitalization) and asthma-related urgent health care usage (eg, hospitalization, acute care, and emergency department visits). Adverse events also were captured throughout the study.

Statistical Analysis

Summary statistics were used for demographic and clinical characteristics. The presence of patient-reported asthma comorbidities was summarized as individual conditions and a grouping of allergic conditions (allergic rhinitis, eczema and atopic dermatitis, food allergy, allergic conjunctivitis, seasonal allergy, prior anaphylactic reaction, nasal polyps³⁰). The following cutoff points were used to stratify patients by biomarker status: FeNO³¹ (<25 vs ≥25 ppb), eosinophils³² (<300 vs ≥300 cells/μL), and periostin (<50 vs ≥50 ng/mL).⁹ Because periostin measurements have been challenging to interpret in adolescents, owing to the confounding contributions of periostin produced by osteoblasts during growth,³³ no predefined cutoffs were specified for adolescents. Correlation coefficients were calculated among PROs, lung function, and biomarkers. Pearson *R* test was used to calculate correlation coefficients among PRO scores and between PRO scores and lung function. Spearman rank-order test was used to determine how eosinophils, FeNO, and periostin correlate with total IgE and how all these biomarkers correlate with airway reversibility (as measured by percentage of change from pre- to postbronchodilator forced expiratory volume in 1 second [FEV₁]), ACT scores, and AQLQ+12 scores.

Results

Baseline Demographics and Clinical Characteristics

Patients (*n* = 806) were 12 to 100 years of age (mean 47.3, SD 17.4); 8.6% (*n* = 69) were adolescents; and 91.4% (*n* = 737) were at least 18 years of age (Table 1). Enrollees were primarily white (adolescents, 58.0%; adults, 71.5%). The adolescent population was predominantly male (63.8%), whereas the adult population was

predominantly female (66.1%). Median total IgE was 506.7 IU/mL (range 2.9–68,628.0) in adolescents and 175.4 IU/mL (range 1.1–8659.2) in adults. Mean pre-bronchodilator FEV₁ was 87.9% (SD 16.9) of predicted in adolescents and 74.2% (SD 20.6) of predicted in adults; bronchodilator reversibility was 7.9% in adolescents and 8.0% in adults; mean postbronchodilator FEV₁ was 93.6% (SD 16.4) of predicted in adolescents and 78.9% (SD 19.5) of predicted in adults; overall, 28.4% of patients had a postbronchodilator ratio of FEV₁ to forced vital capacity lower than 0.7. Most investigators prescribing omalizumab in this study were allergists; however, 123 of 801 patients (15.4%) were prescribed omalizumab by a pulmonologist.

Asthma Burden at Study Entry

At study entry, physicians classified patients as having mild (4.1%), moderate (48.1%), or severe (47.8%) asthma (Table 1). Almost all patients (99.3%) reported use of at least 1 asthma medication before study entry; patients might have been prescribed more than 1 formulation containing an ICS. In the 12 months before omalizumab initiation, most patients (82.4%) had received at least 1 treatment with combinations of an ICS and a long-acting β -agonist (LABA), 64.4% had received a leukotriene receptor modifier, and 34.2% had received an ICS not in combination with another medication (Table 1). A total of 46.4% of patients reported the use of systemic corticosteroids (chronically or for exacerbation management) 90 days before or on the day of study entry. For drug combinations, of the 696 patients receiving ICS and/or LABA (separately or in combination), 115 (16.5%) received only ICS and/or LABA, 223 patients (32.0%) received ICS and/or LABA and leukotriene receptor agonist, 96 (13.8%) received ICS and/or LABA and LTRA with supplemental ICS, 87 (12.5%) received ICS and/or LABA with leukotriene receptor agonist and an anticholinergic, 87 (12.5%) received ICS and/or LABA, leukotriene receptor agonist, and an anticholinergic with supplemental ICS, 35 patients (5.0%) received ICS and/or LABA and an anticholinergic, 31 (4.4%) received ICS and/or LABA with supplemental ICS, and 22 (3.2%) received ICS and/or LABA and an anticholinergic with supplemental ICS.

Patients reported a mean of 3.0 (SD 3.3) asthma exacerbations and 22.1% reported at least 1 asthma-related hospitalization in the 12 months before study entry. Most patients (83.8%) reported not well-controlled asthma (ACT score ≤19), and 61.0% of patients reported very poorly controlled asthma (ACT score ≤15; Fig 1). Mean ACT score was 16.4 (SD 5.1) in adolescents and 13.7 (SD 4.9) in adults.

