

Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study



Thomas B. Casale, MD^a, Allan T. Luskin, MD^b, William Busse, MD^c, Robert S. Zeiger, MD, PhD^{d,e}, Benjamin Trzaskoma, MS^f, Ming Yang, PhD^f, Noelle M. Griffin, PhD^{f,*}, and Bradley E. Chipps, MD^g Tampa, Fla; Madison, Wis; and San Diego, Pasadena, South San Francisco, and Sacramento, Calif

What is already known about this topic? Omalizumab efficacy has been demonstrated in controlled research settings, but knowledge of its effectiveness in a real-world setting, including the use of biomarkers or clinical characteristics to guide response, is limited.

What does this article add to our knowledge? Omalizumab initiation in patients with moderate to severe allergic asthma in a real-world setting yielded a positive treatment response, measured by multiple parameters, in 87% of patients independent of baseline characteristics or biomarker levels.

How does this study impact current management guidelines? These data suggest that once the decision to treat with omalizumab has been made, biomarker levels may not be predictive of treatment outcomes.

BACKGROUND: Omalizumab has demonstrated efficacy in clinical trials of patients with asthma, but real-world data are needed.

OBJECTIVE: To assess outcomes after omalizumab initiation in patients with asthma in a real-world setting.

METHODS: Patients aged 12 years and older with allergic asthma who were candidates for omalizumab on the basis of physician-assessed need were enrolled in a US-based, prospective, single-arm, 48-week multicenter study, the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab. Monthly assessments included exacerbations, health care utilization, asthma control test (ACT), and adverse events. At baseline, 6 months, and end of study, biomarkers (blood eosinophils and

fractional exhaled nitric oxide) were collected and spirometry performed.

RESULTS: Of 806 enrollees, 801 (99.4%) received omalizumab and 622 (77.2%) completed the study. The exacerbation rate significantly improved from a mean of 3.00 ± 3.28 in the 12 months before baseline to 0.78 ± 1.37 through month 12 ($P < .001$) and was similar in adults and adolescents; there was a reduction of 81.9% in the percentage of patients with 1 or more hospitalizations. Lung function remained generally unchanged. A mean improvement of 4.4 ± 4.9 in ACT scores was observed. Eighty-seven percent of patients were responders on the basis of clinical improvement in exacerbations, lung function, or ACT scores. Baseline biomarker status was associated with ACT scores and lung function improvement, but the magnitude of this

^aUniversity of South Florida, Tampa, Fla

^bHealthyAirways, Madison, Wis

^cUniversity of Wisconsin School of Medicine and Public Health, Madison, Wis

^dDepartment of Allergy, Kaiser Permanente Southern California, San Diego, Calif

^eDepartment of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, Calif

^fGenentech, Inc, South San Francisco, Calif

^gCapital Allergy and Respiratory Disease Center, Sacramento, Calif

This study was funded by Genentech, Inc (South San Francisco, Calif) and Novartis Pharma AG (Basel, Switzerland). Genentech, Inc, was involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interest: T. B. Casale has received research grants from AstraZeneca, Boehringer Ingelheim, Sanofi/Regeneron, Genentech, Inc, and Novartis; and is a consultant for AstraZeneca, Boehringer Ingelheim, Genentech, Inc, Novartis, Sanofi/Regeneron, and Teva. A. T. Luskin has received consulting and lecture fees, research and travel support, and payment for developing educational presentations from Genentech, Inc; and has received lecture fees from Merck. W. Busse is a consultant for Genentech, Inc, GlaxoSmithKline, Novartis, Sanofi/Regeneron, AstraZeneca, and Teva; participates on data monitoring boards for Boston Scientific and Genentech, Inc; and is on a study oversight committee for

ICON. R. S. Zeiger is a consultant with AstraZeneca, Genentech, Inc, GlaxoSmithKline, Novartis, Patara Pharma, Sanofi/Regeneron, Teva, and Theravance Biopharma; and has received research support from Aerocrine, AstraZeneca, Genentech, Inc, GlaxoSmithKline, MedImmune, and Merck. B. Trzaskoma and M. Yang are employees of Genentech, Inc. N. M. Griffin is a former employee of Genentech, Inc, and is employed by Aimmune Therapeutics. B. E. Chipps is a consultant; and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Inc, Novartis, and Teva.

Received for publication December 14, 2017; revised April 5, 2018; accepted for publication April 30, 2018.

Available online May 22, 2018.

Corresponding author: Noelle M. Griffin, PhD, Genentech, Inc, 1 DNA Way, South San Francisco, CA 94080. E-mail: noelle.griffin@gmail.com.

* N. M. Griffin is no longer employed at Genentech, Inc.

2213-2198

© 2019 The Authors. Published by Elsevier Inc, on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jaip.2018.04.043>

Abbreviations used

ACT- asthma control test

AE- adverse event

FENO- fractional exhaled nitric oxide

MID- minimally important difference

OR- odds ratio

PROSPERO- Prospective Observational Study to Evaluate
Predictors of Clinical Effectiveness in Response to
Omalizumab

SAE- serious adverse event

improvement was not clinically relevant. No new safety signals emerged.

CONCLUSIONS: Omalizumab initiation in patients with asthma resulted in improved exacerbation rates, reduced hospitalizations, and improved ACT scores compared with pretreatment values, regardless of biomarker status. © 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;7:156-64)

Key words: Asthma; Asthma burden; Biomarker profile; Comorbidities; Omalizumab; Patient-reported outcomes; Real-world study

INTRODUCTION

Asthma remains a common global chronic respiratory disease with an increasing prevalence in some populations.¹ Despite treatment guidelines, asthma in many patients remains uncontrolled. Almost half (47%) of adults report very poorly controlled asthma and another 24% report asthma not well controlled.² In children, the prevalence of uncontrolled asthma is similar to that in adults (46%).³

Biologic therapies for asthma are a means to achieve asthma control, especially when patients remain symptomatic on Global Initiative for Asthma step 3 and higher treatments.¹ Although many of these biologics are new, and thus clinical experience with them is limited, omalizumab has been available for clinical use in patients with moderate to severe persistent allergic asthma for more than a decade.

