Exhaled Nitric Oxide in Children With Asthma Receiving Xolair (Omalizumab), a Monoclonal Anti-Immunoglobulin E Antibody

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ABSTRACT. *Objective.* **To evaluate the effect of a humanized monoclonal antibody to immunoglobulin E, omalizumab (Xolair, Novartis Pharmaceuticals, East Hanover, NJ; Genentech Inc, South San Francisco, CA), on airway inflammation in asthma, as indicated by the fractional concentration of exhaled nitric oxide (FE_{NO}), a noninvasive marker of airway inflammation. Xolair was approved recently by the US Food and Drug Administration for moderate-to-severe allergic asthma in adolescents and adults.**

Study Design. **As an addendum at 2 sites to a randomized, multicenter double-blind, placebo-controlled trial, FE_{NO} was assessed in children with allergic asthma over 1 year. There were 3 consecutive study periods: 1) stable dosing of inhaled beclomethasone dipropionate (BDP) when the dose was optimized (period of 16 weeks); 2) inhaled steroid-reduction phase (period of 12 weeks), during which BDP was tapered if subjects remained stable; and 3) open-label extension phase, during which subjects receiving placebo were switched to active omalizumab (period of 24 weeks). The primary outcome was area under the FE_{NO} versus time curve (AUC) for adjusted FE_{NO}, defined as the ratio of FE_{NO} at each time point compared with the value at baseline.**

Results. **Twenty-nine subjects participated and were randomized to omalizumab ($n = 18$) and placebo ($n = 11$) treatment groups in a 2:1 ratio dictated by the main study. There was a significant difference for age, resulting in a difference in absolute forced expiratory volume in 1 second but no difference in asthma severity based on the forced expiratory volume in 1 second percentage predicted. Baseline BDP dose was comparable between groups, as were baseline values of mean FE_{NO} (active: 38.6 ± 25.6 ppb; placebo: 52.7 ± 52.9 ppb). The degree of BDP dose reduction during the steroid-reduction and open-label phases was equivalent between the omalizumab and placebo-treated groups; subjects in the omalizumab- and placebo-treated groups had reduced their BDP dose by an average of 51% and 60%, respectively, at the end of the steroid-reduction phase and by 68% and 94%, respectively, by the end of the open-label period. In the active and placebo groups, 44% and 27% and 75% and 73% of subjects had stopped use of inhaled corticosteroids at the end of the steroid-reduction and open-label phases, respectively. There was no significant difference between the active and placebo groups during the steroid-stable phase for AUC of adjusted nitric oxide (1.31 ± 1.511 vs 1.45 ± 0.736). However, during the steroid-reduction phase, the variability of adjusted FE_{NO} in the placebo-treated group was greater than that of the omalizumab-treated group at most visits, with a significant difference between groups for AUC of adjusted nitric oxide (0.88 ± 0.69 vs 1.65 ± 1.06). FE_{NO} fell from 82.1 ± 55.6 ppm at the end of the steroid-reduction phase to 33.3 ± 21.6 ppb at the end of the open-label period in the placebo group who were placed on active omalizumab. This decrease occurred while the mean dose of BDP remained very low. Analysis of FE_{NO} over 52 weeks of omalizumab treatment in the active group demonstrated that there was a significant reduction from baseline to the end of the open-label period (41.9 ± 29.0 to 18.0 ± 21.8 ppb) despite a high degree of steroid reduction.**

Conclusion. **In this preliminary study based on FE_{NO}, a noninvasive marker of airway inflammation, treatment with omalizumab may inhibit airway inflammation during steroid reduction in children with allergic asthma. The degree of inhibition of FE_{NO} was similar to that seen for inhaled corticosteroids alone, suggesting an antiinflammatory action for this novel therapeutic agent in asthma. This is in keeping with recent evidence that omalizumab inhibits eosinophilic inflammation in induced sputum and endobronchial tissue.** *Pediatrics* **2004;113:e308–e312. URL: http://www.pediatrics.org/cgi/content/full/113/4/e308; *asthma, exhaled, nitric oxide, omalizumab.***

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Received for publication Apr 9, 2003; accepted Nov 20, 2003.

The authors have not made any financial arrangement whereby the value of the compensation could be influenced by the outcome of the study, have not received significant payments of other sorts from the sponsors (excluding the costs for conducting the study), do not have a proprietary or financial interest in the test product such as patent, trademark, copyright, or licensing agreements, and do not hold significant equity interest in the sponsors of the study. Dr Gupta, holds a permanent position with Novartis.