Health-Related Quality of Life and Work and Activity Impairment at Baseline

Sixty-nine adolescents and 732 adults completed the AQLQ+12. Scores ranged from 1.2 to 6.8 in adolescents and from 1.0 to 7.0 in adults. Mean AQLQ+12 score was 4.7 (SD 1.3) in adolescents and 3.9 (SD 1.3) in adults (Table 2).

Sixty-eight adolescents and 732 adults completed the MiniRQLQ. Scores ranged from 0.0 to 6.0 in adolescents and from 0.0 to 5.9 in adults. Mean MiniRQLQ quality-of-life score was 2.4 (SD 1.4) in adolescents and 2.8 (SD 1.4) in adults (Table 2).

Sixty-seven adolescents and 717 adults completed the WPAI:Asthma percentage of activity impairment. Scores ranged from 0.0 to 100.0 in adolescents and adults. Mean WPAI:Asthma percentage of activity impairment was 36.1 (SD 27.6) in adolescents and 48.8 (SD 28.8) in adults (Fig 2). Three adolescents and 387 adults completed the WPAI:Asthma percentage of overall work impairment. Scores ranged from 0.0 to 49.1 in adolescents and from 0.0 to 100.0 in adults. Mean WPAI:Asthma percentage of overall work impairment score was 20.9 (SD 25.4) in adolescents and 33.6 (SD 28.7) in adults (Fig 2).

Table 1
Demographics and Clinical Characteristics at Baseline

Characteristic	12–17 y of age (n = 69)	≥18 y of age (n = 737)	All patients (N = 806)
Age (y), mean (SD)	14.0 (1.7)	50.4 (14.8)	47.3 (17.4)
Female, n (%)	25 (36.2)	487 (66.1)	512 (63.5)
Race, n (%)			
White	40 (58.0)	527 (71.5)	567 (70.3)
Black	23 (33.3)	109 (14.8)	132 (16.4)
Asian	1 (1.4)	33 (4.5)	34 (4.2)
Other	5 (7.2)	68 (9.2)	73 (9.1)
Weight (kg), mean (SD) ^a	63.1 (23.6)	87.5 (23.2)	85.4 (24.2)
BMI ≥30 kg/m ² , n (%) ^a	12 (17.4)	378 (51.4)	390 (48.5)
Smoking status, n (%) ^a			
Current	0	42 (5.7)	42 (5.2)
Former	1 (1.4)	238 (32.4)	239 (29.7)
Never	68 (98.6)	455 (61.9)	523 (65.0)
Age at asthma diagnosis (y), mean (SD) ^b	4.4 (3.9)	26.7 (20.6)	24.8 (20.7)
Physician-assessed asthma severity, n (%) ^c			
Mild	3 (4.3)	30 (4.1)	33 (4.1)
Moderate	31 (44.9)	356 (48.4)	387 (48.1)
Severe	35 (50.7)	350 (47.6)	385 (47.8)
Pre-bronchodilator % predicted FEV ₁ , mean (SD) ^d	87.9 (16.9)	74.2 (20.6)	75.4 (20.6)
Postbronchodilator % predicted FEV ₁ , mean (SD) ^e	93.6 (16.4)	78.9 (19.5)	80.2 (19.7)
Postbronchodilator FEV ₁ /FVC % predicted <0.7, n (%) ^f	11 (16.7)	210 (29.5)	221 (28.4)
Asthma exacerbations in past 12 mo, n (%)			
0	16 (23.2)	182 (24.7)	198 (24.6)
1	7 (10.1)	110 (14.9)	117 (14.5)
≥2	46 (66.7)	443 (60.1)	489 (60.7)
Asthma exacerbations in past 90 d, n (%)			
0	37 (53.6)	343 (46.5)	380 (47.2)
1	19 (27.5)	200 (27.1)	219 (27.2)
≥2	13 (18.8)	192 (26.1)	205 (25.4)
Asthma-related hospitalizations in past 12 mo, n (%) ^g	19 (35.2)	159 (29.2)	178 (29.8)
History of intubation from asthma exacerbation, n (%) ^c	1 (1.4)	74 (10.1)	75 (9.3)
Seasonal variability of asthma exacerbations, n (%) ^c	56 (81.2)	518 (70.4)	574 (71.3)
Allergen sensitization, n (%)			
1	7 (10.8)	62 (9.3)	69 (9.4)
2	5 (7.7)	82 (12.3)	87 (11.9)
≥3	52 (80.0)	492 (73.8)	544 (74.3)
Past use of allergen immunotherapy, n (%) ^c	39 (56.5)	419 (56.9)	458 (56.9)
Concomitant or ongoing asthma medication use, n (%) ^h			
Short-acting β-agonist	63 (91.3)	659 (89.4)	722 (89.6)
ICS not in combination	23 (33.3)	253 (34.3)	276 (34.2)
ICS + LABA ⁱ	57 (82.6)	607 (82.4)	664 (82.4)
Leukotriene receptor modifier	48 (69.6)	471 (63.9)	519 (64.4)
Anticholinergics ^j	8 (11.6)	240 (32.6)	248 (30.8)
Systemic corticosteroids ^k	26 (37.7)	348 (47.2)	374 (46.4)

