

Asthma control, lung function, symptoms, and corticosteroid sparing after omalizumab initiation in patients with allergic asthma

Dominic Pilon, M.A.,¹ Abhishek Kavati, Ph.D.,² Benjamin Ortiz, M.D.,² Brandee Paknis, Pharm.D.,² Ashok Vegesna, Pharm.D.,² Bradd Schiffman, M.S.,³ Maryia Zhdanova, M.A.,¹ Patrick Lefebvre, M.A.,¹ and Brian Stone, M.D.³

ABSTRACT

Background: Omalizumab is approved in patients with moderate-to-severe allergic asthma with symptoms uncontrolled, despite the mainstay therapy.

Objective: Electronic medical records (EMR) were used to increase the knowledge of omalizumab effectiveness in a real-world setting.

Methods: Patients with uncontrolled moderate-to-severe allergic asthma, ages ≥ 12 years old, initiated on omalizumab (index date), with ≥ 12 months of pre- and postindex data, were identified in an EMR data base. An Asthma Control Test score (≥ 20 is considered well controlled), forced expiratory volume in 1 second as a percentage of the predicted value ($< 80\%$ considered below normal), symptoms, and oral corticosteroid (OCS) and inhaled corticosteroid (ICS) use were compared in the 12-month post- versus the preindex period with univariate generalized estimating equations adjusted for repeated measurements.

Results: A total of 208 patients (mean $\pm$ standard deviation[SD] age, 41 ± 19 years; 64.9% women; 71.2% white; and with a mean $\pm$ SD serum total immunoglobulin E level of 455.4 ± 644.7 IU/mL) were identified. In the post- versus preindex period, the patients were significantly more likely to have well-controlled asthma (odds ratio [OR] 1.72 [95% confidence interval {CI}, 1.11–2.64]) and less likely to have a lung function value below normal (nonsignificant) after omalizumab initiation. The patients experienced significantly less coughing (OR 0.66 [95% CI, 0.49–0.91]), shortness of breath (OR 0.60 [95% CI, 0.44–0.83]), and wheezing (OR 0.59 [95% CI, 0.43–0.81]), with no improvement in chest tightness. A significantly lower likelihood of new OCS prescriptions (OR 0.58 [95% CI, 0.41–0.82]) was observed. A lower likelihood of new high- and medium-dose ICS prescriptions was nonsignificant.

Conclusion: Omalizumab was associated with beneficial effects on asthma control and symptoms, and the likelihood of requiring new OCS prescriptions. An observed trend of improved lung function and lower likelihood of requiring high- and medium-dose ICS did not reach statistical significance.

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Asthma is a chronic respiratory condition characterized by airflow inflammation and causes symptoms of wheezing, shortness of breath, chest tightness, and cough.^{1,2} Its prevalence in the United States is rising and, according to the latest estimates,

comprises $\sim 7.7\%$ among adults and $\sim 9.6\%$ among children.³ Although asthma severity is broad, up to 75% of patients with asthma have a mild form of the disease.^{4–8} Despite affecting a smaller percentage of patients, moderate-to-severe asthma is driving a substantial part of asthma-related costs.^{5,9}

Management of severe cases of poorly controlled asthma despite guideline-based therapies is complicated due to the disease's heterogeneity.^{10–12} In such a context, therapies that target specific asthma phenotypes have a potential to improve outcomes.^{7,13} Among patients with asthma, allergic asthma, in which symptoms are triggered by allergens such as house-dust mites or pollen, is the most common asthma phenotype observed in $\sim 70\%$ of cases; $\sim 50\%$ of patients with severe asthma are estimated to have allergic asthma.^{14–16} The allergic asthma phenotype is characterized by elevated serum levels of immunoglobulin E (IgE).¹⁶

From the ¹Analysis Group Inc., Montreal, Quebec, Canada, ²Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, and ³Allergy Partners P.A., Asheville, North Carolina

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Address correspondence to Dominic Pilon, M.A., Analysis Group, Inc., 1000 De La Gauchetière West, Suite 1200, Montréal, QC H3B 4W5 Canada

E-mail address: dominic.pilon@analysisgroup.com

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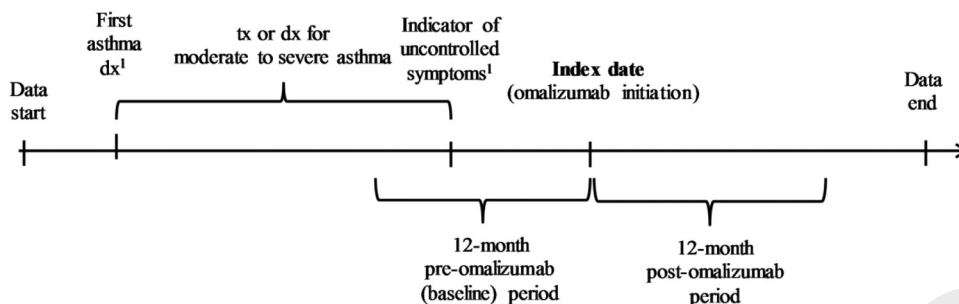


Figure 1. Study design. dx = Diagnosis; tx = treatment. Note: 1. These dates might fall within or outside the 12-month baseline period.

