ORIGINAL ARTICLE

Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children

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ABSTRACT

BACKGROUND

Research has underscored the effects of exposure and sensitization to allergens on the severity of asthma in inner-city children. It has also revealed the limitations of environmental remediation and guidelines-based therapy in achieving greater disease control.

METHODS

We enrolled inner-city children, adolescents, and young adults with persistent asthma in a randomized, double-blind, placebo-controlled, parallel-group trial at multiple centers to assess the effectiveness of omalizumab, as compared with placebo, when added to guidelines-based therapy. The trial was conducted for 60 weeks, and the primary outcome was symptoms of asthma.

RESULTS

Among 419 participants who underwent randomization (at which point 73% had moderate or severe disease), omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease ($P<0.001$). Similarly, omalizumab significantly reduced the proportion of participants who had one or more exacerbations from 48.8 to 30.3% ($P<0.001$). Improvements occurred with omalizumab despite reductions in the use of inhaled glucocorticoids and long-acting beta-agonists.

CONCLUSIONS

When added to a regimen of guidelines-based therapy for inner-city children, adolescents, and young adults, omalizumab further improved asthma control, nearly eliminated seasonal peaks in exacerbations, and reduced the need for other medications to control asthma. (Funded by the National Institute of Allergy and Infectious Diseases and Novartis; ClinicalTrials.gov number, NCT00377572.)

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Studies of inner-city children, adolescents, and young adults with asthma show that symptom control is improved and exacerbations are decreased when there is either a reduction in household exposure to allergens[1] or aggressive implementation of guidelines-based therapy.[2] Nonetheless, achieving disease control remains difficult, necessitating a need for additional treatment.

For patients with allergies who have asthma that is not controlled with implementation of the higher treatment steps of the most recent guidelines from the National Asthma Education and Prevention Program (NAEPP) (Expert Panel Report 3), omalizumab, a humanized monoclonal anti-IgE antibody, is recommended.[3-9] Anti-IgE treatment reduces exacerbations, symptoms and, in some patients, the dose of inhaled glucocorticoids needed to maintain disease control.[4-9]

Because of the increased morbidity associated with a high prevalence of allergic sensitization and the heavy burden of allergen exposure among inner-city residents,[10,11] this population in particular may benefit from an IgE-targeted treatment. We hypothesized that the addition of omalizumab would improve disease control by reducing symptoms and exacerbations in inner-city children, adolescents, and young adults with persistent asthma.

Methods

Enrollment Criteria

The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of omalizumab in 419 inner-city children, adolescents, and young adults (6 to 20 years of age) with persistent allergic asthma. A physician's diagnosis of asthma or documentation of symptoms of asthma for more than 1 year before study entry was required. Patients receiving long-term therapy for disease control were also required to have symptoms of persistent asthma or evidence of uncontrolled disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry. Those not receiving long-term control therapy were eligible for enrollment only if they had both persistent symptoms and uncontrolled asthma. In addition, all patients were required to have at least one positive skin test for a perennial allergen, to weigh between 20 and 150 kg, and have total serum levels of IgE between 30 and 1300 IU per milliliter.

The protocol, which includes the statistical analysis plan, was approved by the institutional review boards of all participating institutions and is available with the full text of this article at NEJM.org. Written informed consent was obtained from each participant or the participant's parent or legal guardian. Participants who were younger than 18 years of age provided assent.

Study Design

At screening visits, each participant was assessed for asthma symptoms, previous treatment, pulmonary function, allergen sensitivity (with a skin-prick test), and serum levels of total IgE and allergen-specific IgE. Female participants who had reached menarche underwent a urine pregnancy test. Using our treatment algorithm (see Table 1A, 1B, and 1C in the Supplementary Appendix, available at NEJM.org), study physicians determined the appropriate asthma regimen on the basis of symptoms, percentage of predicted forced expiratory volume in 1 second (FEV_1), and current level of therapy, with the goal to achieve disease control. This regimen was administered for a 4-week run-in period. Asthma medications covered by the participant's insurance were prescribed but not directly supplied, with the exception of omalizumab or placebo and oral prednisone for exacerbations. Caregivers and participants received education about environmental allergen remediation and were given bedding covers, pest traps, and a vacuum cleaner.

After the 4-week run-in period, each participant underwent randomization to receive subcutaneous injections of omalizumab or placebo every 2 or 4 weeks for a total of 60 weeks (15 or 30 injections). The injection dose of omalizumab (75 to 375 mg) was calculated on the basis of individual weight and total serum IgE level to ensure a minimum monthly dose of 0.016 mg per kilogram of body weight per international unit of IgE per milliliter. The dosing table had an expanded range for weight and total level of IgE as compared with that of the dosing information provided on the label (Table 2 in the Supplementary Appendix). Placebo was administered in the same volume and with the same frequency as omalizumab by study nurses who were aware of the treatment assignments; all other study procedures were performed by study

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staff who were unaware of the treatment assignments, as were the study participants.