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β-agonist.

^aPatients at least 18 years of age (n = 735) and all patients (n = 804).

^bPatients at least 18 years of age (n = 733) and all patients (n = 802).

^cPatients at least 18 years of age (n = 736) and all patients (n = 805).

^dPatients 12 to 17 years of age (n = 67), at least 18 years of age (n = 728), and all patients (n = 795).

^ePatients 12 to 17 years of age (n = 65), at least 18 years of age (n = 713), and all patients (n = 778).

^fPatients 12 to 17 years of age (n = 66), at least 18 years of age (n = 713), and all patients (n = 779).

^gPatients 12 to 17 years of age (n = 54), at least 18 years of age (n = 544), and all patients (n = 598).

^hMost common asthma medicines listed; use of other medications such as ICS, theophylline, and LABA also were reported but are not listed here; patients 12 to 17 years of age (n = 69), at least 18 years of age (n = 731), and all patients (n = 800).

ⁱPatients might have been prescribed more than 1 ICS.

^jIncludes tiotropium use in 12–17 years of age, n = 1 (1.4%); ≥18 years of age, n = 136 (18.5%); all patients, n = 137 (17.0%).

^kReflects maintenance use and acute corticosteroid use (eg, steroid burst to manage worsening of asthma and asthma exacerbations).

There was a strong positive correlation between ACT and AQLQ+12 scores ($r = 0.805$; Table 3). The correlation between ACT and WPAI:Asthma scores was moderate to strong and negative ($r = -0.681$). There was a weak positive correlation between ACT or AQLQ+12 score and FEV₁ ($r = 0.260$, $r = 0.225$, respectively).

Allergy and Comorbidity Burden at Baseline

The most frequently reported comorbid conditions, reported by at least 10% of the cohort, were allergic rhinitis, gastroesophageal reflux disease, sinusitis or chronic sinusitis, and hypertension (Fig 3). Most patients (84.2%) reported at least 1 comorbid allergic condition at study entry.

Most patients had polysensitivity. For the panel of specific IgEs measured, 80% of adolescents and 73.7% of adults demonstrated sensitization to at least 3 allergens.

Biomarker Values at Baseline

Median FeNO and eosinophil values were similar in adolescents and adults (Table 4). Median periostin values were approximately 2-fold higher in adolescents than in adults (94.7 vs 51.1 ng/mL, respectively). Median IgE was almost 3-fold higher in adolescents than in adults (506.7 vs 175.4 IU/mL, respectively) and the range was greater in adolescents than in adults. Eosinophil counts showed a right-skewed distribution (Fig 4A). IgE values also

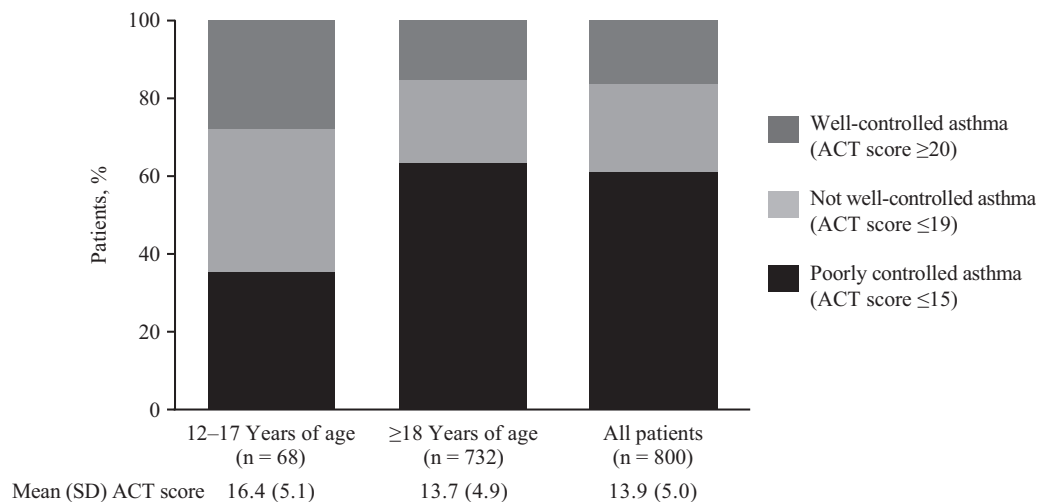


Figure 1. Asthma Control Test (ACT) scores at baseline.