Data are emerging that specific biomarkers, including peripheral blood eosinophils and fractional exhaled nitric oxide (FENO),⁴ may help identify patients who are more likely to respond to biologics, allowing for a more personalized approach to the treatment of asthma.⁵⁻¹⁵ Evaluation of on-treatment response using biomarkers or patient characteristics would add depth to asthma management, but data consistently linking specific disease characteristics with treatment responses are lacking.

The Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) was designed to investigate response to omalizumab in a real-world setting where omalizumab was initiated on the basis of physician-assessed need rather than as per protocol, as in randomized controlled trials. Specifically, we sought to better characterize asthma outcomes after omalizumab initiation and evaluate whether a biomarker profile or specific patient characteristics would be predictive of treatment response, with a goal of

providing useful guidance for clinical decision making. PROSPERO was thus designed to address 2 objectives: (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 of a study such as the one described here, and (2) to understand how reported clinical parameters may be associated with distinct outcomes. The first goal was addressed in a previous publication.¹⁶ Patients enrolled in PROSPERO had a significant asthma burden, including multiple previous exacerbations, variable comorbid conditions (both allergic and nonallergic), as well as a heterogeneous biomarker profile. This article presents data from PROSPERO that relate to the second goal: the efficacy and safety outcomes, including a responder analysis, for patients 48 weeks after omalizumab initiation to understand whether any specific patient characteristic is associated with response to omalizumab.

METHODS

PROSPERO was a multicenter, prospective, 48-week effectiveness study of omalizumab conducted in the United States (clinicaltrials.gov identifier: NCT01922037). Physicians identified patients 12 years and older with allergic asthma who, in their opinion, were eligible for omalizumab (approved for patients as young as age 6 years; however, at the time of the study, approval was limited to patients 12 years or older). Patients were enrolled from June 2013 to March 2015. Each investigator determined a patient's asthma severity and treatment on the basis of individual clinical practice; there was no protocol-specified treatment regimen. Patients were required to have access to omalizumab through their insurance or other funding.

At baseline, demographic and clinical characteristics were documented.¹⁶ Patients reported exacerbations, defined as worsening of asthma symptoms requiring the use of oral corticosteroids, emergency department visit, or hospitalization, as well as adverse events (AEs) monthly. Biomarkers (blood eosinophils and FENO) were collected and spirometry was performed (according to the American Thoracic Society criteria¹⁷) at baseline, 6 months, and end of study (week 48). IgE level data were collected at baseline.¹⁶ Only the following protocol-defined safety events, collected monthly throughout the study, were reported: all serious adverse events (SAEs), non-SAEs of special interest (suspected anaphylaxis due to omalizumab or suspected transmission of infectious agent by medicinal product), pregnancies, and non-SAEs assessed as being causally related to omalizumab or when causality was unknown.

The asthma control test (ACT)¹⁸ was completed monthly along with assessments of exacerbations. Each question on the 5-item ACT is scored from 1 (poor control of asthma) to 5 (complete control of asthma); overall ACT scores range from 5 to 25. ACT scores of 20 and higher reflect well-controlled asthma, scores of 16 to 19 suggest asthma is not well controlled, and scores of 15 and lower indicate asthma that is very poorly controlled.¹⁸ The minimally important difference (MID) for the ACT is 3.¹⁹

All participants signed an informed consent approved by an institutional review board. 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, the US Food and Drug Administration regulations, and any applicable local, state, and national laws.

Statistical analysis

Summary statistics were used for demographic and clinical characteristics. Continuous outcomes variables were analyzed using ANOVA and supplemented with nonparametric analyses. The following prespecified cutoff points were used to create subgroups on the basis of biomarker status: FENO²⁰ (<25 and $\geq$ 25 ppb) and eosinophils²¹ (<300 and $\geq$ 300 cells/ μ L). Because of the small adolescent sample size and different cutoff points for biomarkers in this population, biomarker-related outcomes are reported only for patients 18 years and older. Logistic regression was used to predict which patients would experience an exacerbation during the study using a prespecified list of covariates: previous exacerbations (includes emergency department visits or asthma-related hospitalizations), log of eosinophils, log of FENO, log of total IgE at baseline, age, body mass index, FEV₁ (continuous variable), eosinophil (<300 and $\geq$ 300 cells/ μ L) and FENO (<25 and $\geq$ 25 ppb) cutoff points, and use of beclomethasone (or equivalent, continuous variable) at baseline. When exacerbations were evaluated as a binary outcome, any patient who discontinued from the study was treated as if he or she experienced an exacerbation at the time of the discontinuation. To account for early terminations, additional analyses were done by adjusting the number of in-study exacerbations for time in study for each patient.

Responder analysis

Patients were defined as omalizumab responders if any 1 of the following criteria was met: (1) exhibited an exacerbation reduction of 50% or more from baseline (patients had to have reported at least 1 exacerbation in the previous 12 months),^{8,9,11,14,22} (2) changed from uncontrolled at baseline based on ACT score of 19 or less to controlled at the end of the study (ACT $\geq$ 20) or who achieved at least a 3-point improvement (MID) in ACT score,¹⁹ and (3) achieved at least a 120-mL improvement in FEV₁ from baseline to end of the study.^{23,24} Number and percentage of patients defined as responders by 1, 2, or 3 of the aforementioned criteria were calculated. Responder definitions were prespecified and expanded post hoc on the basis of clinician input. Logistic regression analysis was used to identify which predefined demographic and clinical characteristics were predictors of response to omalizumab (as defined by 1 or more of the aforementioned criteria: exacerbation, ACT, or lung function).