During the 60-week treatment period, in addition to site visits for injections every 2 or 4 weeks, visits for evaluation and management of care were scheduled every 3 months, at which time treatment adjustments were made on the basis of the symptoms that occurred during the previous 2 weeks, adherence to the study regimen and other asthma treatments, and FEV_1. Asthma control was assessed and assigned a level in accordance with the levels defined in report 3 of the NAEPP guidelines, with level 1 defined as asthma that was well controlled, levels 2 and 3 as asthma that was not well controlled, and level 4 as asthma that was poorly controlled.[3] Ongoing treatment adjustments were made to achieve good control of asthma (level 1). Six treatment steps (Table 1B in the Supplementary Appendix) were established to standardize prescribing patterns and corresponded to the levels of asthma severity as defined in the NAEPP guidelines, with steps 1 and 2 applying to mild asthma, step 3 to moderate asthma, and steps 4 through 6 to severe asthma.[3]

STUDY ASSESSMENTS

Adherence to all asthma treatments was assessed by means of study interviews, corroborated by study physicians, and encouraged by asthma counselors every 3 months. Allergen skin testing consisted of a panel of 14 extracts: mouse and rat epithelia, dog epithelium, dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), cat hair, an American–German cockroach mix, German cockroach, molds (*Penicillium notatum*, aspergillus species, *Alternaria tenuis*, and *Cladosporium herbarum*), timothy grass, and a ragweed mix (Greer Laboratories). A positive test was defined as a wheal that was larger than the negative control by 3 mm or more.

Total serum levels of IgE and allergen-specific IgE levels for dust mites, German cockroach, and *A. tenuis* were measured. Dust from the participant's bed and bedroom floor was collected with the use of a validated self-collection procedure[12] and assayed for dust mite (Der p 1 and Der f 1), German cockroach (Bla g 1), cat (Fel d 1), dog (Can f 1), and mouse (Mus m 1).

Nasal-secretion samples were collected and frozen at four of the eight research sites at week 48 and within 7 days after the onset of an asthma exacerbation. Total RNA was extracted and analyzed by means of multiplex reverse-transcriptase–polymerase-chain-reaction assay[13,14] with the use of primers and probes specific for rhinoviruses, influenza virus, parainfluenza virus, coronavirus, respiratory syncytial virus, metapneumovirus, enterovirus, adenovirus, and bocavirus.

OUTCOME MEASURES

The primary outcome evaluated at each 4-week visit for an injection was the number of days with symptoms during the previous 2 weeks, as used in previous studies of inner-city asthma.[1,2] Other outcomes included exacerbations, defined as a need for systemic glucocorticoids, hospitalization, or both, in accordance with a recent report by the American Thoracic Society and European Respiratory Society[15]; the dose of inhaled glucocorticoids needed to maintain asthma control; spirometric measurements; the score on the Childhood Asthma Control Test (C-ACT)[16]; and the score on the Asthma Control Test (ACT).[17] Scores on the C-ACT and ACT range from 0 to 27 and 5 to 25, respectively, with scores of 20 or more indicating asthma control. The minimally important difference is 3 points for the ACT score[18]; it is not defined for the C-ACT score.

STUDY OVERSIGHT

This study was funded by the National Institute of Allergy and Infectious Diseases (NIAID) and an unrestricted grant from Novartis. The protocol was monitored by the NIAID data and safety monitoring board. Omalizumab was used under a Food and Drug Administration investigational-new-drug application (number 100,210) sponsored by NIAID. Omalizumab and matching placebo were donated by Novartis, which had the opportunity to comment on the study design but had no role in the performance of the trial, data analysis, manuscript preparation, or the decision to submit the manuscript for publication. EpiPens were donated by Dey Pharma.

STATISTICAL ANALYSIS

A sample of 200 participants per study group was calculated to provide 90% power to detect a clinically meaningful difference of 30% in the number of days with symptoms during a period of 2 weeks. The first 12 weeks of the double-blind phase served as a wash-in period and were not

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included in the analysis in order to make sure that enough time was provided for omalizumab to achieve the maximum effect.[19] The analysis included data from weeks 12 through 60 and was performed with the use of linear mixed-effects models with random intercept and slope (to account for the within-subject correlation over time) and with visit and group as fixed effects; the models were adjusted for baseline variables, site, dosing schedule, and season. Group differences in utilization outcomes were tested by means of logistic regression. Twenty-one prespecified subanalyses were conducted to assess the heterogeneity of treatment effects across nine characteristics, with a statistical test for interaction, in accordance with guidelines for subgroup analyses[20] (for details, see Table 3 and the text in the Supplementary Appendix). Statistical analyses were performed with SAS software, version 9.2 (SAS Institute). The nonlinear seasonal variation was fitted with the use of generalized additive mixed-effects models, calculated with the mgcv package[21] in statistical software system R, version 2.12.1.[22] No adjustments for multiple comparisons were made, given the a priori nature of the hypotheses tested. Analyses were performed according to the intention-to-treat principle, with a two-sided alpha level of 0.05. A per-protocol analysis was performed for the 272 participants who missed less than 25% of the treatment visits.