showed a right-skewed distribution (Fig 4B). Based on the chosen biomarker cutoffs, type 2 biomarkers levels were high in less than half the adult population (eosinophils ≥ 300 cells/ μ L, 35.4%; FeNO ≥ 25 ppb, 44.3%; periostin ≥ 50 ng/mL, 44.7%). Of 739 patients with eosinophil, FeNO, and periostin measurements at baseline, 120 (16.2%) had elevations of all 3 biomarkers. Weak correlations were noted among total serum IgE, eosinophils, FeNO, AQLQ+12 score, and airway reversibility at baseline (eTable 2). ACT scores were weakly correlated with IgE levels, eosinophils, and FeNO. There was no clear correlation between periostin and IgE, airway reversibility, or ACT or AQLQ+12 scores.

Discussion

PROSPERO provides a unique opportunity to understand the clinical characteristics of patients initiating omalizumab treatment in a real-world setting. It also allows the assessment of the disease burden and unmet needs of these patients before starting therapy.

Similar to other cohort studies of omalizumab in patients with asthma,^{34,35} patients enrolled in PROSPERO were predominantly white (70.3%) and largely female (63.5%). The adolescent population in PROSPERO was different from adults; only 58.0% were white and 36.2% were female. In the United States, women have a higher asthma prevalence than men (10.7% vs 6.5%) whereas the prevalence of asthma is higher in boys than in girls up to 17 years of age (10.0% vs 7.4%).³⁶ Some patients enrolled in PROSPERO had IgE levels outside the manufacturer's dosing table; it is unlikely that these patients would meet entrance criteria for a randomized clinical trial; thus, they could represent a previously unstudied population. In addition, given the biomarker requirements for entry

into other biologic studies (eg, blood eosinophils >300 cells/ μ L), more than 65% of PROSPERO-enrolled patients could have been excluded from those studies based on the biomarker requirement alone.

Patients enrolled in PROSPERO reported a substantial asthma burden. On average, they experienced 3 exacerbations in the year before study entry, which is higher than is reported in clinical trials of some biologics for asthma—1.9 to 2.1 reported by patients with inadequately controlled asthma⁵ and 2.7 reported by patients with severe uncontrolled asthma⁷—and lower than the 3.5 to 3.8 severe episodes in patients with severe eosinophilic asthma that also have been reported.^{10,13} It is important to note that although exacerbation rates are mentioned for reference, the enrolled populations of these studies differ and true direct comparisons cannot be made. Overall, 55% of patients reported at least 1 asthma-related hospitalization in their lifetime before baseline, with 22.1% reporting an asthma-related hospitalization within the year before study entry, which is higher than reported in the omalizumab pivotal asthma studies and in EXTRA,^{14,15,18} yet lower than the 34% of omalizumab-treated patients enrolled in an international, noninterventional, observational registry who reported at least 1 hospitalization in the 12 months before initiating omalizumab.³⁷ In the present study, almost half the patients had been treated with a systemic corticosteroid at study entry or in the 90 days before enrollment. Data capture methodology precluded us from determining whether use was for a recent asthma exacerbation or as maintenance medication. Before the beginning of omalizumab therapy, this cohort reported poorly controlled asthma as measured by ACT score. PROSPERO enrollees reported a mean score of 12.9 (SD 4.9) at baseline compared with the mean ACT score of 15.0 (SD 4.7) reported by omalizumab initiators in another prospective real-world study of omalizumab (EXCELS).²⁶ In PROSPERO, 61% of patients reported poorly controlled asthma (ACT score ≤ 15) and 26.5% reported not well-controlled asthma (ACT score ≥ 16 and ≤ 19). In EXCELS, for omalizumab initiations, these numbers were 52.0% and 22.9%, respectively.²⁶