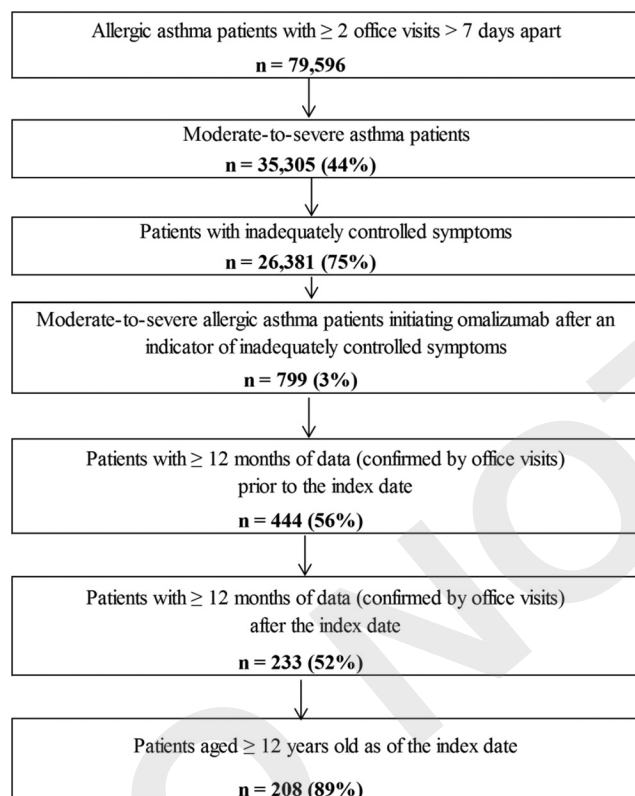


Figure 2. Sample selection flow chart.

Omalizumab is a biologic treatment that targets IgE and is approved for patients $\geq$ ages 6 years with moderate-to-severe asthma and with allergic asthma phenotype who are inadequately controlled with inhaled corticosteroids (ICS).¹⁷ The standard of care has evolved since the publication of omalizumab pivotal trials, and, currently, the treatment is recommended as an add-on to medium- and high-dose ICS and long-acting β_2 -agonists (LABA).^{1,2} Multiple clinical trials demonstrated efficacy, safety, and tolerability of omalizumab as an add-on to current asthma therapy.^{18–21}

To fully understand the treatment value for the general population, complementing information from clinical trials with that from a real-world setting becomes important. A number of U.S. and international studies demonstrated omalizumab effectiveness in a real-world setting.^{22–32} The eXpErience registry study used

patients' clinical information to assess the real-world effectiveness of omalizumab; however, it was descriptive in nature.²² The present study used electronic medical records (EMR) data from the largest U.S. single-specialty network of allergists and immunologists to assess the real-world effectiveness of omalizumab through comparison of patient clinical outcomes before and after omalizumab initiation, and to contribute to the current understanding of omalizumab performance in the U.S. real-world setting.

METHODS

Data Source

The longitudinal EMR (2007–2016) of Allergy Partners, P.A. (Asheville, NC) network was used. The network consists of >120 providers, spans >20 states, and encompasses >110 service locations. Available data included patient demographics (e.g., age, gender, ethnicity, insurance type, and state), diagnoses (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] and *International Classification of Diseases, 10th Revision, Clinical Modification* [ICD-10-CM] codes, and physicians' description), prescription medications (Generic Product Identifier, generic and brand names, date of prescription start, strength and administration instructions), lung function measured as forced expiratory volume in 1 second (FEV₁) as a percentage of predicted value (FEV₁% predicted), laboratory test results (e.g., IgE values, allergen sensitivities), Asthma Control Test (ACT)^{33,34} results and patient-reported asthma-related symptoms. The study did not use any patient-identifiable information and was exempted from an independent review board review by the New England Independent Review Board (Needham, MA).

Study Design

The study had a retrospective pre-post design in which the patients were their own controls (Fig. 1). The index date was the date of omalizumab initiation. Patient baseline characteristics were measured during the 12 months preceding the index date (asthma medication use) or as of the index date (asthma-related con-

Table 1 Patient baseline characteristics (N = 208)

