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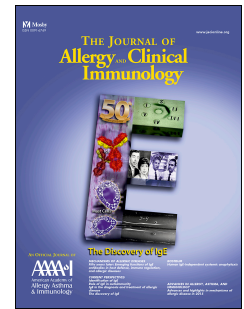
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**A Randomized, Multicenter Study Evaluating Xolair® Persistency Of Response After Long-Term
Therapy (XPORT)**

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ABSTRACT

Background: Few data are available to assist clinicians with decisions regarding long-term use of asthma therapies, including omalizumab.

Objective: To evaluate the benefit and persistency of response in subjects continuing or withdrawing from long-term omalizumab treatment.

Methods: Evaluating the Xolair® Persistency Of Response After Long-Term Therapy (XPORT) was a randomized, double-blind, placebo-controlled withdrawal study that included subjects with moderate-to-severe persistent asthma receiving long-term omalizumab. Subjects were randomized using a hierarchical dynamic randomization scheme, to continue their same dose of omalizumab or withdraw to placebo and were then followed every 4 weeks for 1 year. Primary outcome: any protocol-defined severe asthma exacerbation. Secondary outcome: time to first protocol-defined severe asthma exacerbation. Exploratory outcomes included changes in Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) scores.

Results: Significantly more subjects in the omalizumab group (67%) had no protocol-defined exacerbation than in the placebo group (47.7%); absolute difference of 19.3% (95% CI: 5.0%, 33.6%) represents a 40.1% relative difference. Time to first protocol-defined exacerbation analysis revealed a significantly different between-group exacerbation pattern that was consistent with the primary analysis. Subjects continuing omalizumab had significantly better asthma control (mean [SD] change from baseline to Week 52: ACT, -1.16 [4.14] vs placebo, -2.88 [5.38]; $P = .0188$ and ACQ, 0.22 [0.66] vs placebo, 0.63 [1.13]); $P = .0039$. Discontinuation of omalizumab was associated with an increase in free IgE and an increase in basophil expression of the high-affinity IgE receptor. No safety concerns were noted.

Conclusion: Continuation of omalizumab following long-term treatment results in continued benefit as evidenced by improved symptom control and reduced exacerbation risk.

Clinical Implications

Patients continue to benefit from ongoing use of omalizumab after long-term treatment; FeNO and blood eosinophil counts may be useful biomarkers to guide treatment decisions.

Capsule Summary

Continuation of omalizumab after long-term use results in improved symptom control and a reduced exacerbation risk. Use of biomarkers (FeNO and peripheral blood eosinophil counts) may further inform omalizumab treatment decisions.

Key words: Asthma, omalizumab, persistence, eosinophilia, exacerbations, IgE, high-affinity IgE receptor, long-term treatment, FeNO

83 Abbreviations

84 ACQ: Asthma Control Questionnaire

85 ACT: Asthma Control Test

86 AE: Adverse event

87 ED: Emergency department

88 FcεRI: High-affinity IgE receptor

89 FeNO: Fractional exhaled nitric oxide

90 FEV₁: Forced expiratory volume in one second

91 HR: Hazard ratio

92 ICS: Inhaled corticosteroid

93 LABA: Long-acting beta agonist

94 MESF: Molecules of equivalent, soluble fluorochrome units

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96 OR: odds ratio

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98 SAE: Serious adverse event

99 s-IgE: Specific IgE

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INTRODUCTION

Omalizumab (Xolair®, Genentech, Inc. South San Francisco, California) is a recombinant, DNA-derived, humanized IgG1κ monoclonal antibody that selectively binds to human IgE and is approved for management of moderate-to-severe allergic asthma.¹ Guidelines recommend consideration of the addition of omalizumab for individuals with allergic asthma who are not adequately controlled with high dose inhaled corticosteroids (ICS) plus a long-acting beta agonist (LABA).^{2,3} In vivo, omalizumab selectively binds to unbound (free) human IgE at the same Fc site as the high affinity IgE receptor (FcεRI), thereby blocking the interaction of IgE with FcεRI.^{4,5} The expression of FcεRI on mast cells and basophils is also reduced, resulting in a reduction of mast cell and basophil mediator release.⁶ Treatment with omalizumab reduces the risk of exacerbations in allergic asthma in clinical studies up to 1 year,⁷⁻¹⁰ but there are limited data regarding the long-term efficacy or persistency of a beneficial effect after its discontinuation.^{4,5,11-13}

The Evaluating the Xolair® Persistency Of Response After Long-Term Therapy (XPORT; ClinicalTrials.gov identifier: NCT01125748) study was designed to determine whether subjects receiving long-term treatment with omalizumab demonstrate persistency of treatment effect after omalizumab discontinuation and to examine whether the benefits of omalizumab are sustained when therapy is continued.