Patients who initiated omalizumab reported significant allergy and comorbidity burden. Patients with asthma and comorbid conditions have been associated with severe uncontrolled asthma.³⁸ Almost 75% of patients had a positive reaction for more than 3 allergens (based on specific IgE testing at baseline). Although allergic comorbidities were common (eg, allergic rhinitis [75.3%], food allergy [18.0%], atopic dermatitis [39.1%]), other comorbidities such as gastroesophageal reflux disease (43.6%), hypertension

Table 2
Quality-of-Life Questionnaire Scores at Baseline

Patient-reported outcome	12–17 y of age (n = 69)	≥ 18 y of age (n = 737)	All patients (N = 806)
AQLQ+12, n	69	732	801
Score, mean (SD)	4.7 (1.3)	3.9 (1.3)	4.0 (1.4)
Score, median (IQR)	5.0 (1.7)	3.9 (2.1)	3.9 (2.2)
MiniRQLQ, n	68	732	800
Score, mean (SD)	2.4 (1.4)	2.8 (1.4)	2.7 (1.4)
Score, median (IQR)	2.2 (1.9)	2.7 (2.1)	2.7 (2.2)

Abbreviations: AQLQ+12, Asthma Quality of Life Questionnaire for 12 Years and Older; IQR, interquartile range; MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire.

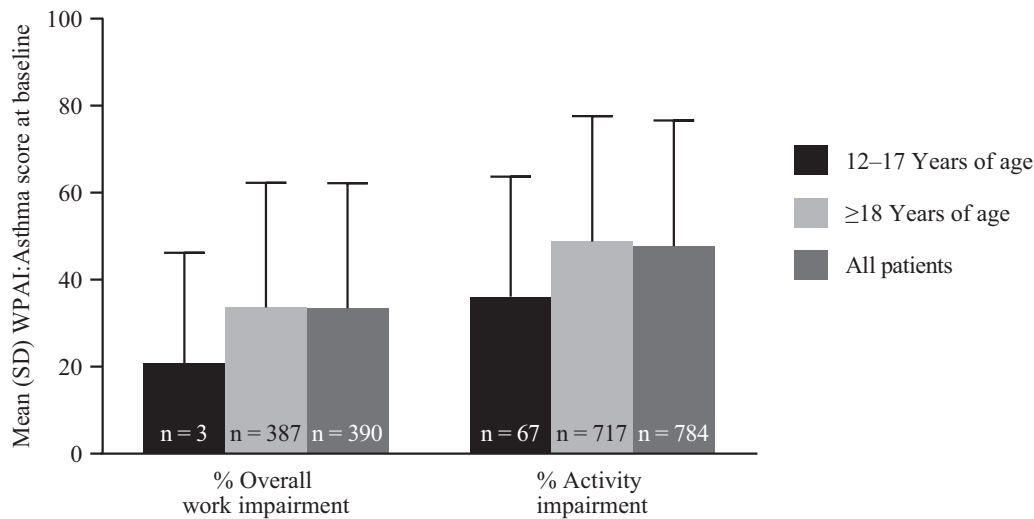


Figure 2. Work Productivity and Activity Impairment: Asthma (WPAI:Asthma) scores at baseline.

(35.5%), depression (22.1%), and anxiety (10.4%) also were present. Allergic comorbidity with asthma is a well-recognized association. Gastroesophageal disease has been documented as a risk factor for poor asthma symptom control³⁹ and severe asthma.⁴⁰ The high rates of hypertension, depression, and anxiety noted in enrolled patients are often overlooked, yet their association with increased asthma severity has been described.^{41–44} Comorbid anxiety and depression also have been associated with poor asthma control.^{45,46} These are important comorbidities and require consideration in the overall management of the patient to achieve asthma control. In addition, almost half the patients were obese (body mass index >30 mg/m²). The association between asthma and obesity is complex.^{47–51} Although some studies have noted that obesity is associated with a higher frequency of asthma exacerbations⁵² and symptoms⁵³ in addition to poor asthma control and increased asthma severity,⁴⁸ other researchers have not found these associations.⁵⁴ Uncontrolled asthma has been noted to contribute to obesity owing to an increased use of corticosteroids^{55–57} or inactivity resulting from a substantial asthma symptom burden.^{58–60} A link between early- and late-onset allergic asthma and obesity has been described.⁶¹

The presence of allergen sensitization can increase health care resource use in adults and children^{62–65} and has been reported to increase the risk of exacerbations in adults.⁶⁶ In addition, the combination of asthma with nonallergic comorbidities, such as depression, increases health care resource use.⁶⁷ Overall, a constellation of chronic conditions (hypertension, obesity, noncompliance, diabetes, and asthma) occur in patients who use proportionally more health care than their counterparts without chronic conditions; this population is expected to increase to 4 million cases by 2022.⁶⁸