RESULTS

ENROLLMENT

From November 2006 through April 2008, eight centers screened 996 subjects, and 419 underwent randomization: 208 to omalizumab and 211 to placebo (Fig. 1 in the Supplementary Appendix). At enrollment, the average number of days in the preceding 2 weeks on which participants had symptoms of asthma was 4.9. Participants had mean ACT and C-ACT scores of 19 or less, indicating a lack of asthma control,[16,17] and in the prior year 24.8% had been hospitalized at least once for an asthma-related event. The mean (±SD) FEV_1 was 92.1±17.1% of the predicted value, but the mean ratio of FEV_1 to forced vital capacity (FVC) was 77.0±9.9%, reflecting airflow obstruction. The baseline characteristics of the two study groups were similar (Table 1): for both groups, the average age was 10.8 years (interquartile range, 8 to 14), 58% were male, 60% were between 6 and 11 years of age, 60% were black, and 37% were Hispanic.

INITIAL CHANGES IN ASTHMA CONTROL

After the 4-week run-in period, during which our guidelines-based treatment algorithm was implemented, use of the medications participants had been taking for asthma control increased significantly, with a mean daily increase in the budesonide-equivalent dose of an inhaled glucocorticoid of 204 μg (95% confidence interval [CI], 161 to 247) and a mean increase in the proportion of participants receiving a long-acting beta-agonist (LABA) of 42% (95% CI, 37 to 47). These changes reduced the number of days with asthma symptoms per 2-week period by 1.8 (95% CI, 1.4 to 2.3) (Fig. 1). The ACT and C-ACT scores improved by 1.5 points (95% CI, 0.9 to 2.1) and 1.7 points (95% CI, 1.2 to 2.2), respectively, but no changes occurred in pulmonary function. At randomization, in accordance with medication use as defined in report 3 of the NAEPP guidelines, 73% of participants had asthma that was classified as moderate or severe.[3]

RESPONSE TO INTERVENTION

More than 90% of participants (386) were included in the primary-outcome analysis (Fig. 1 in the Supplementary Appendix). As compared with placebo, treatment with omalizumab reduced the mean number of days per 2-week interval on which participants had symptoms from 1.96 to 1.48, a difference of 24.5% (P<0.001) (Fig. 1 and Table 2). Similarly, the percentage of participants with exacerbations during the study was 48.8% in the placebo group as compared with 30.3% in the omalizumab group (P<0.001), and the percentage who were hospitalized because of asthma was 6.3% as compared with 1.5%, respectively (P=0.02). Improved asthma control with omalizumab was achieved with significantly lower doses of inhaled glucocorticoids (P<0.001) and LABA (P=0.003) (Fig. 1 and Table 2). The effects of omalizumab on these outcomes were similar in patients of all ages and at all levels of asthma severity at randomization. Lung function did not change.

Although the primary outcomes were not assessed until after 12 weeks of treatment, effects were observed after only 4 weeks (Fig. 1): as compared with placebo, treatment with omalizumab resulted in a reduction in the number of

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Table 1. Characteristics of Study Participants at Randomization.*

Characteristic	Placebo (N=211)	Omalizumab (N=208)	P Value
Demographic			
Age — yr	10.8±3.4	10.9±3.6	0.99
Male sex — no. (%)	120 (57)	122 (59)	0.71
Race or ethnic group — no. (%)			0.48
Black	121 (57)	131 (63)	
Hispanic	84 (40)	71 (34)	
Other or mixed	6 (3)	6 (3)	
Caretaker completed high school — no. (%)	160 (76)	143 (71)	0.13
≥1 household member employed — no. (%)	163 (77)	139 (67)	0.02
Annual household income <$15,000 — no. (%)	113 (54)	111 (53)	0.95
Clinical			
Duration of asthma — yr	7.0±3.8	7.5±4.0	0.28
Asthma control†			
C-ACT score in the previous month, age 4 to 11 yr	20.7±3.9	20.5±3.8	0.89
ACT score in the previous month, age 12 yr or older	20.3±3.1	20.3±3.8	0.86
Asthma-related symptoms — no. of days in 2 wk preceding visit‡	3.1±3.6	3.0±3.5	0.96
Wheezing	2.6±3.4	2.5±3.1	0.85
Interference with activity	1.6±2.7	1.5±2.4	0.59
Nighttime sleep disruption	0.84±1.96	1.03±2.22	0.19
Missed school — no. of days§	0.25±0.63	0.23±0.76	0.34
Lung function			
FEV_1 — % of predicted value	92.2±17.6	92.9±18.7	0.44
FEV_1:FVC ×100	77.6±9.4	77.3±10.0	0.80
Medication — no. (%)¶			
Step level equal to 1 or 2	60 (28)	53 (25)	0.50
Step level equal to 4 to 6	111 (53)	115 (55)	0.58
Asthma-related health care use in previous yr — no. (%)			
≥1 Hospitalization	52 (25)	52 (25)	0.93
≥1 Unscheduled visit	163 (77)	165 (79)	0.60

* Plus–minus values are means ±SD. P values for the comparison of means and percentages were calculated with the use of the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. FEV_1 denotes forced expiratory volume in one second, and FVC forced vital capacity.

† Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.

‡ The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

§ The number of school days missed was available for 339 of the 419 study participants.

¶ Six treatment steps were established, consistent with report 3 of the National Asthma Education and Prevention Program guidelines to standardize prescribing patterns according to levels of asthma severity; these steps are provided in full in the Supplementary Appendix and are summarized here.[3] Steps 1 and 2 apply to mild asthma, step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation is for no asthma-control medication or albuterol as needed; at step 1, budesonide — 180 μg once a day; at step 2, budesonide — 180 μg twice a day; at step 3, budesonide — 360 μg twice a day; at step 4, fluticasone–salmeterol (Advair, GlaxoSmithKline) — 250 μg fluticasone and 50 μg salmeterol twice a day; at step 5, Advair — 250 μg and 50 μg twice a day plus montelukast once a day; and at step 6, Advair — 500 μg and 50 μg twice a day plus montelukast once a day. (The doses for montelukast are 5 mg per day for children ≤14 years of age and 10 mg per day for those ≥15 years of age.)

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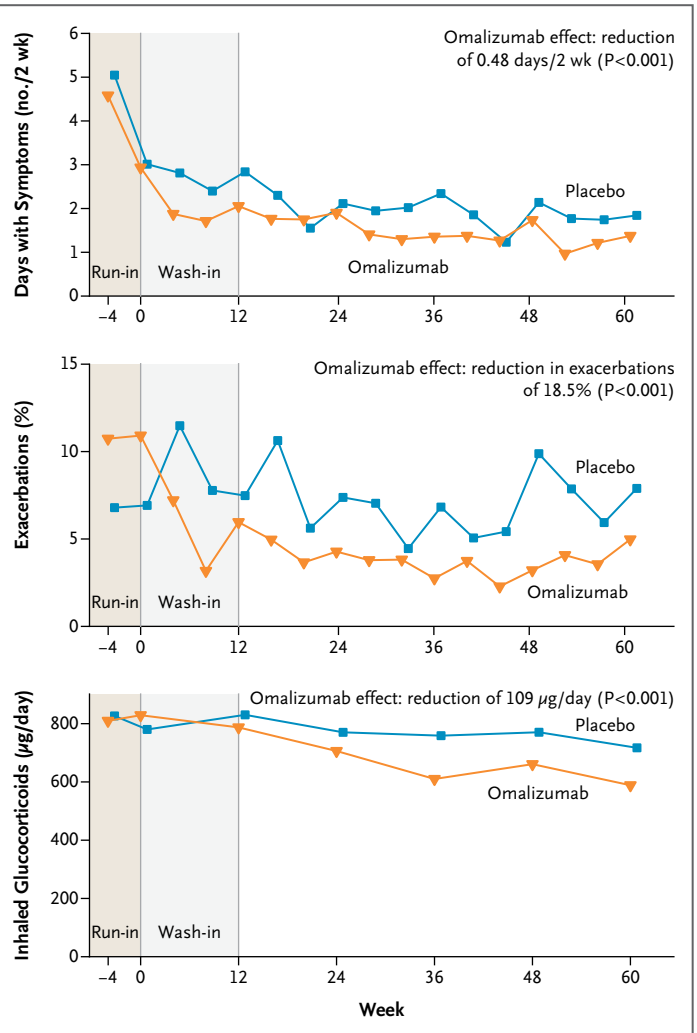

Figure 1. Number of Days with Symptoms in a 2-Week Interval, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids over the Course of the Study.

days with asthma symptoms per 2-week interval of 1.04 (95% CI, 0.46 to 1.62) and a reduction in the percentage of participants with exacerbations from 10.2% to 6.1%. All analyses were rerun in the per-protocol population of 272 participants, and the results were nearly identical to those for all enrolled participants (data not shown).

SUBGROUP ANALYSES

Among participants who were both sensitized and exposed to cockroach allergen (Bla g1 in house dust ≥2 U per gram), those receiving omalizumab had a reduction of 1.1 days with symptoms per 2-week interval (95% CI, 0.4 to 1.8), as compared with those receiving placebo, for a treatment effect of 48.5%. Those participants who were not sensitive to or not exposed to cockroach antigen had a reduction of only 0.4 days (95% CI, 0.1 to 0.7) as compared with those receiving placebo, for a treatment effect of 20.5% (Table 3, and Fig. 2 in the Supplementary Appendix).