RESULTS

Baseline features of cohort

A total of 806 patients were enrolled in PROSPERO.¹⁶ Of the enrolled population, 801 (99.4%) patients were treated with omalizumab and 622 (77.2%) completed the 12-month study (Figure 1). Most patients (91.4%) were adults (median [min, max] age, 49 [12, 100] years), white (70.3%), and female (63.5%). Physicians classified their enrolled patients as having asthma that was moderate (48%), severe (48%), and mild (4%). Asthma was generally not well controlled, with 83.8% (670 of 800) of patients reporting ACT scores of 19 or less and 61.0% (488 of 800) reporting scores of 15 or less (very poorly controlled). In the previous 12 months, 60.7% patients reported 2 or more exacerbations, 84.2% reported at least 1 other comorbid allergic condition, 35.5% reported hypertension, 22.1% reported depression, and 10.4% reported anxiety.¹⁶

Of 711 patients with eosinophils measured at baseline (min, max, 0, 2340 cells/ μ L), 35.4% had a high count ($\geq$ 300 cells/

μ L). Of 722 patients with FENO measured at baseline (min, max, 5, 266 ppb), approximately 44.3% had a high level ($\geq$ 25 ppb).

Median (min, max) total IgE level was 193.3 (1.1, 68,628.0) IU/mL in the full population, 506.7 (2.9, 68,628.0) IU/mL in adolescents, and 175.4 (1.1, 8659.2) IU/mL in adults. IgE levels outside the recommended limits of the dosing table from omalizumab US prescribing information (<30 or >700 IU/mL)²⁵ were noted in 23.8% (191 of 801) of patients. Most of these patients (n = 120) had an IgE level that was above the upper limit of the dosing table (>700 IU/mL), with the remainder (n = 71) having an IgE level that was below the lower limit of the dosing table (<30 IU/mL). Omalizumab dosing in these patients ranged from 150 mg every 4 weeks (IgE <30 IU/mL) to 450 mg every 2 weeks (IgE >700 IU/mL).

Omalizumab treatment

Median time on omalizumab was 11.2 months. Omalizumab planned dosing frequency was almost evenly split between every 2- and 4-week dosing intervals (50.9% vs 49.1%, respectively). Fifty-six patients switched dosing frequency during the study: 28 (50.0%) switched from every 2 to every 4 weeks and 21 (37.5%) switched from every 4 to every 2 weeks. The remaining 7 patients were switched to alternative schedules. During the study, the median (min, max) omalizumab dose was 450 mg (150, 3000 mg/month cumulative dose, irrespective of dosing frequency).

Approximately 60% of patients missed at least 1 omalizumab dose (range, 0 to $\geq$ 16). The percentage was higher among patients with more frequent dosing: 72.1% versus 48.1% in patients receiving every 2- and 4-week dosing, respectively.

Outcomes after 12 months of omalizumab

Exacerbation rate. The exacerbation rate significantly improved from a mean baseline rate of 3.00 ± 3.28 in the 12 months before baseline to a rate of 0.78 ± 1.37 through month 12 ($P < .001$) (Figure 2, A). Baseline and through month 12 outcomes were similar in the adolescent (2.80 ± 2.64 to 0.46 ± 0.82) and adult (3.00 ± 3.34 to 0.81 ± 1.41) subgroups. Overall, 62.4% (497 of 796) of patients experienced no exacerbations during the study period compared with 24.6% in the year before the baseline visit.

After initiating omalizumab treatment, a significant decrease in asthma exacerbations was noted over a 12-month period irrespective of biomarker status in adults (Figure 2, B). Patients whose IgE levels fell outside the limits of the dosing table also experienced reductions in exacerbations from the 12 months before study entry to the 12 months on study: mean of 2.94 ± 3.63 to 1.23 ± 1.85 for patients with IgE levels of less than 30 IU/mL²⁵ and from 3.18 ± 3.73 to 0.71 ± 1.35 for patients with IgE levels of more than 700 IU/mL²⁵ (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Statistically significant predictors of experiencing an on-study exacerbation included an exacerbation in the year before study entry and a low baseline FEV₁ (Table I).

Hospitalizations. A reduction of 81.9% in the percentage of patients with 1 or more hospitalizations was observed; 22.1% of patients reported 1 or more hospitalizations in the 12 months before baseline versus 4.0% during the 12-month study (Figure 3, A). This reduction was similar across biomarker subgroups (Figure 3, B). The percentage of adolescents with 1 or