Table 3
Correlations^a Between Patient-reported Outcome Scores at Baseline

	ACT	AQLQ+12	MiniRQLQ	WPAI:A	FEV ₁
ACT					
r	1.000	0.805	−0.420	−0.681	0.260
n	800	797	797	781	790
AQLQ+12					
r	0.805	1.000	−0.570	−0.729	0.225
n	797	801	798	782	792
MiniRQLQ					
r	−0.420	−0.570	1.000	0.465	0.018
n	797	798	800	783	791
WPAI:Asthma					
r	−0.681	−0.729	0.465	1.000	−0.223
n	781	782	783	784	776
FEV ₁					
r	0.260	0.225	0.018	−0.223	1.000
n	790	792	791	776	795

Abbreviations: ACT, Asthma Control Test; AQLQ+12, Asthma Quality of Life Questionnaire for 12 Years or Older; FEV₁, forced expiratory volume in 1 second; MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; WPAI:Asthma, Work Productivity and Activity Impairment: Asthma questionnaire.

^aCorrelation coefficients were calculated using the Pearson R test.

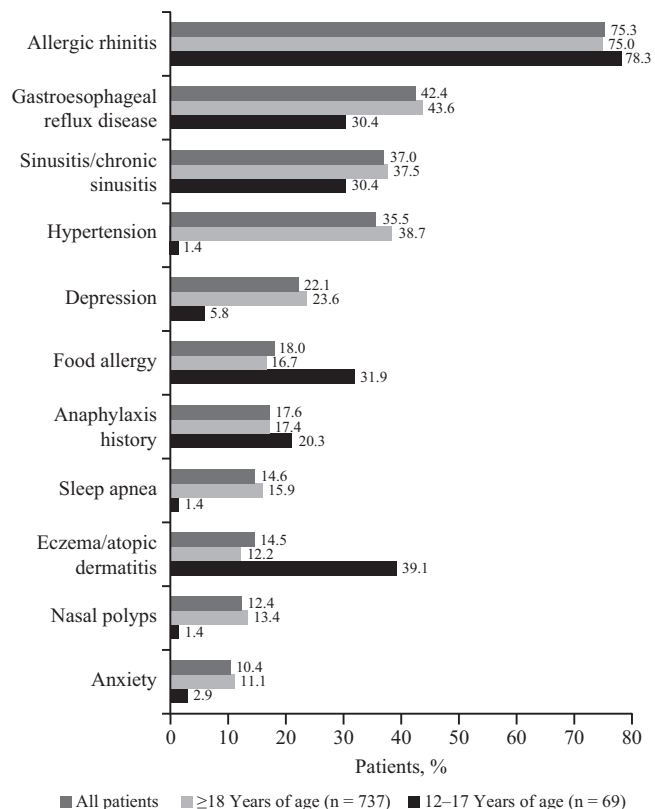


Figure 3. Comorbidities in at least 10% of the overall population at baseline.

Table 4
Biomarker Values at Baseline

Characteristic	12–17 y of age (n = 69)	≥18 y of age (n = 737)	All patients (N = 806)
FeNO (ppb), n	68	722	790
Mean (SD)	38.4 (39.4)	33.9 (33.1)	34.3 (33.7)
Median (IQR)	23.5 (31.5)	22.0 (29.0)	22.0 (29.0)
Eosinophils (cells/ μ L), n	66	711	777
Mean (SD)	316 (210)	295 (260)	297 (256)
Median (IQR)	275 (270)	220 (240)	230 (250)
Periostin (ng/mL), n	65	707	772
Mean (SD)	94.7 (30.7)	51.1 (17.0)	54.7 (22.1)
Median (IQR)	93.3 (47.9)	48.2 (18.5)	49.7 (21.2)
IgE (IU/mL), n	66	722	788
Mean (SD)	1,999.0 (8,544.9)	451.1 (953.8)	580.7 (2,654.8)
Median (IQR)	506.7 (374.2)	175.4 (960.7)	193.3 (402.1)

Abbreviations: FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IQR, interquartile range.