METHODS

Study design

XPORT was a 52-week, randomized, double-blind, placebo-controlled, multicenter study conducted in the United States from May 2010 to August 2013. The primary objective was to evaluate the persistency of response to omalizumab in subjects with moderate-to-severe persistent allergic asthma who discontinued omalizumab therapy after long-term use. The secondary objective was to evaluate the safety of omalizumab discontinuation or continuation following long-term use. All subjects provided written informed consent for study participation. The study was conducted according to the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, the US Food and Drug Administration regulations, and any applicable national laws. Visits, conducted at the investigator's clinical site, were scheduled at 4-week (± 4 days) intervals over the 1-year study, beginning with the screening (baseline) visit at Week 0. At screening, demographic information, concomitant medications, and medical/surgical/smoking history were documented. A physical examination, chest x-ray, and spirometry were performed and other clinical laboratory assessments were collected. Some centers performed fractional exhaled nitric oxide (FeNO) measurements at baseline. In addition, each subject's personal best peak expiratory flow was documented. A checklist of prior asthma medications was completed and number of protocol-defined severe exacerbations per year in the previous 5 years was collected. Additional measures assessed at baseline included the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ).

The majority of subjects in this study were recruited from a previously completed long-term, observational, epidemiologic study (EXCELS, ClinicalTrials.gov identifier: NCT00252135). EXCELS included subjects ≥ 12 years of age with moderate-to-severe asthma with a history of a positive skin test or in vitro reactivity to a perennial aeroallergen.¹⁴ Subjects from EXCELS must have completed EXCELS and not discontinued omalizumab since completion of EXCELS. A protocol amendment based on investigator request added the following: subjects could be included in XPORT even if they had not participated in EXCELS but had received long-term (~ 5 years) treatment with omalizumab before randomization as substantiated by injection records. Subjects were randomized 1:1 to continue their pre-enrollment dose of omalizumab (omalizumab group) or were withdrawn from omalizumab and switched to placebo treatment (placebo group). Randomization was stratified for ICS use at baseline and level of asthma control at baseline (well-controlled, ACT Score ≥ 20 vs. not well-controlled, ACT Score < 20), for the omalizumab dosing interval that the subject received at baseline (2 vs. 4 weeks), and for study site. A

hierarchical dynamic randomization scheme was used to achieve approximate, overall balance between treatment groups and within each stratum. At randomization, subjects entering the study from outside of EXCELS were stratified separately from the subjects who had participated in EXCELS to ensure that both subgroups were adequately balanced. An interactive voice response system was used for randomization.

At each subsequent study visit, a physical examination and spirometry were performed, vital signs were measured, concomitant medications and unscheduled asthma-related medical visits were documented, and the ACT and ACQ were administered. Blood samples collected at baseline and Weeks 12, 24, 36, and 52 were analyzed for total, free, and specific IgE (s-IgE), basophil FcεRI expression measured by flow cytometry, and other clinical laboratory assessments. FeNO data were collected at Weeks 12, 24, 36, and 52 in some centers.