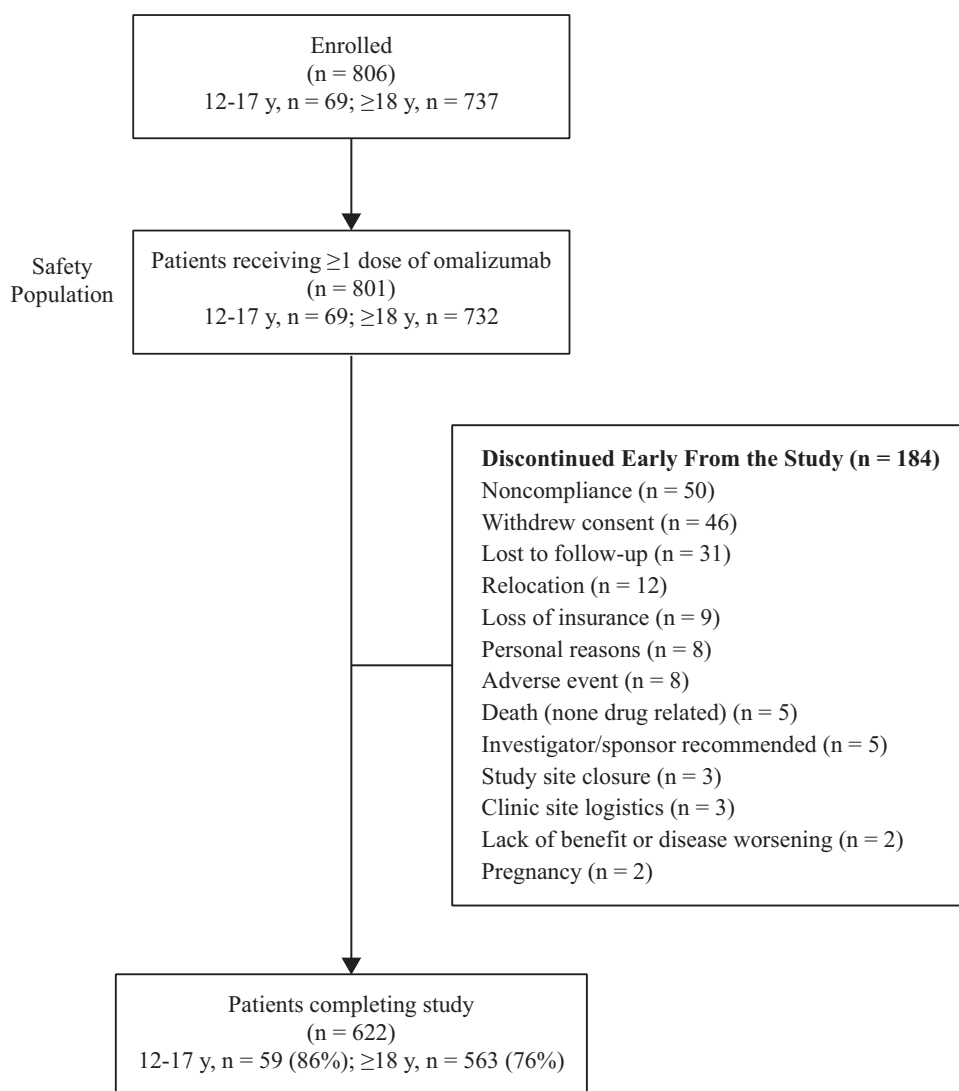


FIGURE 1. Patient disposition. Noncompliance was defined as an indication that a patient has not agreed with or followed the instructions related to the protocol.

more hospitalizations decreased from 28% in the 12 months before baseline to 4% during the 12 months on omalizumab.

Lung function. Overall, lung function remained relatively unchanged from baseline across the total cohort (Figure 4); mean improvement in prebronchodilator FEV₁ was 40 mL. In the adolescent population, prebronchodilator FEV₁ improved by 170 mL from baseline to end of study/early termination, whereas in adults the improvement was 30 mL.

Significantly greater improvements in lung function were noted in the adult high-biomarker subgroups compared with the low-biomarker subgroups (Table II); the magnitude of the change was modest, but statistically significant.

Mean postbronchodilator FEV₁ in the total cohort was 2.41 L (0.81) at baseline and 2.47 L (0.81) at month 12. Greater improvements were observed in the adolescent cohort compared with the adult cohort: 2.79 L (0.77) at baseline and 3.00 L

(0.76) at month 12 versus 2.38 L (0.81) at baseline and 2.42 L (0.80) at month 12, respectively.

Asthma symptom control

In the 12 months after omalizumab initiation, an improvement in ACT score was observed (Figure 5, A). On average, MID improvement was achieved across the cohort. Mean improvement from baseline was 3.9 ± 5.0 in adolescents (n = 67), 4.5 ± 4.9 in adults (n = 721), and 4.4 ± 4.9 overall (n = 788). About 50% of the approximately 85% of patients who were uncontrolled at baseline reported good asthma control (ACT score, ≥ 20) at the end of the study.

ACT score improvement was similar in patients with baseline physician-assessed asthma severity that was mild/moderate versus severe (Figure 5, B); mean change from baseline was 4.1 ± 4.8 for patients with asthma assessed as mild/moderate (n = 378) and 4.9 ± 5.0 for patients with asthma assessed as severe (n = 343).

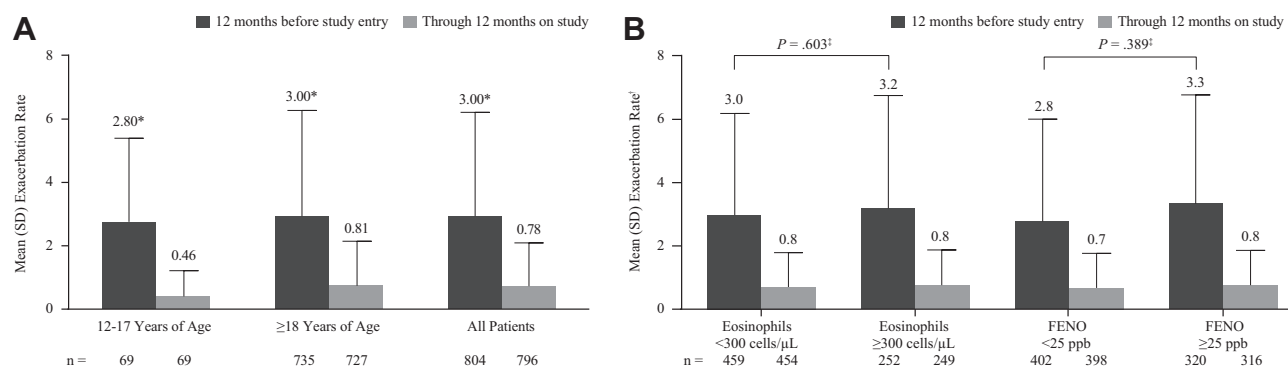


FIGURE 2. Mean exacerbation rate by (A) age group and (B) biomarker status. * $P < .0001$ for comparison of before study entry to through 12 months on study for each age group (calculation based on simulation). Sum of exacerbations is not adjusted to patient's time on study. † Baseline: mean $\pm$ SD; through month 12: least squares (mean). ‡ P values reflect adjustments for differences in baseline characteristics.

TABLE I. Significant risk factors* for a study-related asthma exacerbation during omalizumab treatment

Risk factor	Parameter estimate	Standard error	OR	95% CI for OR	P value
Exacerbation in 12 mo before baseline ‡	0.78	0.18	2.19	1.55–3.08	<.001
FEV ₁ at baseline	–0.42	0.09	0.65	0.54–0.79	<.001
Log FENO at baseline	0.15	0.09	1.17	0.98–1.39	.09

*Variables included previous exacerbations, log of eosinophils, log of FENO, log total IgE level, age, body mass index, FEV₁, eosinophil (<300 and $\geq$ 300 cells/ μ L) and FENO (<25 and $\geq$ 25 ppb) cutoff points, and use of beclomethasone at baseline.