The PRO data suggest that patients experienced substantial limitations in their health-related quality of life. Most adult patients reported an AQLQ+12 score no higher than 3.9; a score no higher than 4 indicates moderate to poor health-related quality of life in adults.⁶⁹ The low score (median 2.9) on the MiniRQLQ at baseline also reflects the significant asthma and comorbidity burden, specifically rhinitis. These poor health-related quality-of-life outcomes corresponded to notable impairment in work and daily activities, reflected in the WPAI:Asthma scores. On average, PROSPERO enrollees reported that their limitations of daily activities reached up to 49% and their work activities were limited up to 35%. In contrast, EXCELS enrollees who initiated omalizumab reported 35% daily activity impairment and 26% work impairment based on the WPAI:Asthma score.²⁶

As expected, AQLQ+12 scores strongly correlated with ACT scores, indicating that patients with very poor asthma control experienced the greatest impairment in quality of life. The strong negative correlation between ACT scores and WPAI:Asthma scores indicates that as asthma control worsens (ACT scores decrease), work productivity and activity impairment increase (WPAI:Asthma scores increase). These results concur with previous publications reporting the highest WPAI:Asthma scores in patients with the worst asthma control.^{70,71} The correlation between ACT score and FEV₁ was weak and insignificant; the presence and absence of a correlation between these measures have been previously reported.^{27,29,72} These findings suggest that asthma affects multiple

aspects of patients' health-related quality of life and limits their ability to work, effectively engage in daily activities, and enjoy their daily life.

Given the disease burden in enrollees described by baseline data, it is not surprising that physicians rated most participants (95.9%) in PROSPERO as having moderate to severe asthma. However, based on their exacerbation rate and ACT scores, most of these patients should have been classified as having severe asthma according to the National, Heart, Lung, and Blood Institute guideline,²⁸ suggesting that (1) physicians were unaware of the guideline; (2) physician classification underestimated the severity of disease in this population; (3) there was a perception that the guideline is not reflective of or easy to apply to real-world patients; or (4) physicians have limited knowledge about assessing asthma severity in patients already on medication because the guideline assesses severity in patients not on medication. In addition, physicians assessed asthma severity as mild in 4.1% of patients. This assessment was subjective and no parameters were provided in the protocol to guide physician designation of disease severity. Because asthma severity is dynamic, these patients might have entered the study being classified as having mild asthma based on their current assessment but might have had seasonal exacerbations in the prior year that would have given them a severe classification. Given that their exacerbation risk was highest in a given season, this might have justified their inclusion in the study to the treating physician.^{73,74}

As expected, IgE levels showed a right-skewed distribution⁶⁶; most patients (76%) had total IgE ranges within the current US prescribing information dosing table.¹⁷ Conditions such as allergic bronchopulmonary aspergillosis or atopic dermatitis likely resulted in a higher mean than was expected. Because mean blood eosinophil counts were consistent with previous omalizumab publications and studies for interleukin-5 target therapies,^{4,5,10,12,13,18} eosinophil levels alone might not be sufficient to determine eligibility for one therapy over another because there is a substantial number of patients with high levels of eosinophils who also have an allergy. Although, on average, patients had FeNO values at baseline that would be classified as intermediate (mean 34.3, SD 33.7), most patients had low FeNO levels (<25 ppb) according to the American Thoracic Society guidelines, with a baseline median value of 22.0 ppb (range 5.0–266.0).

PROSPERO included a population of limited ethnic diversity, who are typically under-represented in clinical trials, and results might not be generalizable to the entire population with asthma. The study also included a relatively small adolescent cohort, and