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ABBREVIATIONS. IgE, immunoglobulin E; FcεRI, high-affinity IgE receptor; ICS, inhaled corticosteroid; NO, nitric oxide; NOS, NO synthase; FE_{NO}, fractional concentration of exhaled NO; BDP, beclomethasone dipropionate; FEV_1, forced expiratory volume in 1 second; SD, standard deviation; AUC, area under curve.

Omalizumab is a recombinant humanized monoclonal anti-immunoglobulin E (anti-IgE) antibody that recognizes IgE at the same site as the high-affinity receptor for IgE (FcεRI). The monoclonal antibody complexes with free IgE, thereby blocking the binding of IgE to cell membrane FcεRI and inhibiting cell activation and mediator release.[1,2]. Phase III studies of omalizumab in patients with moderate-to-severe allergic asthma ad-

ministered as a subcutaneous injection at intervals of 2 or 4 weeks have demonstrated that omalizumab reduces the incidence and frequency of exacerbations and has a steroid-sparing effect, as indicated by reduced use of inhaled corticosteroid (ICS).[3–5] Omalizumab dramatically reduces free serum IgE immediately after the first injection[6] and attenuates both early- and late-phase asthmatic reactions to inhaled allergens after a course of therapy.[7,8] The latter studies have shown additionally an association between reductions in circulating and sputum eosinophilia and nonspecific bronchial hyperresponsiveness. Similarly, studies in seasonal allergic rhinitis[9,10] have demonstrated that omalizumab prevents the seasonal increase in nasal and ocular symptoms and decreases the use of rescue medication. Collectively, these studies support the concept that anti-IgE therapy is likely to be efficacious in the management of allergic airway disease, probably as a consequence of its antiinflammatory effects. The US Food and Drug Administration approved omalizumab for moderate and severe adult allergic asthma in July 2003.

Nitric oxide (NO) is a highly reactive central mediator in biological systems, including the vascular endothelium, the immune system, and the nonadrenergic, noncholinergic inhibitory nervous system.[11] NO is produced from L-arginine by the action of NO synthase (NOS), which exists as 3 isoforms: 2 constitutively expressed (types I and III NOS) and 1 inducible (type II). Although the constitutive isoforms of NOS synthesize endogenous NO at picomolar concentrations and mediate physiologic functions (eg, smooth muscle relaxation), type II NOS is expressed in pathologic states in response to proinflammatory cytokines and synthesizes NO at nanomolar concentrations. These large concentrations of NO lead to the generation of toxic metabolites such as peroxynitrite, which can subsequently lead to widespread oxidative damage.[12,13]

Immunohistochemical studies have demonstrated that not only is there increased expression of type II NOS in asthmatic airway epithelial cells but also that ICSs decrease the expression of this enzyme.[12,14] Correspondingly, several studies have demonstrated that the fractional concentration of exhaled NO (FE_{NO}) is increased in patients with asthma[15] and that these levels fall after treatment with ICSs and oral corticosteroids.[15,16] Other studies have shown correlations between levels of FE_{NO} and other variables of asthma, in particular bronchial hyperresponsiveness,[17] airway eosinophilia,[18] and corticosteroid responsiveness,[19] thereby suggesting that measurement of FE_{NO} may provide a surrogate, easy-to-use, and noninvasive means for monitoring inflammation in asthmatic airways.[20]

In this study, we evaluated the effects of omalizumab on FE_{NO} in children with moderate-to-severe allergic asthma before and during ICS withdrawal. We hypothesized that, in children treated with omalizumab, FE_{NO} would remain stable during reduction in beclomethasone dipropionate (BDP) dose but would rise in children receiving placebo. Preliminary data from this study have appeared in an abstract[21] that also appeared in a book chapter.[22]

METHODS

Trial Design

This preliminary study, conducted as an addendum to a multicenter study of omalizumab,[6] was performed at 2 US centers (National Jewish Medical and Research Center, Denver, CO [study center 1] and Creighton University, Omaha, NE [study center 2]). After randomization, 29 children entered a 16-week, double-blind, steroid-stable phase of treatment with omalizumab or placebo while maintained on stable doses of BDP (Table 1). Thereafter, patients entered a 12-week, double-blind, steroid-reduction phase, during which patients' BDP dose was reduced by 25% every 2 weeks (provided that their asthma did not worsen). In a 24-week open-label extension, all patients previously receiving placebo were switched to omalizumab treatment. Study treatments were administered by subcutaneous injection at intervals of 2 or 4 weeks. The dose of omalizumab was based on each patient's serum total IgE level and body weight at baseline to provide a dose of at least 0.016 mg/kg per IU/mL of IgE per 4-week period.