‡ Reference group is the group without previous exacerbations.

Patients with IgE levels outside the limits of the dosing table²⁵ had a mean improvement in ACT score from baseline to month 12: 3.8 ± 4.6 for patients with IgE levels of less than 30 IU/mL ($n = 70$) and 5.0 ± 4.9 for patients with IgE levels of more than 700 IU/mL ($n = 118$).

In adults, those in the eosinophil-high group had a higher least squares mean (standard error) change in ACT score compared with those in the eosinophil-low group (Figure 6, A). A significant difference was noted between the eosinophil subgroups, but both reached the MID. The difference between the FENO-high and FENO-low subgroups was not statistically significant. At month 12, a greater proportion of patients in the high-biomarker subgroups were well controlled (ACT ≥ 20) than patients in the low-biomarker subgroups (Figure 6, B).

Responder analysis

On the basis of our responder definitions, 86.9% (691 of 795) of patients met 1 or more responder criteria and were characterized as responders: 77.8% (495 of 636) by an exacerbation reduction of 50% or more, 64.7% (510 of 788) by ACT improvement, and 35.9% (226 of 630) by FEV₁ improvement (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Individuals were responders by more than 1 definition: 54.1% (340 of 629) by exacerbation reduction and ACT score improvement, 29.4% (148 of 504) by exacerbation reduction and lung function improvement, and 26.6% (167 of 627) by ACT score and lung function improvement. Of the 501 patients who had nonmissing values in all 3 domains, 23.0% (115) were responders in all 3 categories.

Multiple logistic regression analysis indicated that males were less likely to be responders (using all 3 criteria) than females (odds ratio [OR], 0.49; 95% CI, 0.277–0.863; $P = .014$).

Patients were significantly more likely to be responders if they had 1 or more (OR, 4.36; 95% CI, 1.38–16.92; $P = .019$) positive allergen-specific IgE test results compared with 0 positive results.

Patients with high baseline eosinophil levels were more likely to be ACT responders (OR, 1.65; 95% CI, 1.100–2.512; $P = .017$) compared with those with low baseline eosinophil levels; patients with controlled asthma (ACT ≥ 20) at baseline were less likely to be lung function responders (OR, 0.49; 95% CI, 0.25–0.91; $P = .029$) and patients receiving asthma medications in addition to inhaled corticosteroid/long-acting β_2 agonist alone were more likely to be lung function responders (OR, 2.63; 95% CI, 1.38–5.35; $P = .005$). Aside from increased number of exacerbations 12 months before the study and sex, no factor was associated with increased odds of being a responder by exacerbation definition.

Safety

Overall, 11.2% (90 of 801) of patients experienced a total of 144 SAEs: 7.2% (5 of 69) of adolescents experienced a total of 7 SAEs and 11.6% (85 of 732) of adults experienced a total of 137 SAEs. The most common SAEs were asthma in 3.2% (26 of 801), pneumonia in 1.4% (11 of 801), chronic obstructive pulmonary disease in 0.5% (4 of 801), and pulmonary embolism and status asthmaticus in 0.4% (3 of 801) each. There were 7 deaths from AEs during the study, 6 in adults (car accident, cardiogenic shock, cardiac arrest, malignant neoplasm, pneumonia, and intracerebellar hemorrhage) and 1 in an adolescent (non-Hodgkin lymphoma diagnosed after study entry). None of the adult deaths were determined to be related to omalizumab; causality of the death in the adolescent was unknown. Four (0.5%) patients reported 10 anaphylactic events, including 5

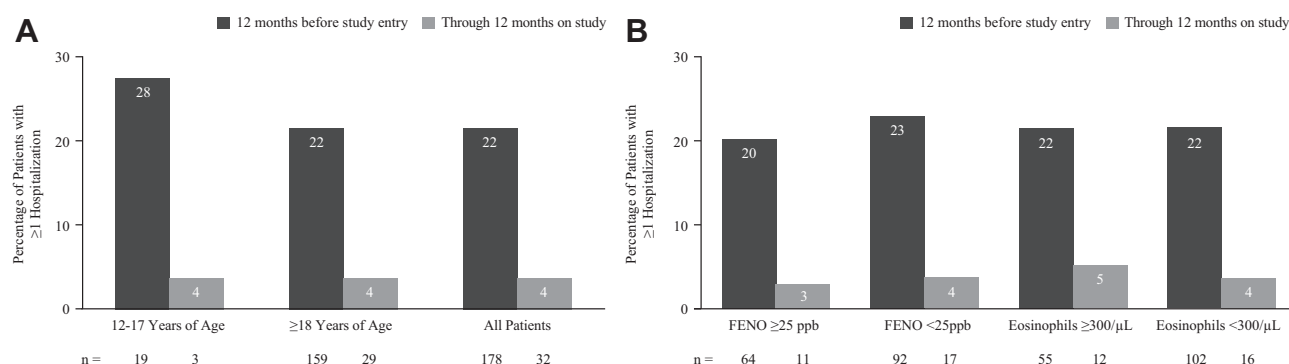


FIGURE 3. Percentage of patients with 1 or more hospitalizations by (A) age group and (B) biomarker status.

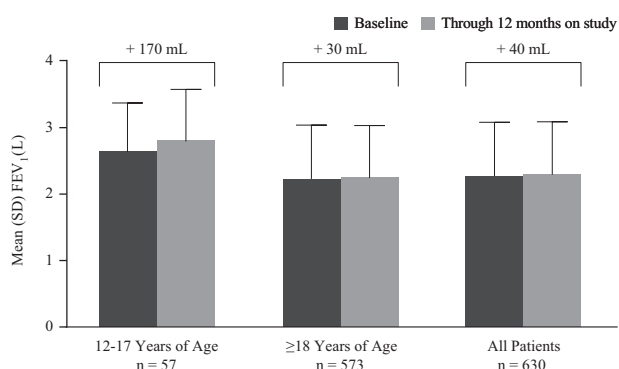


FIGURE 4. Mean prebronchodilator FEV₁ (L) by age group (for patients with spirometry at baseline and end of the study).