The primary efficacy endpoint was any protocol-defined severe asthma exacerbation, defined as a clinically significant worsening of asthma during the study period (52 weeks), which in the clinical judgment of the investigator, required at least one of the following: 1) initiation of systemic corticosteroid treatment (tablets, suspension, injection); 2) any clinically significant worsening of asthma requiring ≥ 3 days of treatment with ≥ 20 -mg increase in the average daily dose of prednisone or a comparable dose of systemic corticosteroid in subjects already on chronic oral corticosteroids; or 3) a hospitalization or emergency department (ED) visit because of asthma requiring administration of systemic corticosteroids. The secondary efficacy outcome measure was the time to first protocol-defined severe asthma exacerbation. Protocol-defined exploratory outcome measures included the change from baseline in ACT, ACQ, spirometry (forced expiratory volume in 1 second [FEV₁]), FeNO (measured in selected study sites using a hand-held portable device, NIOX MINO®, Aerocrine (now Circassia), Solna, Sweden), free and total serum IgE concentrations, and basophil FcεRI expression. Safety outcome measures included the frequency and severity of adverse events (AEs) and serious AEs (SAEs), vital signs, and clinical laboratory assessments including hematology, serum chemistry, and urinalysis.

After the primary endpoint was met at the first exacerbation, unblinding was permitted and subjects could have their therapy altered at the discretion of the treating physician. Subjects receiving placebo at the time of exacerbation subsequently could be treated with omalizumab. Adjustments were made to include these subjects in the omalizumab exposure safety population.

Study subjects

Subjects were eligible for study inclusion if they were aged 17 to 70 years inclusive, had continuous omalizumab exposure (having missed $\leq 25\%$ of scheduled omalizumab doses) with omalizumab dose and dosing schedule consistent with US prescribing information,¹ and received stable doses of other asthma therapies for ≥ 2 months before enrollment. Exclusion criteria included: current participation in another clinical study; acute asthma exacerbation within 2 months of screening that required initiation of systemic corticosteroids, increase in systemic corticosteroid dose, doubling of ICS dose, ED visit or hospitalization within 2 months of study entry; significant or unstable systemic disease; active lung disease other than asthma; ≥ 10 pack-year smoking history; use of an experimental drug within 30 days before study screening; pregnancy, lactation, or any planned pregnancy during the study year; or elevated serum IgE levels for reasons other than allergy.

Treatments

Study treatments (omalizumab or placebo) were administered subcutaneously following the subject's pre-enrollment dose and dosing interval unless there was a significant change in body weight since initial dosing and the omalizumab dose was adjusted, if necessary, based on the US prescribing information. The minimum dose of omalizumab was 0.008 mg/kg/IgE (IU/mL) every 2 weeks or 0.016 mg/kg/IgE (IU/mL) every 4 weeks from Week 0 through 48 (13 or 26 total doses). Doses >150 mg were divided among more than one injection site. Placebo treatment contained the same ingredients excluding the omalizumab component.

Use of specific concomitant medications was permitted: ICS, LABAs, leukotriene receptor antagonist, 5-lipoxygenase inhibitors, anticholinergics (oral, inhaled, and/or nasal), mast-cell stabilizers, theophylline, and/or chronic oral corticosteroids (prednisone equivalent 2-40 mg/day or 5-80 mg every other day for at least 4 weeks prior to screening). Allergen immunotherapy was permitted but not tracked because it was not anticipated to impact the study outcome.

Analysis

Sample size calculations were based on precision estimates. We estimated that a sample size of 90 subjects in each group (omalizumab and placebo) would have a precision of 0.11 (placebo) and 0.15 (treatment difference) assuming a persistency response of 0.40 for the placebo group and 0.70 for the omalizumab group and a 10% drop-out rate before reaching the primary endpoint. The intent-to-treat population included all randomized subjects based on randomized treatment groups regardless of actual treatment. The per-protocol population included all subjects who were not included in the major

protocol violation listing based on blinded clinical review. The safety population was described in two ways: 1) at least one injection population (included all subjects who had received at least one injection [active drug or placebo]), and 2) omalizumab exposure population (included all subjects who received at least one injection of omalizumab while on study including placebo subjects who received omalizumab after a protocol-defined exacerbation and subsequent unblinding).

The primary efficacy analysis included counts and proportions of the subjects without any protocol-defined severe asthma exacerbations for each treatment group among all subjects as well as in the subgroup of subjects receiving ICS at baseline. Precision of the estimates was evaluated by including 95% CIs. The difference in the proportions of responders between the treatment groups was calculated, in addition to a 95% CI, using normal approximation to the binomial distribution. Sensitivity analysis for the primary efficacy endpoint was conducted by repeating the analysis for the per-protocol population.