Patient Characteristics	
Age, mean $\pm$ SD (median); Q1–Q3 (IQR)*	41.38 $\pm$ 18.78 (44); 24–55 (32)
Women, no. (%)	135 (64.9)
Race, no. (%)#	
White	148 (71.2)
Black or African American	50 (24.0)
Other	4 (1.9)
Unknown	6 (2.9)
Region, no. (%)	
South	175 (84.1)
West	19 (9.1)
Midwest	13 (6.3)
Northeast	1 (0.5)
Health care insurance, no. (%)	
Private	155 (74.5)
Medicare	34 (16.3)
Medicaid	16 (7.7)
Self-pay	2 (1.0)
Unknown	1 (0.5)
Year of index date, no. (%)	
2008	7 (3.4)
2009	9 (4.3)
2010	18 (8.7)
2011	20 (9.6)
2012	39 (18.8)
2013	22 (10.6)
2014	60 (28.8)
2015	33 (15.9)
Patients with baseline serum IgE value, no. (%)§	201 (96.6)
Serum IgE value (IU/mL), mean $\pm$ SD (median); Q1–Q3 (IQR), IU/mL	455.42 $\pm$ 644.66 (209); 82–558 (476)
Top three asthma-related conditions, no. (%)	
Allergic rhinitis	205 (98.6)
Gastroesophageal reflux disease	75 (36.1)
Chronic sinusitis	58 (27.9)
Asthma medication use, no. (%)	
ICS, any dose	172 (82.7)
Medium-dose ICS and LABA	109 (52.4)
High-dose ICS and LABA	91 (43.8)
LTM	122 (58.7)
OCS	137 (65.9)

SD = Standard deviation; Q1 = first quartile; Q3 = third quartile; IQR = interquartile range; IgE = immunoglobulin E; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LTM = leukotriene modifier; OCS = oral corticosteroid.

*Measured as of the index year.

#“Hispanic” was not included as a possible value for the “Race” variable; instead, a separate variable “Ethnicity” had values “Hispanic,” “non-Hispanic,” and “Unknown”; among the 208 patients, 8 (3.8%) were Hispanic and 196 (94.2%) were non-Hispanic.

§Measured before and included the index date; the value closest to the index date was selected.

||Conditions active as of the index date were identified by using International Classification of Diseases, 9th Revision, Clinical Modification and International Classification of Diseases, 10th Revision, Clinical Modification codes.

||Measured during the 12-month baseline period before the index date (not including the index date).