SAEs (not related to the study drug) and 5 non-SAEs (all related to the study drug). Of the 4 patients, 1 patient with a history of mast cell activation disorder (also had moderate to severe uncontrolled allergic asthma) reported a total of 7 events of anaphylactic reaction. In 3 of the 4 patients, the study drug was permanently discontinued.

There were only 3 (0.4%) AEs of special interest that were reported. All 3 events were anaphylactic events of moderate severity and related to omalizumab. All events were reported in adults; no events were reported in the adolescent population.

DISCUSSION

In the 12-month period after omalizumab initiation in PROSPERO, patients experienced significant reductions in exacerbations, fewer hospitalizations, and clinically significant improvement in ACT scores when compared with the 12 months before treatment. These improvements were generally similar among age-defined subgroups. Patients in the study were described by their physician as being approximately 50% moderate and 50% severe. Measured ACT scores and number of exacerbations suggest that more patients had severe asthma than was classified by the prescribing physician. Asthma symptom control, as measured by ACT, showed greater improvement in the high- versus low-biomarker subgroups. Most patients who were uncontrolled at study entry became controlled at the study end; a greater percentage of patients in the high-biomarker subgroups became well controlled by study end compared with

patients in the low-biomarker subgroups. These findings are consistent with the results of a meta-analysis evaluating omalizumab effectiveness in real-world settings that described the association of omalizumab with treatment response and asthma symptom control.²⁶

Omalizumab was effective across a range of biomarker values. Biomarkers were useful in predicting ACT score change, but given that all biomarker subgroups achieved or exceeded the MID, their usefulness in predicting response remains to be determined. Also, although differences in FEV₁ were noted to be statistically significant between high- and low-biomarker groups, the magnitude of the change was modest (60–70 mL improvement in low- vs high-biomarker group), and thus the clinical relevance remains to be determined. Multivariate analysis of responder data suggested that males were less likely to respond than females, and patients with at least 1 positive allergen-specific IgE test result were more likely to respond than were patients without. However, the absence of a placebo arm limits the interpretation of these findings. Previous analysis of pooled clinical studies identified parameters that were predictive of a response to omalizumab treatment in patients with allergic asthma: high doses of inhaled corticosteroid, history of emergency asthma treatment in the past year, and a low FEV₁ (≤65% predicted).²⁷ Other pooled analyses of omalizumab data in patients with severe allergic asthma suggest there was no baseline characteristic that predicted response to omalizumab.²⁸

The importance of comparing our results with previously published data in the proper context is paramount. Published placebo-controlled data have suggested that biomarkers may be useful to clinicians attempting to identify patients who would benefit from treatment with omalizumab versus not treating them.^{21,29,30} For example, in the *post hoc* analysis of the Study of Omalizumab (Xolair) in Subjects with Moderate to Severe Persistent Asthma (EXTRA), reductions in exacerbation frequency were the greatest in omalizumab-treated patients with high levels of baseline biomarkers when compared with placebo, suggesting that patients with higher baseline biomarkers experience a greater benefit from treatment.³⁰ As was the case in a *post hoc* analysis of data from the omalizumab pivotal trials,³¹ it is the high exacerbation rate in the untreated/placebo arm that is driving the response difference between the high- and low-biomarker groups. In PROSPERO, patients responded equally well to omalizumab regardless of their baseline blood eosinophil or FENO levels. Similarly, a close examination of the data from only the omalizumab-treated patients in EXTRA reveals an

TABLE II. Relationship of change in FEV₁ (L) to baseline biomarker during omalizumab treatment

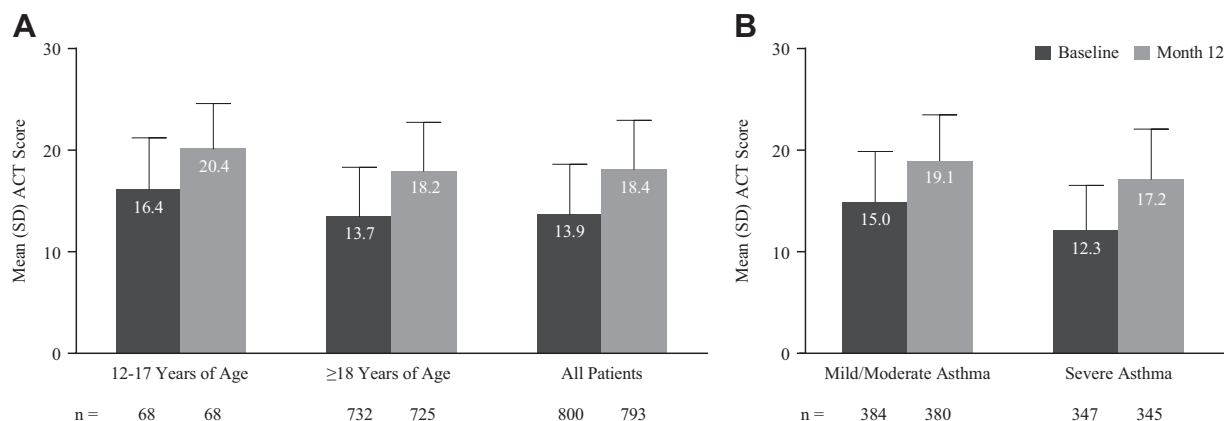
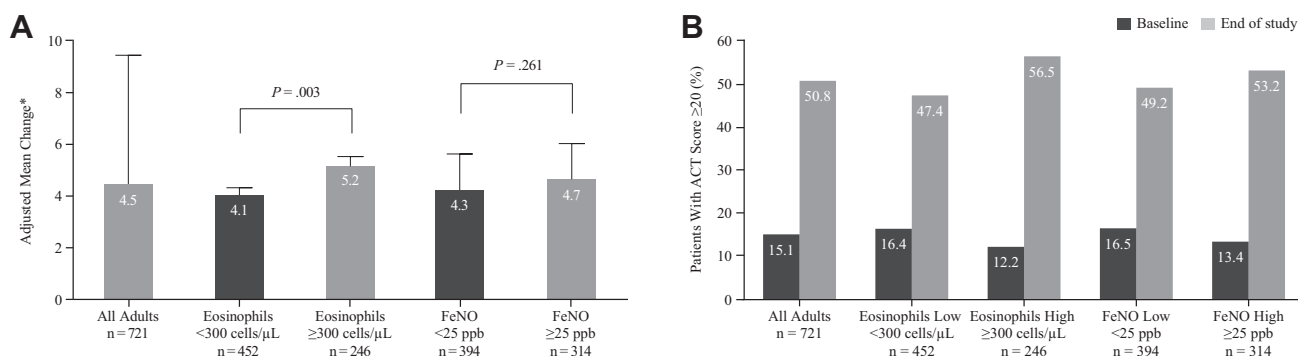
Adjusted mean change: FEV ₁ (L)	n*	Baseline mean $\pm$ SD	Change from baseline LSMean (95% CI)†	Adjusted P value (low vs high)‡
Eosinophils low (<300 cells/ μ L)	362	2.28 $\pm$ 0.82	−0.01 (−0.04 to 0.03)‡	.011
Eosinophils high ($\geq$ 300 cells/ μ L)	188	2.19 $\pm$ 0.78	0.08 (0.03 to 0.13)‡	
FeNO low (<25 ppb)	310	2.25 $\pm$ 0.78	−0.02 (−0.06 to 0.02)‡	.002
FeNO high ($\geq$ 25 ppb)	253	2.28 $\pm$ 0.83	0.08 (0.03 to 0.12)‡	