The secondary efficacy analysis was performed for all subjects as well as the subgroup of subjects receiving ICS at baseline. For the time to first protocol-defined severe asthma exacerbation, the hazard ratio (HR) comparing the two treatment groups was calculated and the 95% CI reported, based on a Cox proportional hazards model with treatment as the only predictor in the model. For the exploratory outcome measures, analysis included descriptive summaries of continuous changes and the difference between study groups; *P* values were derived using Student's *t*-test. Whenever an exploratory endpoint was categorical in nature, a chi-square test was used in conjunction with descriptive summaries of the counts and proportions within each study group to evaluate the statistical differences between the groups. AEs were summarized by the treatments actually administered for the controlled period of observation as well as the uncontrolled period after a subject was unblinded.

If a subject discontinued before the end of the 1-year treatment period and had not reached the primary endpoint, the subject was considered a nonresponder (imputed as "having a severe exacerbation") for the primary endpoint. For the calculation of time to nonresponse, subjects were censored at the point of discontinuation and the discontinuation date was used as the event time. For the exploratory outcome measures, if a subject discontinued before the end of the 1-year treatment period, the data after the point of discontinuation were imputed using the last observation carried forward (LOCF) method. This method was chosen because the study had good subject completion rates.

As a post hoc analysis, a univariate logistic regression was used to determine if the change in FeNO from baseline to Week 12 (date of first measurement) was predictive of future exacerbations.

RESULTS

Subject population

The intent-to-treat and safety populations included 176 subjects who were randomized to continuation of treatment with omalizumab (n = 88) or to withdrawal and placebo treatment (n = 88; Fig 1). Twenty subjects, 9/88 (10.2%) and 11/88 (12.5%) in the omalizumab and placebo groups, respectively, discontinued the study without first experiencing a protocol-defined severe exacerbation and required an imputation of their primary endpoint. The omalizumab-exposed safety population (n = 121) included subjects continuing omalizumab (n = 88) and placebo subjects (n = 33) who were given omalizumab after a protocol-defined exacerbation and subsequent unblinding.

Most baseline demographics and disease characteristics were similar across treatment groups (Table I). The average subject age was 51.5 years and most (69.9%) subjects were female. The majority (69.2%) of subjects had never smoked. Most of the subjects were from the EXCELS study (~85% in each group). ICS were used by 83.5% of subjects at baseline. Diabetes mellitus was noted in more subjects in the omalizumab group than in the placebo group (20.5% vs 13.6%), as was a higher exposure to biguanides (eg, metformin; 14.9% vs 6.8%). Regular use of nonsteroidal anti-inflammatory agents was also higher in the omalizumab group than in the placebo group (33.1% vs 19.3%).

Most (150/176, 85%) subjects entered XPORT following participation in EXCELS. Baseline demographics and characteristics by EXCELS participation are provided in Table E1 in the Online Repository.

Primary efficacy endpoint

A significantly greater number of subjects had no protocol-defined exacerbations in the omalizumab group (n = 59, 67.0%) versus the placebo group (n = 42, 47.7%). This absolute difference of 19.3% (95% CI: 5.0%, 33.6%) represents a 40.1% relative difference. The unadjusted odds ratio (OR) and 95% CI for omalizumab was 0.45 (0.24, 0.83). The OR (95% CI) adjusted for age, sex, ICS use, EXCELS study participation, number of severe exacerbations in year before study entry, and percent predicted FEV₁ was similar (0.44 [0.23, 0.82]). Similar results were observed in the subgroup of subjects receiving ICS at baseline: a greater number of subjects had no protocol-defined exacerbations in the omalizumab group (n = 51, 69.9% [95% CI: 59.3%, 80.4%]) versus the placebo group (n = 35, 47.3% [95% CI: 35.9%, 58.7%]). The overall and adjusted OR (95% CI) for subjects receiving ICS at baseline was 0.39 (0.20, 0.76). Per-protocol analysis supported these results (see Table E2 in the Online Repository).