The subgroup of participants who were sensitized and exposed to cockroach allergen also had a greater reduction in the dose of inhaled glucocorticoids as compared with other participants — 284 μg per day (95% CI, 124 to 444), for an effect of 32.9%, versus 91 μg per day (95% CI, 17 to 64), for an effect of 11.9%. This subgroup also had a greater reduction in asthma exacerbations as compared with other participants — with an odds ratio of 3.7 (95% CI, 1.7 to 8.1), for an effect of 71.2%, versus 1.7 (95% CI, 1.2 to 2.4), for an effect of 38.4% (Table 3, and Fig. 2 in the Supplementary Appendix). For the comparison of participants who were sensitized and exposed to cockroach allergen with those who were not, the P values for interaction were as follows: P equals 0.06 for asthma symptoms, P equals 0.03 for dose of inhaled glucocorticoids, and P equals 0.06 for exacerbations. Participants sensitive to dust mites (allergen-specific IgE level ≥0.35 IU per milliliter) also had a greater reduction in days with symptoms and in use of inhaled glucocorticoids as compared with those who were not sensitized.

POST HOC ANALYSIS OF OMALIZUMAB ON SEASONAL EXACERBATIONS

Asthma has a seasonal pattern of disease activity, with a nadir during the summer and peaks in the spring and fall (Fig. 2).[23-25] The effects of omalizumab were evident in seasonal patterns of both symptoms and exacerbations. In a post hoc analysis, the average monthly rate of asthma exacerbations nearly doubled in the placebo group during the fall and spring as compared with summer (9.0% and 8.1%, respectively, vs. 4.6%; P<0.001). This seasonal spike in exacerbations was not observed in the omalizumab group (4.3% in fall and 4.2% in spring vs. 3.3% in summer), and the difference between the placebo and omalizumab groups was significant (P<0.001 for interaction). A monthly exacerbation rate of approximately 4% remained throughout the year among participants in the omalizumab group (Fig. 2). Finally, the daily dose of inhaled glucocorticoids varied little during the year in the omalizumab group,

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Table 2. Adjusted Treatment Effect on Asthma Symptoms and Health Care Use during 48 Weeks of Follow-up.*

Variable	Placebo (N=211)	Omalizumab (N=208)	Difference (95% CI)†	P Value
Asthma-related symptoms — no. of days in 2 wk preceding visit‡	1.96±0.10	1.48±0.10	−0.48 (−0.77 to −0.20)	<0.001
Wheezing	1.76±0.09	1.32±0.09	−0.44 (−0.70 to −0.17)	0.001
Interference with activity	0.98±0.07	0.70±0.07	−0.28 (−0.47 to −0.09)	0.003
Nighttime sleep disruption	0.59±0.05	0.42±0.05	−0.17 (−0.31 to −0.03)	0.02
Missed school — no. of days§	0.25±0.03	0.16±0.03	−0.09 (−0.18 to −0.01)	0.038
Asthma control¶				
C-ACT score in previous month, age 4 to 11 yr	22.2±0.21	23.0±0.21	0.78 (0.21 to 1.35)	0.007
ACT score in previous month, age 12 yr or older	22.3±0.22	22.5±0.22	0.19 (−0.42 to 0.79)	0.54
Lung function				
FEV_1 — % of predicted value	91.7±0.64	92.6±0.60	0.92 (−0.81 to 2.64)	0.30
FEV_1:FVC ×100	77.5±0.38	77.3±0.36	−0.13 (−1.16 to 0.91)	0.81
Medication				
Adherence — %	88.6±1.80	84.6±1.78	−3.96 (−8.95 to 1.02)	0.12
Step level equal to 1 or 2 — %‖	26.7±3.3	43.6±4.0	16.9 (6.6 to 27.1)	0.001
Step level equal to 4 to 6 — %‖	50.8±4.0	31.2±3.5	−19.6 (−30.1 to −9.1)	<0.001
Inhaled glucocorticoids prescribed — μg/day**	771±23.5	663±23.3	−109 (−172 to −45)	<0.001
Long-acting β_2 agonists prescribed — %	65.5±2.47	55.4±2.44	−10.1 (−16.8 to −3.4)	0.003
Asthma-related health care use — %††				
≥1 Hospitalization	6.3±1.8	1.5±0.9	−4.7 (−8.6 to −0.9)	0.02
≥1 Exacerbation‡‡	48.8±3.7	30.3±3.3	−18.5 (−28.2 to −8.8)	<0.001