LS, Least squares.

*n reflects the number of patients with biomarker measurement and variable measured.

†LSMean refers to statistical methodology designed to estimate a mean for a balanced population. LSMean and P values come from baseline adjustments.

‡LSMean change from baseline.

**FIGURE 5.** Mean ACT score 12 months after omalizumab initiation by (A) age group and (B) asthma severity.**FIGURE 6.** Impact of biomarker status on ACT outcomes. (A) Mean change from baseline in ACT score 12 months after omalizumab initiation in adults. (B) Percentage of patients with well-controlled asthma. P values reflect adjustment for difference in baseline characteristics. *Baseline mean $\pm$ SD; through month 12 least squares mean (SE).

absence of substantial differences in exacerbation frequency between high- and low-biomarker subgroups. It suggests that even patients in the low-biomarker subgroup can benefit from omalizumab treatment.

PROSPERO confirms that patients exhibit different unmet asthma control needs: some are exacerbation-prone, whereas others exhibit poor lung function or symptom impairment. We noted that 86.9% of patients were classified as responders on the basis of meeting at least 1 of the responder criteria. Most of them were responders on the basis of exacerbation reduction. However, a significant number of patients experienced lung function improvements or gained control of their asthma symptoms independent of experiencing a reduction in exacerbations,

indicating that individual patients obtain different benefits after initiating treatment with omalizumab.

Clinically significant variability in total IgE levels measured in patients with moderate to severe persistent asthma over a 1-year period has been described.³² In PROSPERO, 23.8% of patients had IgE levels that fell outside the recommended limits of the dosing table.²⁵ In these patients, a wide range of omalizumab doses were used, many outside the dosing table from omalizumab US prescribing information recommendations. However, patients dosed outside the recommendations had similar outcomes, on the basis of reduction in exacerbations and improvement in ACT scores, compared with patients who were dosed as per the prescribing guidelines. There have been several reports in

the literature describing the use and benefit of omalizumab in patients with IgE or IgE and body weight outside the limits of the US dosing table.³³⁻³⁶ Some of those are based on the European Union dosing table, which allows for IgE levels of up to 1500 IU/mL, whereas others are based on the dosing formula (from which the table is derived) of either a minimum of 0.008 mg/kg/IgE (IU/mL) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks, up to a maximum dose of 750 mg every 4 weeks.³⁷ Given that these reports are based on different derivations of the US dosing table, it is not surprising that such patients have exhibited evidence of benefit.

On average across the entire population, improvement in lung function was observed to only a clinically relevant level³⁸ in the adolescent population. Increase in lung function in children and adolescents after omalizumab initiation has been described previously³⁹; the observed change also may be the result of normal growth over the study period.⁴⁰ We did identify a subgroup of patients (35.9%) within the entire population who experienced significant improvements in lung function after omalizumab initiation, and these patients tended to be on controller medications in addition to inhaled corticosteroid and long-acting β_2 agonist, likely reflective of lower baseline lung function. In adults, those with high levels of T2 biomarkers at baseline had significant improvements in percent-predicted FEV₁ compared with the low-biomarker subgroup, but the absolute improvement was modest.

Study limitations

The major limitation of PROSPERO is its lack of a control arm, with all the inherent shortcomings this presents. PROSPERO reflects actual use of omalizumab and reports patient outcomes after treatment initiation. PROSPERO included patients who may not have qualified for placebo-controlled trials. Formal causal inference about omalizumab efficacy or inference about the comparative effectiveness of omalizumab was beyond the scope of this study. The responder analysis was conducted in a population without a placebo arm, and thus these results must be interpreted with caution.

CONCLUSIONS

In patients with asthma, 12 months after initiating omalizumab treatment there was evidence of clinically significant improvements in asthma control reflected through improved exacerbation rates, reduced hospitalizations, and improved ACT scores compared with pretreatment baseline values. These improvements were similar for patients with IgE levels that were outside the limits of the omalizumab dosing table. Biomarker status at baseline was associated with ACT scores and lung function improvement, although the clinical relevance of these differential improvements remains to be determined. Although improvements in lung function were observed across the entire population, they were clinically relevant only in the adolescent population. Most patients whose asthma was uncontrolled at study entry became controlled by study end. AEs were consistent with the safety profile in the current product label. Once the decision was made to initiate omalizumab, biomarker status had minimal influence on omalizumab treatment outcomes.

Acknowledgements

We thank Linda Wagner of Envision Pharma Inc for providing third-party writing assistance.