Secondary and exploratory outcome measures

Analyses using Cox proportional hazard modeling demonstrated that time to first protocol-defined exacerbation showed a significantly different between-group exacerbation pattern that was consistent with the primary analysis (Fig 2); it was longer in the omalizumab group compared with the placebo group (HR:0.49 [95%CI:0.28, 0.86]). These results were similar for the subgroup of subjects receiving ICS at baseline. Symptom control was also significantly greater in the omalizumab group versus the placebo group as evidenced by the mean (SD) change from baseline to Week 52 in ACT and ACQ scores (Fig 3).

Total and free IgE levels remained stable from baseline to Week 52 in the omalizumab group while in the placebo group total IgE decreased and free IgE increased (Table II). The mean (SD) change from baseline to Week 52 in basophil expression of FcεRI was significantly greater in subjects in the placebo group compared with the omalizumab group (2136.36 [1087.65] molecules of equivalent, soluble fluorochrome units [MESF] vs 64.72 [348.65] MESF, $P < .0001$). There was no statistically significant difference between treatment groups in the change in FEV₁ from baseline to Week 52.

At baseline, there was no statistically significant difference in peripheral eosinophil counts between the placebo and omalizumab arms ($P = 0.70$) and the lack of a significant between-group difference was sustained at week 52 ($P = 0.76$). However, after omalizumab withdrawal, the difference in peripheral eosinophil count was statistically significantly higher in the placebo group with exacerbations compared with the group without exacerbations ($P < .001$). In contrast, pairwise comparison in peripheral eosinophil counts between the omalizumab group without exacerbations versus the group with exacerbations was not statistically significant (Fig 4).

Seventy-eight subjects had FeNO measurements (43 in the omalizumab cohort and 35 in the placebo cohort). There were no statistically significant differences between treatment groups at Weeks 12, 24, 36, and 52 as measured by change from baseline in FeNO. However, a univariate logistic regression analysis revealed that an increase in FeNO from baseline to Week 12 after omalizumab discontinuation was a positive predictor of exacerbations ($P = .038$). Similarly, when this regression analysis was repeated for the subset of subjects receiving an ICS at baseline, an increase in FeNO from baseline to Week 12 after omalizumab discontinuation was again seen as a positive predictor of exacerbations ($P = 0.047$). For subjects in the placebo group who experienced an exacerbation, there was a sharp rise in FeNO from baseline to Week 12 (Figure 5). Subjects in the omalizumab group who experienced an exacerbation also had a rise in FeNO from baseline to Week 12 but it was less pronounced. Subjects in either treatment group who did not experience an exacerbation showed no

increase in FeNO from baseline to Week 12. Rather, FeNO levels remained generally flat (placebo) or decreased (omalizumab).

Safety

During the study, there were 33 subjects who transitioned from placebo to omalizumab; therefore, AE rates were calculated per exposure time. Overall, the rate of AEs per 100 patient-years was similar in both treatment groups (placebo, 425.9 vs omalizumab, 413.2). The most common AEs reported (per 100 patient-years) were asthma (placebo, 71.8; omalizumab, 66.6), sinusitis (placebo, 30.8; omalizumab, 35.2), upper respiratory infection (placebo, 22.2; omalizumab 27.4) , and acute sinusitis (placebo, 25.7; omalizumab, 14.7). SAE rates per 100 patient-years were similar between the two treatment groups (placebo, 9.1; omalizumab, 8.3). The most common SAE reported (per 100 patient-years) was asthma (placebo 6.8, omalizumab 5.9). Two malignancy SAEs were reported in the study: adenocarcinoma of the colon in a subject in the omalizumab group and a mixed Müllerian tumor in a subject in the placebo group. One death was reported (placebo group) 7 months after the subject was withdrawn from the study for an SAE of a mixed Müllerian tumor that was diagnosed on Day 129. No subjects in the omalizumab group experienced an AE leading to study withdrawal. Two subjects in the placebo group experienced an AE leading to study withdrawal (mixed Müllerian tumor and angioedema).