* Plus–minus values are means ±SE, adjusted for study site, visit, season, dosing, and baseline levels, unless noted otherwise. FEV_1 denotes forced expiratory volume in one second, and FVC forced vital capacity.
† Unrounded values were used to determine the difference between groups.
‡ The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.
§ The number of school days missed was available for 339 of the 419 study participants.
¶ Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.
‖ Six treatment steps were established, consistent with report 3 of the National Asthma Education and Prevention Program guidelines to standardize prescribing patterns according to levels of asthma severity; these steps are provided in full in the Supplementary Appendix and are summarized here.[3] Steps 1 and 2 apply to mild asthma, step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation is for no asthma-control medication or albuterol as needed; at step 1, budesonide — 180 μg once a day; at step 2, budesonide — 180 μg twice a day; at step 3, budesonide — 360 μg twice a day; at step 4, fluticasone–salmeterol (Advair, GlaxoSmithKline) — 250 μg fluticasone and 50 μg salmeterol twice a day; at step 5, Advair — 250 μg and 50 μg twice a day plus montelukast once a day; and at step 6, Advair — 500 μg and 50 μg twice a day plus montelukast once a day. (The doses for montelukast are 5 mg per day for children ≤14 years of age and 10 mg per day for those ≥15 years of age.)
** The dose of inhaled glucocorticoids was converted to the budesonide-equivalent dose.
†† Asthma-related health care use was adjusted for study site and dosing because of the scarce data for baseline levels.
‡‡ An exacerbation was defined as a prednisone burst (a minimum of 20 mg per day of prednisone, or the equivalent, taken for any 3 of 5 consecutive days) or a hospitalization.

whereas in the placebo group, dose adjustments were required to achieve asthma control.

In an exploratory substudy, 100 nasal samples were collected in association with an asthma exacerbation and 165 were collected at week 48, in the absence of an exacerbation. During exacerbations, respiratory viruses were detected at a similar frequency in both the placebo group (50% [30 of 60 samples]) and the omalizumab group (58% [23 of 40 samples]), with rhinoviruses being

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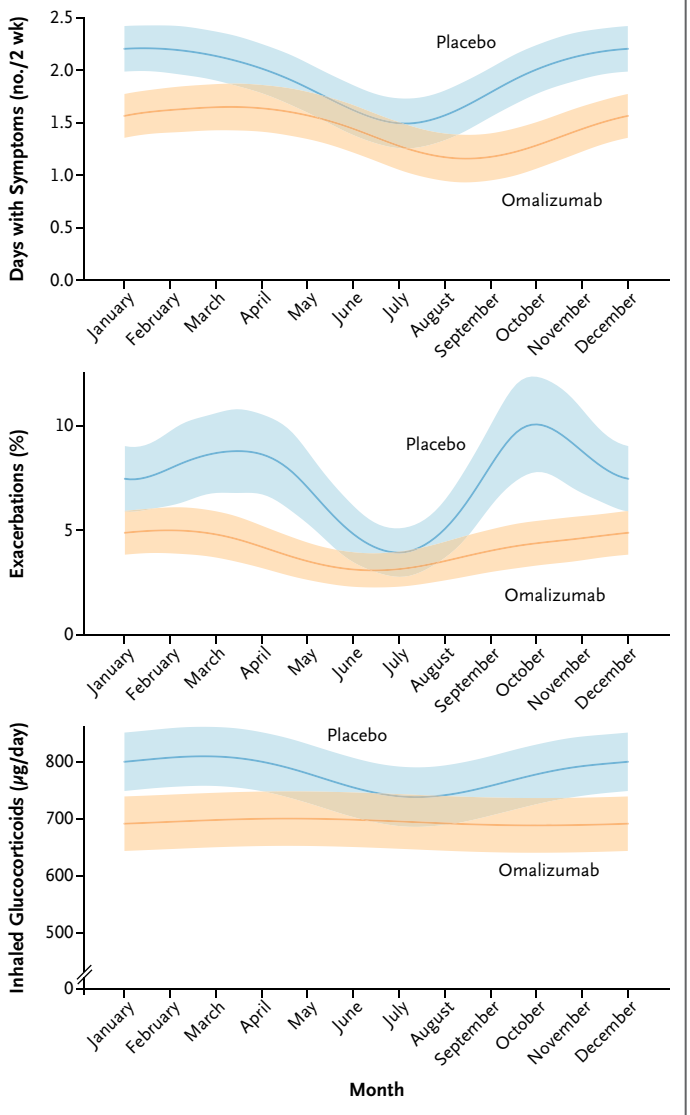

Figure 2. Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids.

The width of the bands represents the 95% confidence interval.

the most frequently detected virus in each case (accounting for 67% and 74% of virus-positive specimens, respectively). The frequency of virus detection during an exacerbation was greater than the frequency at week 48 (53% vs. 32%, P=0.001). Treatment with omalizumab did not affect the rate of virus detection at week 48 (34% [26 of 76 samples] in the placebo group and 30% [27 of 89] in the omalizumab group).

SAFETY

The observation procedures followed after injection of omalizumab were in accordance with published recommendations.[26] One or more adverse events were reported in 47.4% of participants in the placebo group and 39.4% of those in the omalizumab group (P=0.06) (Table 3); one or more serious adverse events were reported in 13.7% of participants in the placebo group and 6.3% of those in the omalizumab group (P=0.02). The majority of serious adverse events were asthma-related hospitalizations. Comparisons of major adverse-event categories between the two study groups showed that the omalizumab group had significantly more gastrointestinal disorders but significantly fewer hematologic disorders as compared with the placebo group. Seven participants had anaphylaxis: six in the placebo group and one in the omalizumab group. The patient receiving omalizumab had a mild cough and throat pruritus after receiving the final injection during the study.