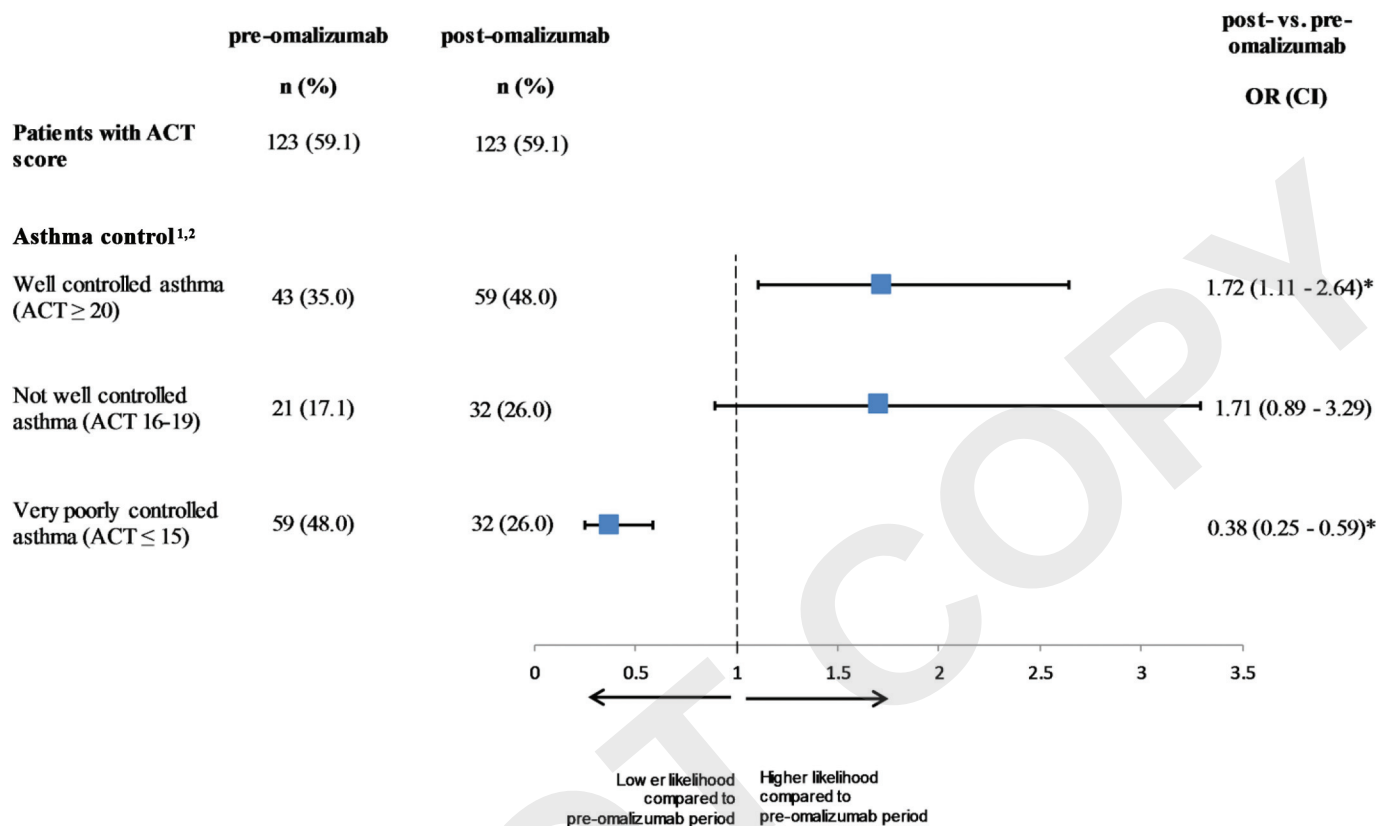


Figure 3. Asthma control. ACT = Asthma Control Test; CI = confidence interval; OR = odds ratio. *Denotes statistical significance at 5%. Notes: 1. Outcomes were compared by using univariate generalized estimating equations with adjustment for repeated observations, binominal distribution, and a logit link, and the results are reported as OR (95% CI); 2. Measured as of the last assessment during the 12-month pre- and postindex periods.

ditions). Asthma-related conditions marked as “active” in the EMR system as of the index date were included. The IgE value closest to the index date was used in this analysis. Outcomes were measured and compared over the 12 months before the index date (pre-omalizumab period) versus the 12 months after the index date (postomalizumab period). The 12-month pre- and postomalizumab periods were chosen to exclude any potential seasonality impact from the analysis. To be included in the study, the patients were required to have at least two asthma-related visits (*ICD-9-CM*, 493.xx; *ICD-10-CM*, J45.xxx) >7 days apart, allergic moderate-to-severe asthma with uncontrolled symptoms (see definitions below), and at least one prescription order or injection of omalizumab after an indicator of uncontrolled symptoms. Patients <12 years of age as of the index date, or with <12 months of pre- and postindex data were excluded.

The allergic status was based on either a positive serum-specific IgE test result, a positive allergy skin test result, a diagnosis of perennial allergic rhinitis (*ICD-9-CM*, 477.8; *ICD-10-CM*, J30.89), or allergic rhinitis to animal hair or dander (*ICD-9-CM*, 477.2; *ICD-10-CM*, J30.81). The patients had to have their allergic status confirmed before the index date. Moderate-to-

severe asthma was identified based on either a diagnosis (*ICD-10-CM*, J45.4 or J45.5, or physician’s description) or treatments (medium- to high-dose ICS with LABA or leukotriene receptor antagonist, theophylline, or zileuton^{1,2}). Uncontrolled symptoms were identified based on the ACT score of <20, FEV₁% predicted value of <80%, or initiation of oral corticosteroids [OCS]. At least one indicator of uncontrolled symptoms had to be observed after the moderate-to-severe asthma status was confirmed.

Outcome Measures

Asthma control was analyzed based on the ACT, a patient-reported outcome measure that assesses asthma interference with activities, shortness of breath, nocturnal symptoms, rescue medication use, and self-rated asthma control with a 4-week recall period.^{33,34} The ACT score, which ranged from 5 to 25, was reported as a continuous variable and as a set of categorical variables: well-controlled asthma (ACT score, ≥20), not well-controlled asthma (ACT score, 16–19), and very poorly controlled asthma (ACT score, ≤15).² Scores from the last assessments in the pre- and postomalizumab periods were used. Patients’ lung func-