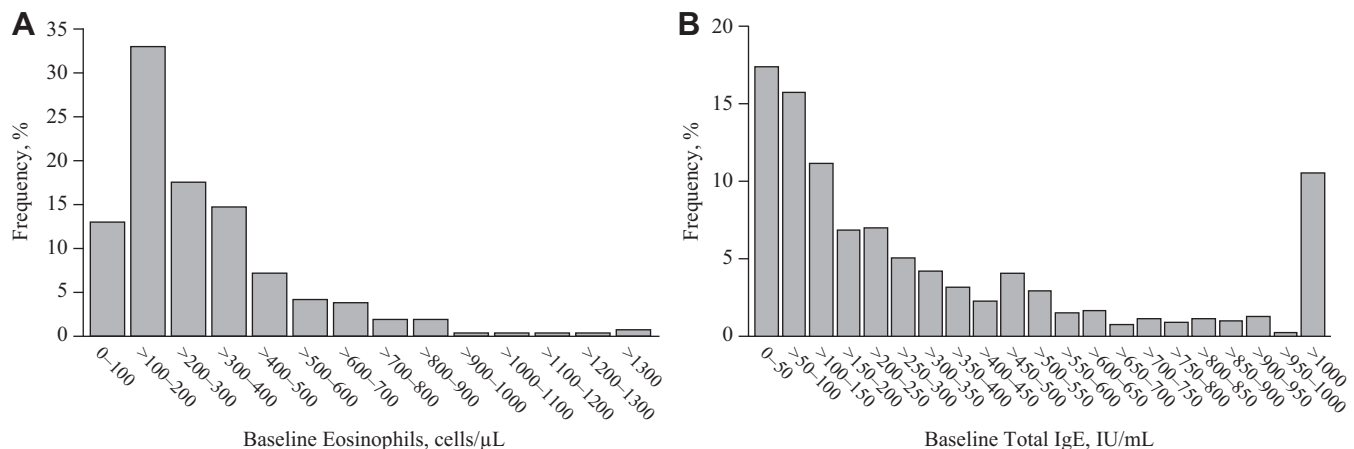


Figure 4. Distribution of (A) eosinophils and (B) immunoglobulin E (IgE) at baseline.

differences noted between adults and adolescents might not be sustained in a larger, more balanced study population. In addition, there was no formal evaluation of therapy adherence beyond omalizumab and a lack of adherence might have had an adverse effect on baseline asthma severity and/or treatment outcomes.

Patients initiating omalizumab as part of PROSPERO reported poorly controlled moderate to severe asthma with substantial work and activity impairment, a burden on other aspects of health-related quality of life, and a heterogeneous biomarker profile. Patients had multiple comorbidities, some of which might have resulted in exclusion from an asthma clinical trial. These data show that there is not a set clinical profile that defines patients initiated on omalizumab treatment, suggesting that the unmet need is patient specific. The analysis of data generated 12 months after initiation of omalizumab therapy will provide insight into real-world post-treatment initiation outcomes and could provide insight into specific outcomes in subgroups of patients with different needs.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2017.09.056>.

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Supplementary Data

eTable 1
PROSPERO Assessment Timing

Data collected	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	End of study (month 12) or early termination
Medical history	X												
Demographic data	X												
Smoking history	X												
Residential and occupational exposure	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Medications used to treat adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests													
CBC with differential	X						X						X
Periostin	X						X						X
Total IgE	X						X						
Specific IgE in vitro	X												
Free IgE													X
Spirometry or pulmonary function tests													
FEV ₁ pre- and postbronchodilator (albuterol 4 puffs)	X						X						X
FVC	X						X						X
FEF _{25–75}	X						X						X
FeNO	X						X						X
Patient-reported outcomes													
AQLQ+12	X						X						X
ACT	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI:Asthma	X						X						X
MiniRQLQ	X						X						X
Exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X
GETE													X

Abbreviations: ACT, Asthma Control Test; AQLQ+12, Asthma Quality of Life Questionnaire for 12 Years and Older; CBC, complete blood cell count; FEF_{25–75}, forced expiratory flow between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GETE, Global Evaluation of Treatment Effectiveness; IgE, immunoglobulin E; MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; WPAI:Asthma, Work Productivity and Activity: Asthma questionnaire.

eTable 2Correlations^a of Biomarkers With Total Serum IgE, Airway Reversibility, ACT Scores, and AQLQ+12 Scores

Measure	IgE (IU/mL)	Eosinophils (cells/ μ L)	FeNO (ppb)	Periostin (ng/mL)
IgE				
r_s	1.000	0.217	0.203	0.058
95% CI	NA	0.1425–0.2888	0.1286–0.2744	–0.0186 to 0.1339
n	677	652	665	656
Airway reversibility				
r_s	0.085	0.161	0.188	0.066
95% CI	0.0085–0.1602	0.0849–0.2354	0.1153–0.2582	–0.0113 to 0.1426
n	658	644	701	643
ACT score				
r_s	–0.089	–0.090	–0.093	0.049
95% CI	–0.1636 to –0.0133	–0.1655 to –0.0135	–0.1669 to –0.0183	–0.0272 to 0.1257
n	670	655	684	654
AQLQ+12 score				
r_s	–0.082	–0.044	–0.065	0.0242
95% CI	–0.1560 to –0.0061	–0.1220 to 0.0324	–0.1392 to 0.0095	–0.0523 to 0.1003
n	675	660	689	659

Abbreviations: ACT, Asthma Control Test; AQLQ+12, Asthma Quality of Life Questionnaire for 12 Years and Older; CI, confidence interval; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; NA, not applicable.

^aCorrelation coefficients were calculated using the Spearman rank-order test.