DISCUSSION

This is the first randomized controlled trial to rigorously compare the risks and benefits of continuing versus discontinuing omalizumab after long-term use in subjects with allergic asthma. The results demonstrate that compared with subjects withdrawn to placebo, continuation of omalizumab resulted in sustained benefit in both domains of asthma control: risk (prevention of exacerbations) and impairment (symptom control). Less clear, however, is the extent to which a persistency of these benefits exists after omalizumab is discontinued, which was the primary rationale for conducting the study. Had the study shown equal and extremely high or extremely low percentages of subjects in both arms without exacerbations, it would be easier to infer that omalizumab had a persistent effect or had lost its efficacy, respectively. Neither of these extremes was seen in this study. Instead, the results are different for the two groups, with 47.7% of the placebo group experiencing no exacerbations and 67.0% of the continuation group experiencing no exacerbations. The relatively large percentage of subjects in the placebo arm with no exacerbations (47.7%) suggests a persistency of benefit in some subjects because these individuals presumably, but not necessarily, experienced frequent exacerbations before starting omalizumab.

To definitively answer the question regarding persistency, one would need to know the exacerbation rates and ACT/ACQ scores for the population before omalizumab initiation; then, one could compare the exacerbation rates and ACT/ACQ scores after omalizumab withdrawal to the rates and scores before omalizumab initiation to see if there was a difference. Unfortunately, this information is not available for the current study and this lack of pretreatment data limits any conclusions. The study is further limited by the fact that even if exacerbation rates prior to omalizumab initiation were known, exacerbation rates could not be calculated for the placebo group because subjects who experienced at least one exacerbation were allowed to be unblinded and switched to known study drug.

The findings regarding symptom control also suggest persistency of benefit from omalizumab in some subjects. ACT/ACQ scores at baseline indicate that subjects were reasonably well controlled on long-term omalizumab therapy, but presumably this was not the case before omalizumab initiation. The fact that ACT/ACQ scores had a statistically significant but relatively small degree of deterioration in the placebo group may also be an indication of persistency of benefit. Furthermore, since the data reflect mean group changes, it is likely that subjects with a persistency benefit experienced minimal or no deterioration while others had a more significant worsening.

It is possible that subjects experienced an improvement in their asthma independent of omalizumab treatment. However, a persistency effect from omalizumab would be consistent with the

study from Nopp et al¹² in which most of 18 adult, atopic subjects treated with omalizumab for 6 years remained clinically stable up to 14 months following omalizumab discontinuation.

Several immunologic changes were observed in the 52 weeks following omalizumab discontinuation, including an increase in free IgE and an increase in basophil expression of FcεRI. These immunologic marker changes correlated with the observed worsening of symptom control and increased risk for exacerbation following discontinuation of omalizumab. These findings are consistent with previous studies and reflective of the current understanding of omalizumab's mechanism of action.^{4-6,13}

While data from the predefined outcome measures do not clearly identify subpopulations of subjects receiving omalizumab who can be withdrawn from treatment without loss of asthma control, the data regarding eosinophil counts and FeNO measurements do provide some insights for clinicians. At baseline, there was no difference in peripheral blood eosinophil counts between the omalizumab and placebo groups. However, when the two treatment arms were divided into subgroups based on whether they experienced an exacerbation, a higher baseline peripheral blood eosinophil count was observed in subjects in the placebo group who experienced an exacerbation. This suggests that subjects with persistently higher blood eosinophil counts during omalizumab treatment are more likely to have an exacerbation when omalizumab is discontinued. In contrast, this difference was not seen in subjects who exacerbated while maintaining omalizumab, suggesting a different mechanism for these exacerbations.

The relationship between FeNO and exacerbation risk identified in this study is more complex. In the group of subjects in which omalizumab was withdrawn, a rise in FeNO at Week 12 is predictive of increased risk of exacerbation. However, in the group continued on omalizumab, FeNO levels remained relatively stable irrespective of asthma exacerbation. This suggests that asthma exacerbations in subjects receiving long-term omalizumab may have triggers not reflected in FeNO changes. This is consistent with the peripheral blood eosinophil observation previously discussed. Furthermore, for subjects on omalizumab who persistently have a relatively high FeNO level, it may be even more important to maintain omalizumab therapy since continuation of therapy sustains benefit in terms of exacerbation risk reduction. While a relationship between changes in FeNO and exacerbations may be evident earlier than 12 weeks, this analysis was limited to looking at the first FeNO measurement 12 weeks after discontinuation of long-term omalizumab therapy.