DISCUSSION

Adding omalizumab therapy to guideline-directed care for inner-city children, adolescents, and young adults with allergic asthma resulted in a significant and clinically meaningful decrease in asthma-related symptoms of 0.48 days per 2-week period, as compared with placebo (from 1.96 to 1.48 days), a reduction in the number of participants with at least one exacerbation (30.3% in the omalizumab group vs. 48.8% in the placebo group), fewer hospitalizations (1.5% vs. 6.3%), and a reduced need for inhaled glucocorticoids to maintain this improved level of asthma control (budesonide-equivalent dose, 663 μg per day in the omalizumab group vs. 771 μg per day in the placebo group). No differences of concern regarding safety were noted between the two groups.

Omalizumab is already indicated for the treatment of moderate-to-severe asthma in patients older than 11 years of age and is recommended for step 5 or step 6 treatment in report 3 of the NAEPP guidelines.[3] Our purpose in designing this study was to examine whether specifically targeting the allergic component in persistent asthma would offer a benefit beyond that provided by conventional treatment for asthma control, regardless of disease severity. Indeed, our

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Table 3. Number of Adverse Events.*

Type of Event	Placebo (N=211)		Omalizumab (N=208)		P Value†
	No. of Events	No. of Patients with Events	No. of Events	No. of Patients with Events	
Eyes, ears, nose, and throat	7	6	2	2	0.23
Gastrointestinal	2	2	11	10	0.02
Hematologic	16	12	1	1	0.002
Anaphylactic	6	6	1	1	0.12
Infection	26	22	18	17	0.32
Injection site	8	6	10	8	0.70
Musculoskeletal	3	3	3	3	0.99
Nervous system	10	7	3	3	0.17
Psychiatric	3	2	0	0	0.50
Respiratory	95	47	57	34	0.07
Skin	24	19	22	16	0.90
Other	22	19	31	27	0.28
Total	222	100‡	159	82‡	0.06

* Data are numbers of adverse events and numbers of patients who had at least one adverse event.
† An exact Mantel–Haenszel chi-square test was used to compare the number of adverse events between groups.
‡ Patients could have more than one event.

study population represented all levels of asthma severity. After the 4-week run-in treatment period, during which conventional medications for asthma control were administered, 54% of the study population could be categorized as having severe asthma and 19% as having moderate asthma, according to report 3 of the NAEPP guidelines.[3] Despite the use of guidelines-based management with scheduled opportunities to adjust the treatment, these levels of disease severity remained the same throughout the study in the placebo group. We chose to study children, adolescents, and young adults living in low-income urban areas because of the importance of allergy in the presentation of asthma in this group and the high associated morbidity.[10,11]

Even though we found omalizumab effective at all levels of asthma severity, we do not advocate its use outside of current recommendations[27-29] given its cost and remaining questions regarding long-term safety in children.[30,31] We do, however, believe that this study provides a strong proof of concept that the allergic component of asthma is crucial in this population. This postulate is further supported by our finding that omalizumab's benefit was greatest in participants who were both sensitized and exposed to cockroach allergen and in those sensitized to dust mites, two major relevant indoor allergens.

A striking additional post hoc finding was the marked reduction in seasonal exacerbations seen with omalizumab (Fig. 2). Viral respiratory infections are a major cause of exacerbations, especially in the fall, with the start of school,[24,25] but they were identified in less than 60% of the samples available for analysis, suggesting that other factors, such as allergen exposure, pollution, stress, or bacteria, also contribute to the risk of exacerbation.[25,32] Omalizumab was equally effective in reducing exacerbations in the fall and the spring, with or without a viral infection, but it did not appear to prevent viral respiratory infections, since the rate of virus detection was similar in the omalizumab and placebo groups at a study visit not associated with an exacerbation.

The effect of omalizumab on exacerbations occurring during the fall and spring supports the notion of an interaction between allergy and viral infections in inducing asthma exacerbations, as previously suggested by epidemiologic research.[33] Although the mechanisms of such an interaction

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have not been defined, a number of theories have been proposed. For example, both allergic inflammation and viral respiratory infections can injure airway epithelium, and one could speculate that they act synergistically to promote exacerbations.[34] Furthermore, since human rhinovirus replication is increased in damaged epithelium, one could also speculate that underlying allergic inflammation serves to enhance viral growth, leading to more severe respiratory infection and thus increasing the chance of an exacerbation.[35,36] Finally, it is possible that IgE-dependent mechanisms interfere with antiviral responses, leading to more severe and prolonged viral illnesses.[37] Notably, neither guidelines-directed treatment nor omalizumab prevented all exacerbations (Fig. 2), suggesting that additional mechanisms underlie the residual risk of asthma exacerbations in this population.