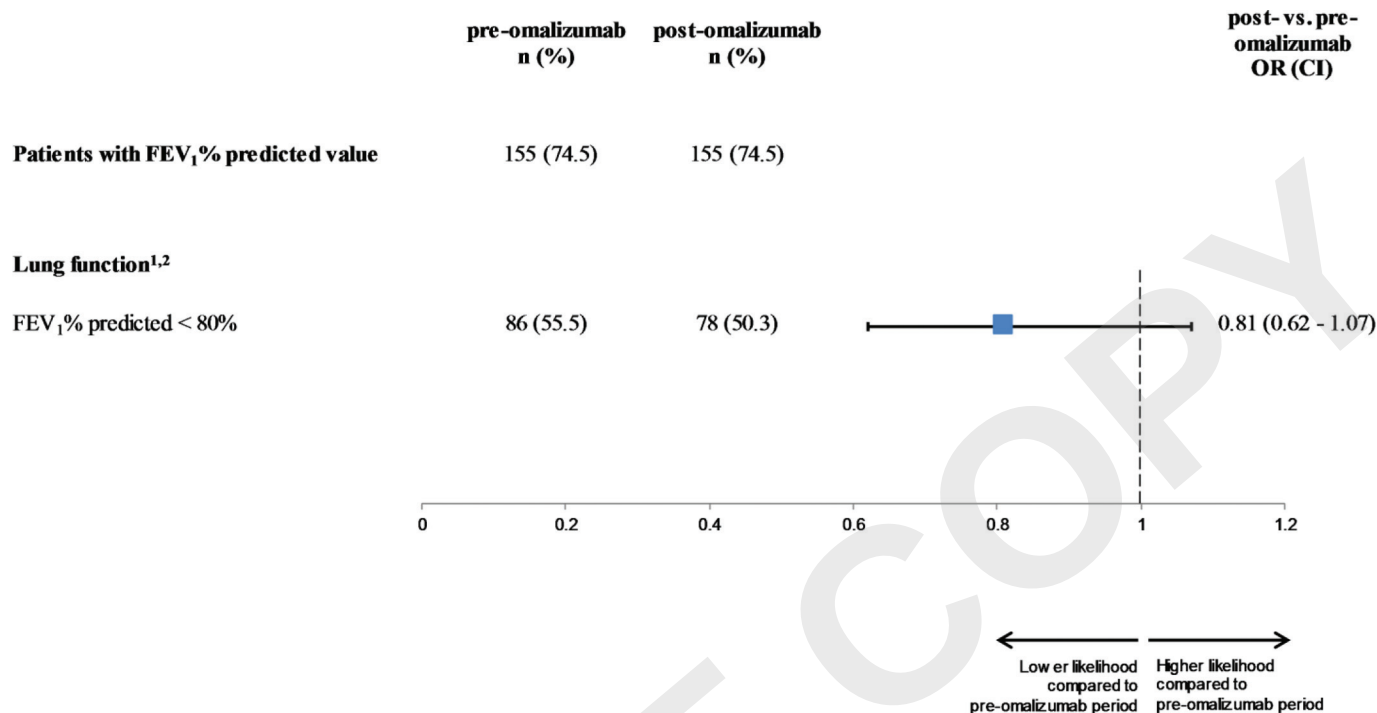


Figure 4. Lung function. CI = confidence interval; FEV₁% predicted = volume exhaled during the first second as a percentage of the predicted value; OR = odds ratio. *Denotes statistical significance at 5%. Notes: 1. Outcomes were compared by using univariate generalized estimating equations with adjustment for repeated observations, binominal distribution, and a logit link, and results are reported as OR (95% CI); 2. Measured as of the last assessment during the 12-month pre- and postindex periods.

tion, measured as FEV₁% predicted, was reported as a continuous and a categorical variable, FEV₁% predicted of <80%, which defined a group of patients with lung function below normal. FEV₁% predicted values from the last assessments in the pre- and postomalizumab periods were used. Wheezing, shortness of breath, chest tightness, and coughing were identified in the data, based either on ICD-9-CM or ICD-10-CM codes, or on patient-reported information any time during the pre- and postomalizumab periods. Corticosteroid sparing was measured as a proportion of patients with a new OCS prescription; the number of OCS prescriptions; and the proportions of patients with new low-, medium-, and high-dose ICS prescriptions.

Statistical Analysis

Patient baseline characteristics and outcomes were described by using mean, median, standard deviation (SD), first quartile (Q1) and third quartile (Q3), and interquartile range (IQR) for continuous variables and frequencies, and proportions for categorical variables. Statistical comparisons between pre- and postomalizumab periods were conducted by using univariate generalized estimating equations with adjustment for repeated measurements (or measurements on the same patient at different points in time). Categorical variables were compared by using binominal distribution and a logit link. Results were reported as odds ratios

(OR) with 95% confidence intervals (CI). For count variables (the number of OCS prescriptions), comparison was done by using negative binominal distribution and a log link, and the results were reported as incidence rate ratios with 95% CIs. Continuous variables were compared by using normal distribution, and the results were reported as mean differences (MD) with 95% CIs. All statistical analyses were conducted by using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Patient Characteristics

A total of 208 patients with moderate-to-severe allergic asthma were initiated on omalizumab after an indicator of uncontrolled symptoms that met study inclusion criteria (Fig. 2). The mean $\pm$ SD age was 41 $\pm$ 19 years (78.8% were $\geq$ 18 years old). The patients were predominately women (64.9%), white (71.2%), resided in the South (84.1%), and with a private health care insurance plan (74.5%) (Table 1). The mean $\pm$ SD serum IgE level available in 96.6% of the patients was 455.4 $\pm$ 644.7 IU/mL. The three most common asthma-related conditions documented in the EMR included allergic rhinitis (98.6%), gastroesophageal reflux disease (36.1%), and chronic sinusitis (27.9%). The majority of patients had at least one ICS prescription (82.1%), including at least one prescription of medium- (52.4%)