Evidence from other studies suggests that peripheral blood eosinophil counts¹⁵⁻¹⁸ and FeNO¹⁵ are predictive of more severe asthma. In this study, the findings regarding FeNO measurements and

eosinophil counts are consistent with the post hoc analysis of the EXTRA study,¹⁹ which showed that omalizumab treatment was associated with greater effects in three high-biomarker subgroups (exhaled FeNO, blood eosinophils, blood periostin).

Thus, a consistent picture is emerging; withdrawal from omalizumab after long-term therapy results in reversal of the effects on IgE and basophils, which correlate with deterioration in asthma control. Additionally, while it is difficult to predict which patients can be safely withdrawn from omalizumab therapy, FeNO and peripheral blood eosinophil counts may be useful for guidance in making treatment decisions regarding omalizumab.

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Table I. Baseline demographics and disease characteristics (ITT population)

	Placebo (omalizumab discontinuation) (n = 88)	Omalizumab continuation (n = 88)	All subjects (N = 176)
Age, yr			
Mean (SD)	51.9 (13.3)	51.1 (11.7)	51.5 (12.5)
Median (range)	55.0 (19.0-70.0)	53.0 (17.0-70.0)	54.0 (17.0-70.0)
Female, n (%)	60 (68.2)	63 (71.6)	123 (69.9)
Race, n (%)			
White	73 (83.0)	75 (85.2)	148 (84.1)
Black	12 (13.6)	9 (10.2)	21 (11.9)
Weight, kg, mean (SD)	88.0 (20.3)	85.6 (24.4)	86.8 (22.4)
BMI, kg/m ² , mean (SD)	32.4 (7.7)	31.0 (8.3)	31.7 (8.0)
FEV ₁ , % predicted, mean (SD)	77.7 (19.2)	75.5 (18.8)	76.6 (19.0)
ACT Score, mean (SD)	21.3 (3.8)	21.3 (3.7)	21.3 (3.7)
ACQ Score, mean (SD)	1.0 (0.8)	1.0 (0.8)	1.0 (0.8)
Receiving ICS at baseline, n (%)	74 (84.1%)	73 (83.0%)	147 (83.5%)
Smoking status,* n (%)			
Current	1 (1.1)	4 (4.7)	5 (2.9)
Previous	32 (36.8)	16 (18.8)	48 (27.9)
Never	54 (62.1)	65 (76.5)	119 (69.2)
Dose interval			
Q 2 wk	29 (33.0)	29 (33.0)	58 (33.0)
Q 4 wk	59 (67.0)	59 (67.0)	118 (67.0)
Duration of asthma, yr, † mean (SD)	27.7 (16.1)	27.3 (17.1)	27.5 (16.6)
Eosinophils (x 10 ³ /μL), ‡ mean (SD)	0.25 (0.22)	0.24 (0.17)	NA
Basophils (x 10 ³ /μL), ‡ mean (SD)	0.06 (0.03)	0.07 (0.04)	NA
Diabetes mellitus, n (%)	12 (13.6)	18 (20.5)	30 (17.0)

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; BMI, Body mass index; FEV₁, Forced expiratory volume in one second; ICS, Inhaled corticosteroid; ITT, Intent to treat; NA, Not available; Q2W, every 2 weeks; Q4W, every 4 weeks.

* Placebo (n = 87), omalizumab (n = 85), all (N = 172).

† Placebo (n = 81), omalizumab (n = 82), all (N = 163).

‡ Placebo (n = 86), omalizumab (n = 86).

Table II. Change in IgE concentrations from baseline to Week 52

Mean percent (SD)	Placebo	Omalizumab	Difference (omalizumab- placebo)	<i>P</i> value*
Free IgE [†] , ng/mL	n = 68 402.4 (464.1)	n = 87 10.9 (62.6)	-391.4 (310.7)	< .0001
IQR of mean percent	0.0 to 689.9	-22.9 to 25.7		
Median of mean percent (range)	298.9 (-79.8 to 2269.7)	0.0 (-82.3 to 275.3)		
Total IgE [†] , IU/mL	n = 88 -42.8 (37.0)	n = 87 2.0 (42.9)	44.9 (40.0)	< .0001
IQR of mean percent	-73.4 to 0.6	-21.9 to 11.6		
Median (range) of mean percent	-57.9 (-89.6 to 103.0)	-4.1 (-91.2 to 184.5)		

IQR, interquartile range.