Previous work to identify patients most likely to have a response to omalizumab has pointed toward IgE levels and asthma severity, but these criteria have limitations.[19,38] Although the effectiveness of omalizumab was noted across many participant characteristics, participants who had been both sensitized and exposed to cockroach allergen had the greatest benefit (a 71.2% reduction in exacerbations); the combination of sensitization and exposure may therefore serve as a criterion to be applied in targeting its use for optimal effectiveness and cost benefits.[27-29] Another potential approach to the same goal would be to focus the use of omalizumab on preventing seasonal peaks in asthma exacerbations; this would require studies examining a short, seasonal course of treatment in those at highest risk. The fact that the maximum effect of omalizumab occurred within 1 month, rather than 3 to 4 months, as previously reported,[19,39-41] supports the potential benefit of this treatment approach.

In summary, omalizumab reduces symptoms and exacerbations in children, adolescents, and young adults with persistent allergic asthma, providing protection beyond that conferred with guidelines-directed care. Our findings may also help identify those patients most likely to have a response to omalizumab and provide insight into novel mechanisms of asthma exacerbations that could lead to improved treatment.

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REFERENCES

1. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068-80.
2. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet 2008;372:1065-72.
3. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.)
4. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-90.
5. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
6. Holgate ST, Djukanović R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy 2005;35:408-16.
7. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-16.
8. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic

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(IgE-mediated) asthma. J Allergy Clin Immunol 2009;124:1210-6.
9. Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-61. [Erratum, Eur Respir J 2001;18:739-40.]
10. Gruchalla RS, Pongracic J, Plaut M, et al. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol 2005;115:478-85.
11. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336:1356-63.
12. Arbes SJ Jr, Sever M, Vaughn B, et al. Feasibility of using subject-collected dust samples in epidemiologic and clinical studies of indoor allergens. Environ Health Perspect 2005;113:665-9.
13. Gern JE, Visness CM, Gergen PJ, et al. The Urban Environment and Childhood Asthma (URECA) birth cohort study: design, methods, and study population. BMC Pulm Med 2009;9:17.
14. Lee WM, Grindle K, Pappas T, et al. High-throughput, sensitive, and accurate multiplex PCR-microsphere flow cytometry system for large-scale comprehensive detection of respiratory viruses. J Clin Microbiol 2007;45:2626-34.
15. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
16. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119:817-25.
17. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117:549-56.
18. 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(4):719.e1-723.e1.
19. 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.
20. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
21. Wood SN. Stable and efficient multiple smoothing parameter estimation for generalized additive models. J Am Stat Assoc 2004;99:673-86.
22. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2010.
23. Gergen PJ, Mitchell H, Lynn H. Understanding the seasonal pattern of childhood asthma: results from the National Cooperative Inner-City Asthma Study (NCICAS). J Pediatr 2002;141:631-6.
24. Johnston NW, Johnston SL, Duncan JM, et al. The September epidemic of asthma exacerbations in children: a search for etiology. J Allergy Clin Immunol 2005;115:132-8.
25. Sears MR, Johnston NW. Understanding the September asthma epidemic. J Allergy Clin Immunol 2007;120:526-9.
26. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol 2007;120:1373-7.
27. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. Allergy 2010;65:1141-8.
28. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. J Allergy Clin Immunol 2004;114:265-9.
29. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. J Allergy Clin Immunol 2007;120:1146-52.
30. Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. Clin Exp Allergy 2009;39:788-97.
31. Deniz YM, Gupta N. Safety and tolerability of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody. Clin Rev Allergy Immunol 2005;29:31-48.
32. Bisgaard H, Hermansen MN, Bønnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. BMJ 2010;341:c4978.
33. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. BMJ 2002;324:763. [Erratum, BMJ 2002;324:1131.]
34. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010;376:826-34.
35. Jakiela B, Brockman-Schneider R, Amineva S, Lee WM, Gern JE. Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. Am J Respir Cell Mol Biol 2008;38:517-23.
36. Lopez-Souza N, Dolganov G, Dubin R, et al. Resistance of differentiated human airway epithelium to infection by rhinovirus. Am J Physiol Lung Cell Mol Physiol 2004;286:L373-L381.
37. Gill MA, Bajwa G, George TA, et al. Counterregulation between the FcepsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. J Immunol 2010;184:5999-6006.
38. Wahn U, Martin C, Freeman P, Blogg M, Jimenez P. Relationship between pretreatment specific IgE and the response to omalizumab therapy. Allergy 2009;64:1780-7.
39. Eckman JA, Sterba PM, Kelly D, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. J Allergy Clin Immunol 2010;125(4):889.e7-895.e7.
40. MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
41. Ong YE, Menzies-Gow A, Barkans J, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. J Allergy Clin Immunol 2005;116:558-64.

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