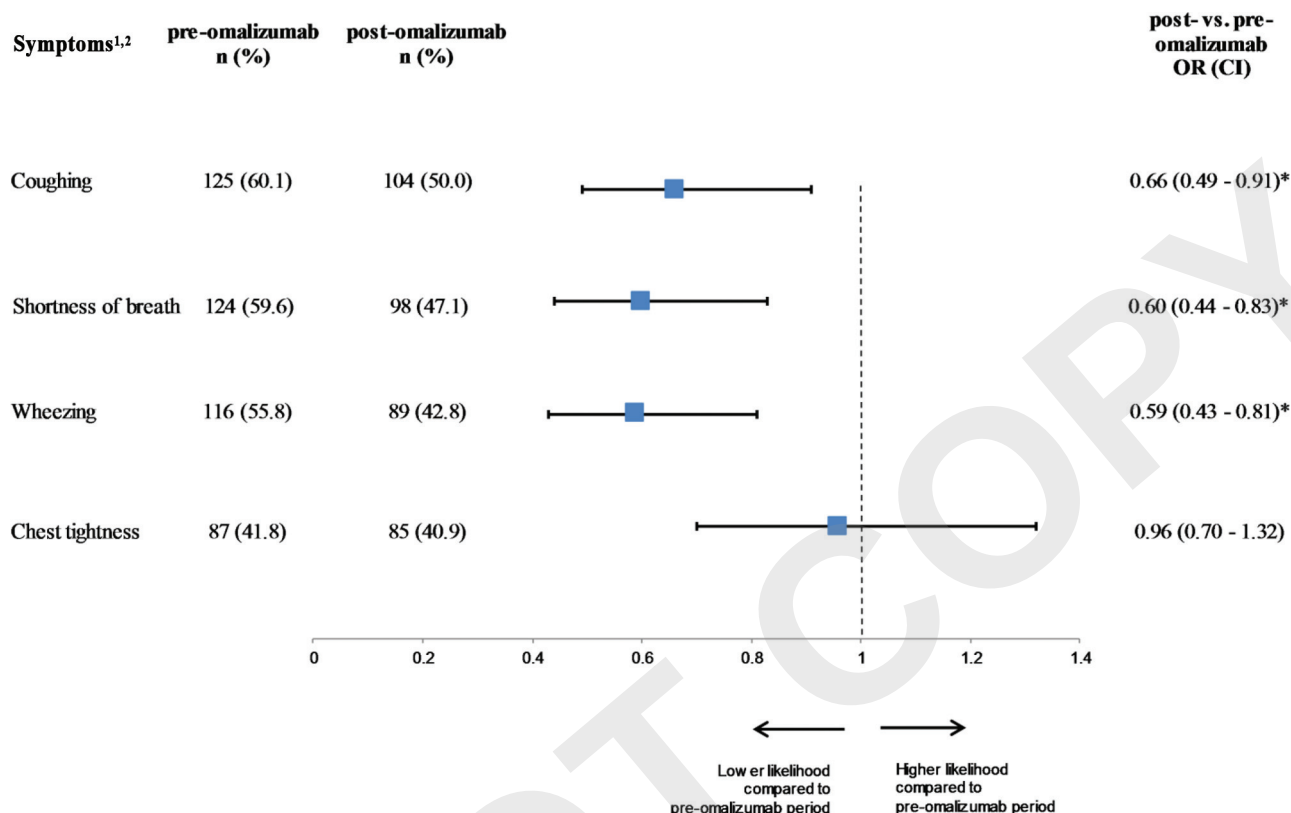


Figure 5. Symptoms. CI = confidence interval; OR = odds ratio. *Denotes statistical significance at 5%. Notes: 1. Outcomes were compared by using univariate generalized estimating equations with adjustment for repeated observations, binominal distribution, and a logit link, and results are reported as OR (95% CI); 2. Measured during the 12-month pre- and postindex periods based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10 CM) codes or patient-reported information.

or high-dose (43.8%) ICS and LABA during the 12-month pre-omalizumab period. Other medications used also included OCS (65.9%) and leukotriene modifiers (58.7%).

Outcomes

Omalizumab was associated with better asthma control as measured by the ACT in the post- versus pre-omalizumab period (Fig. 3). The ACT score was available in 59.1% of patients in the pre- and postomalizumab periods. In the postomalizumab period, the patients were 72% more likely to have well-controlled asthma (OR 1.72 [95% CI, 1.11–2.64]) and 62% less likely to have very poorly controlled asthma (OR 0.38 [95% CI, 0.25–0.59]) compared with the pre-omalizumab period. A higher likelihood of not very well-controlled asthma was not statistically significant. The mean ACT score increased by a statistically significant two points (MD 2.14 [95% CI, 1.15–3.12]), and 47.2% of patients achieved the minimally important difference of three points.³⁴

An FEV₁% predicted value was available in 74.5% of the patients in the pre- and postomalizumab periods (Fig. 4). In the postomalizumab period, the patients

were less likely to have an FEV₁% predicted of <80%, but this improvement was not statistically significant. The mean FEV₁% predicted increased by a statistically significant four percentage points (MD 3.99 [95% CI, 1.97–6.02]).