* *P* values derived from Wilcoxon Rank-sum test.

[†] No direct comparison possible (different units of measure).

Table III. Treatment-emergent adverse events (event rate per 100 patient-years)

TEAE (event rate per 100 patient-years)	Placebo	Any omalizumab exposure*	All subjects
Total no. of TEAEs	249	422	671
Exposure time, patient-years	58.46	102.14	160.60
Rate per 100 patient-years	425.9	413.2	417.8
Ear disorders			
Eustachian tube dysfunction	0.0	2.9	1.9
Eye disorders			
Allergic conjunctivitis	0.0	2.9	1.9
Gastrointestinal disorders			
Gastroesophageal reflux disease	5.1	3.9	4.4
General disorders			
Peripheral edema	3.4	1.0	1.9
Infections and infestations			
Oral candidiasis	8.6	2.0	4.4
Tooth infection	1.7	2.9	2.5
Otitis media	3.4	2.9	3.1
Bronchitis	15.4	9.8	11.8
Acute sinusitis	25.7	14.7	18.7
Nasopharyngitis	10.3	3.9	6.2
Pharyngitis	3.4	2.0	2.5
Sinusitis	30.8	35.2	33.6
Upper respiratory tract infection	22.2	27.4	25.5
Urinary tract infection	12.0	12.7	12.5
Gastroenteritis viral	1.7	6.9	5.0
Viral upper respiratory tract infection	5.1	5.9	5.6
Skin injuries			
Arthropod bite	0.0	2.9	1.9
Procedural pain	3.4	2.9	3.1
Contusion	1.7	2.9	2.5
Laceration	0.0	2.9	1.9
Metabolism and nutrition disorders			
Diabetes mellitus	3.4	2.9	3.1
Hypercholesterolemia	0.0	2.9	1.9
Vitamin D deficiency	5.1	0.0	1.9
Musculoskeletal and connective tissue disorders			
Arthralgia	3.4	6.9	5.6
Back pain	5.1	0.0	1.9
Pain in extremity	3.4	1.0	1.9
Osteoarthritis	1.7	3.9	3.1
Tendonitis	3.4	0.0	1.2
Nervous system disorders			
Headache	5.1	6.9	6.2
Anxiety	1.7	2.9	2.5
Depression	5.1	1.0	2.5
Insomnia	6.8	1.0	3.1
Reproductive disorders			
Postmenopausal hemorrhage	3.4	0.0	1.2

Respiratory, thoracic and mediastinal disorders			
Asthma	71.8	66.6	68.5
Cough	5.1	2.0	3.1
Rhinitis allergic	13.7	1.0	5.6
Nasal polyps	1.7	2.9	2.5
Dysphonia	1.7	2.9	2.5
Oropharyngeal pain	0.0	2.9	1.9
Skin and subcutaneous tissue disorders			
Angioedema	3.4	0.0	1.2
Dermatitis contact	1.7	5.9	4.4
Eczema	3.4	1.0	1.9
Vascular disorders			
Hypertension	5.1	2.9	3.7

TEAE, treatment-emergent adverse event

* Includes placebo-treated subjects who were treated with omalizumab after exacerbation.

Figure legends

FIG 1. Subject disposition. *AE*, Adverse event. Physician decision withdrawals took place because of protocol violations (eg, dosing not per US prescribing information, not meeting inclusion/exclusion criteria). Patient decision withdrawals were initiated by the subject for a variety of reasons that were not consistently captured.

FIG 2. Time to first protocol-defined asthma exacerbation.

FIG 3. Mean (SD) change in ACT and ACQ scores from baseline to Week 52. *ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test.

FIG 4. Eosinophils over time by treatment cohort and exacerbation status. *At baseline, the difference in eosinophils was statistically significant for the placebo groups with and without exacerbations ($P<.001$).

FIG 5. FeNO (ppb) over time by treatment cohort and exacerbation status. *FeNO*, Fractional exhaled nitric oxide.