REFERENCES

- Global Initiative for Asthma. Global strategy for asthma management and prevention; 2016. Available from: www.ginasthma.org. Accessed December 9, 2016.
- Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. *Allergy Asthma Proc* 2012;33:54-64.
- Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). *J Asthma* 2010;47:257-62.
- Anderson HM, Lemanske RF Jr, Arron JR, Holweg CT, Rajamanickam V, Gangnon RE, et al. Relationships among aeroallergen sensitization, peripheral blood eosinophils, and periostin in pediatric asthma development. *J Allergy Clin Immunol* 2017;139:790-6.
- Bjerner L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016;150:789-98.
- Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al, SIROCCO Study Investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
- Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
- Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014;2:879-90.
- Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
- Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.
- FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al, CALIMA Study Investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
- Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016;4:781-96.
- Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax* 2015;70:748-56.
- Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al, MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
- Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J* 2013;41:330-8.
- Chippes BE, Zeiger RS, Luskin A, Busse W, Trzaskoma B, Antonova E, et al. Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO. *Ann Allergy Asthma Immunol* 2017;119:524-532.e522.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
- Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the asthma control test. *J Allergy Clin Immunol* 2009;124:719-723.e1.
- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al, American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.
- Hanania NA, Trzaskoma B, Rosen K, Manga V, Omachi TA. Exploring omalizumab in allergic asthma: an analysis of efficacy by asthma severity and eosinophilic status using pivotal trial studies. *Am J Respir Crit Care Med* 2015;191:A4150.

22. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
23. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD* 2005;2:111-24.
24. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999;14:23-7.
25. Xolair [prescribing information]. South San Francisco, CA: Genentech, Inc, and Novartis Pharmaceuticals Corp; 2016.
26. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. *J Allergy Clin Immunol Pract* 2017;5:1362-1370.e2.
27. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125:1378-86.
28. Bousquet J, Rabe K, Humbert M, Chung KF, Berger W, Fox H, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 2007;101:1483-92.
29. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol* 2013;132:485-486.e11.
30. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
31. Casale TB, Chipps BE, Rosen K, Trzaskoma B, Haselkorn T, Omachi TA, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy* 2018;73:490-7.
32. Hatipoglu U, Subramanian A, Campbell T, Rice R, Mummadi S, Hu B, et al. Intrasubject variability in total IgE levels in patients with moderate to severe persistent allergic asthma over 1 year. *J Allergy Clin Immunol Pract* 2016;4:691-696.e1.
33. Barthwal M, Dutta V, Bhattacharya P, Vora A, Kotnis M. Real-world outcomes in patients receiving omalizumab for allergic asthma in India: analysis by baseline IgE level. *Eur Respir J* 2013;42:P915.
34. Kornmann O, Watz H, Fuhr R, Krug N, Erpenbeck VJ, Kaiser G. Omalizumab in patients with allergic (IgE-mediated) asthma and IgE/bodyweight combinations above those in the initially approved dosing table. *Pulm Pharmacol Ther* 2014;28:149-53.
35. Zielen S, Lieb A, De La Motte S, Wagner F, de Monchy J, Fuhr R, et al. Omalizumab protects against allergen-induced bronchoconstriction in allergic (immunoglobulin E-mediated) asthma. *Int Arch Allergy Immunol* 2013;160:102-10.
36. Kwong KY, Jones CA. Improvement of asthma control with omalizumab in 2 obese pediatric asthma patients. *Ann Allergy Asthma Immunol* 2006;97:288-93.
37. Hew M, Gillman A, Sutherland M, Wark P, Bowden J, Guo M, et al. Real-life effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria. *Clin Exp Allergy* 2016;46:1407-15.
38. Tepper RS, Wise RS, Covar R, Irvin CG, Kerckmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol* 2012;129(Suppl.):S65-87.
39. Deschildre A, Marguet C, Salleron J, Pin I, Rittié JL, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013;42:1224-33.
40. Speizer FE, Tager IB. Epidemiology of chronic mucus hypersecretion and obstructive airways disease. *Epidemiol Rev* 1979;1:124-42.

ONLINE REPOSITORY

TABLE E1. Responder analysis

Responder definition	Yes	No
Met ≥ 1 responder criteria*	691 of 795 (86.9%)	104 of 795 (13.1%)
Exacerbation reduction $\geq 50\%$ from baseline†	495 of 636 (77.8%)	141 of 636 (22.2%)
ACT score improvement‡	510 of 788 (64.7%)	278 of 788 (35.3%)
FEV ₁ improvement§	226 of 630 (35.9%)	404 of 630 (64.1%)

*Responder definition includes exacerbation reduction, ACT improvement, and FEV₁ improvement.

†Patients had to have at least 1 exacerbation in the previous 12 mo.

‡Changed from uncontrolled at baseline on the basis of ACT score of ≤ 19 to controlled at the end of the study (ACT score ≥ 20) or who achieved at least a 3-point improvement (MID) in ACT score.

§Achieved at least a 120-mL improvement in FEV₁ from baseline to end of the study.

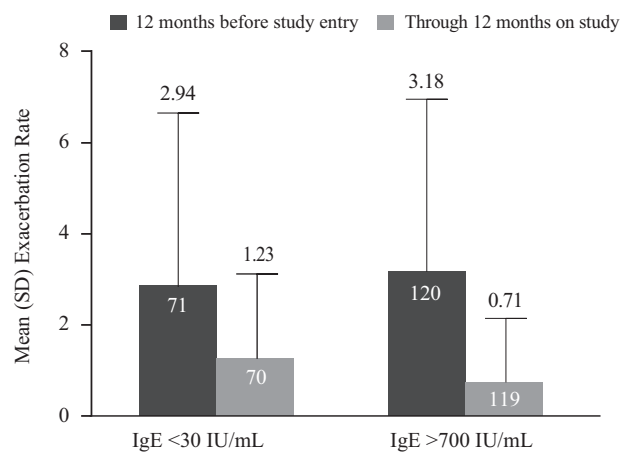


FIGURE E1. Exacerbation rate before study entry and through 12 months on study for patients with IgE levels outside the limits of the omalizumab dosing table.