Omalizumab was associated with a statistically significant improvement in most symptoms in the post- versus pre-omalizumab period (Fig. 5). More specifically, the patients were 34% less likely to experience coughing (OR 0.66 [95% CI, 0.49–0.91]), 40% less likely to experience shortness of breath (OR 0.60 [95% CI, 0.44–0.83]), and 41% less likely to experience wheezing (OR 0.59 [95% CI, 0.43–0.81]). Although a downward trend was observed in the likelihood of experiencing chest tightness, it was not statistically significant.

Omalizumab also was associated with a statistically significant 42% reduction in the likelihood of new OCS prescriptions in the postomalizumab period (OR 0.58 [95% CI, 0.41–0.82]) (Fig. 6). Similarly, the number of new OCS prescriptions reduced slightly (incidence rate ratio 0.82 [95% CI, 0.66–1.01]); however, this change did not reach statistical significance. Moreover, the likelihood of having new medium- or high-dose ICS

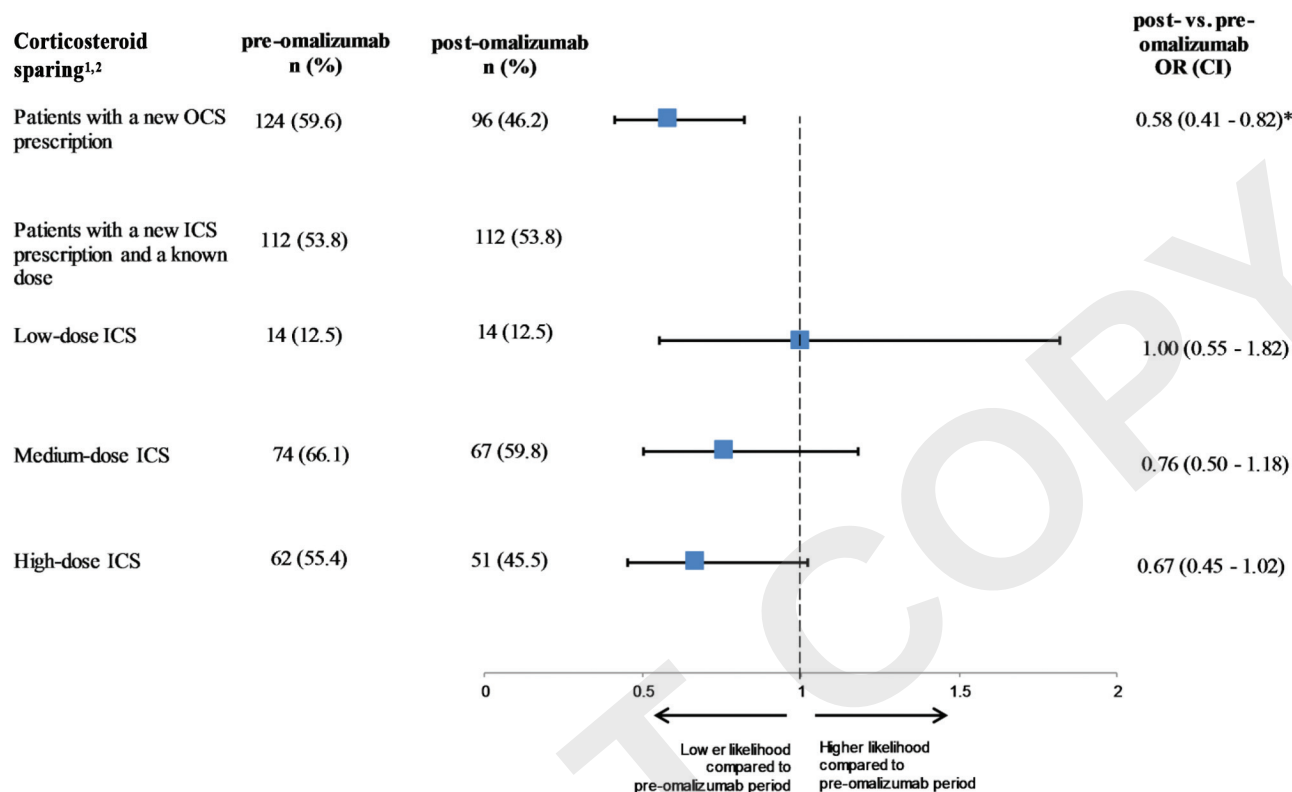


Figure 6. Corticosteroid sparing. CI = confidence interval; ICS = inhaled corticosteroid; OR = odds ratio; OCS = oral corticosteroid; *Denotes statistical significance at 5%. Notes: 1. Outcomes were compared by using univariate generalized estimating equations with adjustment for repeated observations, binominal distribution, and a logit link, and results are reported as OR (CI); 2. Measured during the 12-month pre- and postindex periods.

prescriptions was lower, although not statistically significant (Fig. 6).

DISCUSSION

This study evaluated real-world clinical outcomes in the United States of patients with uncontrolled moderate-to-severe allergic asthma who were exposed to omalizumab. Statistically significant associations were established between exposure to omalizumab and improvements in asthma control and symptoms. Specifically, exposure to omalizumab was related to a higher likelihood of well-controlled asthma and a lower likelihood of very poorly controlled asthma. A higher likelihood of not-very-well-controlled asthma was not statistically significant and possibly captured a part of the upward shift from the lowest, “very poorly controlled asthma” category. The mean ACT score increased; however, the increase was below the minimally important difference of three points.³⁴ In terms of symptoms, the patients were less likely to experience coughing, shortness of breath, and wheezing. In this study, a signal toward improved lung function was observed in the postomalizumab period. The mean FEV₁% predicted increased by a statistically significant four percentage points, but the decrease in the likelihood of

lung function below normal was not statistically significant.

These results are generally consistent with previous literature. Several non-U.S. real-world omalizumab effectiveness studies indicated that omalizumab is associated with improved asthma control as measured by the ACT,^{25–28} lung function,^{29–31} and daytime and nighttime symptoms.^{25,32} The eXpeRience, a 2-year international (Europe, the Americas, and Asia) single-arm, open-label, observational study evaluated the real-world effectiveness of omalizumab by using clinical information such as symptoms, asthma control, and lung function, although statistical comparisons with baseline were not performed.²²

At month 12 compared with baseline, a higher proportion of patients had controlled or partly controlled asthma as measured by the ACT and/or asthma control questionnaire, and normal lung function (FEV₁% predicted of ≥80%), whereas a lower proportion of patients had daytime or nocturnal symptoms and activity limitations. Compared with this study, increases from baseline in the mean ACT score (6.1) and FEV₁% predicted (10.3%) were higher in the eXpeRience study;²² however, patients also seemed to be more severe in terms of asthma control and lung function at

baseline. Although this study did not assess quality-of-life outcomes, the eXpErience study reported omalizumab-associated improvements in quality of life.²²

Previous studies reported omalizumab to be associated with corticosteroid sparing effects.^{24,25,28} Results from the current study point toward a positive trend as well. Exposure to omalizumab was related to a statistically significant decline in the likelihood of new OCS prescriptions and a numerical but nonstatistically significant decrease in the number of OCS prescriptions. In terms of ICS, a nonstatistically significant trend toward a lower likelihood of new medium- and high-dose ICS prescriptions was observed. Closer comparisons with previous studies were complicated due to differences in designs, observation periods, and outcome measures.

EMR data enabled the analysis of clinical outcomes in this study. EMR systems have a potential of bringing clinical research to the next level with their ability to access detailed longitudinal patient information. Such data may help to counterbalance certain challenges of clinical trials, including burdensome data collection and uncertain generalizability of results. However, research opportunities that arise from EMR only become possible if physicians are able to use platform capabilities. Improving data entry, quality, and completeness is one of the challenges in making EMR a reliable and useful research tool.³⁵ Additional technologies, *e.g.*, natural language processing, which extracts clinical information from unstructured EMR text fields, might further advance EMR applications in clinical research.^{36,37}

Limitations

This study was subjected to a number of limitations. EMR data contain information on prescriptions ordered rather than dispensed. Matched pharmacy claims were not available to analyze dispensed prescriptions. A prescription order does not guarantee that a medication was dispensed to the patient, which potentially limited the precision of the corticosteroid sparing analysis and identification of the patients with moderate-to-severe asthma based on treatment patterns. Of note, exposure to omalizumab was defined based on either a prescription order or an injection of omalizumab. Reasons for why OCS were prescribed (chronic daily use or to control exacerbations) were unknown. EMR data were not linked to health care providers outside of the network, and information on the additional care that patients sought (*e.g.*, inpatient and emergency department admissions) was unavailable.

With advances in EMR systems, a more comprehensive assessment of outcomes might be possible. Patient-reported information (*e.g.*, symptoms, answers to

the ACT questionnaire) introduces potential recall bias. However, with respect to the ACT, it should be noted that it is a widely used standardized instrument specifically designed for clinical practice, with a good diagnostic performance in assessing controlled and not-well-controlled asthma.³⁸ Hispanic patients and patients from geographic regions other than the South were underrepresented in these data. No control arm was available to assess the incremental effectiveness of omalizumab compared with another treatment option. As with any data base, coding inaccuracies and missing information were possible, but were not widespread enough to have a substantial impact on the results. Also, as with all observational studies, results should be interpreted with due consideration that factors other than the treatment of interest might confound findings.

CONCLUSION

This real-world study showed that initiation of omalizumab in patients with uncontrolled moderate-to-severe allergic asthma was associated with a beneficial effect on clinical outcomes, including asthma control as measured by the ACT and most asthma-related symptoms. Signals toward improved lung function and corticosteroid sparing in the postomalizumab period were detected. Analysis of clinical outcomes was enabled by the use of EMR data and added to the growing body of literature that demonstrates capabilities of EMR systems for clinical research.

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