Participants

The study enrolled children aged 6 to 12 years with allergic asthma who were well controlled with ICSs at doses equivalent to BDP >168 to 420 μg/day. Baseline forced expiratory volume in 1 second (FEV_1) was ≥60% predicted, with a short-acting β_2-agonist reversibility of ≥12% documented within the previous 12 months. All subjects had positive skin-test reactivity to at least 1 perennial allergen and ongoing exposure to that antigen during the study. The addendum and main study were approved by protocol review boards at both study centers. The subjects and their legal guardians signed separate assent and consent forms, respectively, to the addendum.

TABLE 1. Study Design and Time Points of Assessment of FE_{NO}

	Study Phase				
	Screening	Run-in	Double-Blind Steroid Stable	Double-Blind Steroid Reduction	Open-Label Extension
Visit	1	2	3–7	8–13	14–20
Week	−7	−6 or −4 to 0	0–16	16–28	28–52
Study treatment	None	None	Omalizumab or placebo	Omalizumab or placebo	Omalizumab
ICS dose, μg/d	≥168–420 BDP or equivalent	168–420 BDP*	BDP 168–420 at stable dose	BDP dose tapered over 8 weeks, then stable for 4 weeks	BDP dosed as appropriate for maintenance (24 weeks)
FE_{NO}	—	—	All visits (assessed 4-weekly)	All visits (assessed 2-weekly)	Visits 15 and 19 (weeks 36 and 52)

* During the run-in, any patients on ICSs other than BDP were switched to an equivalent dose of BDP, and the dose was adjusted to maintain asthma control compatible with previous ICS treatment.

NO Measurements

Exhaled NO was measured by using a standardized single-breath method, which conformed to American Thoracic Society recommendations for FE_{NO} measurement.[23] In brief, the seated patient inspired humidified medical compressed air from a reservoir connected to a mouthpiece fitted with a 2-way valve. After inspiration to total lung capacity, the patient exhaled immediately at a constant flow rate of 42 mL/s. The exhaled air was sampled via a side port close to the mouth and analyzed online for NO by using an Ionics-Sievers (Boulder, CO) 280 NOA analyzer, sensitive to 1 ppb and calibrated daily with a standard NO gas of 25 ppm (Scott Specialty Gases, Plumsteadville, MA). Identical NO analyzers were used at both study centers, and NO was measured at several time points over the course of the study as shown in Table 1. NO data from the 2 study centers were checked at the beginning and end of the study by using a NO standard calibration gas and found to be similar for the 2 study centers: 4.9 and 4.7 ppm in study centers 1 and 2, respectively, at the start of the study and 4.8 and 4.6 ppm in study centers 1 and 2, respectively, at the end of the study.

Data Management

Exhaled NO data were stored securely on personal computers in Microsoft Excel (Microsoft Corporation, Seattle, WA). The study sponsor provided supplementary data (including demographic data and drug dosage) after the study was unblinded.

Statistical Methods

Definition of Outcome Variables

Adjusted FE_{NO} was defined as the ratio of FE_{NO} at time point t_L compared with baseline (visit 3). The percent FE_{NO} change at time t_L compared with baseline was defined as:

$$(FE_{NO} \text{ at } t_L - FE_{NO} \text{ at baseline}) \times 100/FE_{NO} \text{ at baseline}. \quad (1)$$

Summary Statistics

Summary statistics (*n*, mean, and standard deviation [SD]) were presented for both active and placebo treatment groups at each visit.

Primary Outcome Variable

The primary outcome variable was the change in area under curve (AUC) of adjusted FE_{NO} during the steroid-reduction phase. Between-group differences were analyzed by using an independent 2-sample *t* test.

Secondary Analyses

The secondary outcome variable was the change in AUC of adjusted FE_{NO} during the steroid-stable phase. Between-group differences were analyzed by using an independent 2-sample *t* test.

Algorithm for Calculation of AUC of Adjusted FE_{NO}

Subjects with missing FE_{NO} at baseline were excluded from calculation. Missing FE_{NO} at a later time point t_L was assigned a value (imputation) by using the last-observation-carry-forward method.

The ratio of FE_{NO} at t_L (after imputation) versus FE_{NO} at baseline was called adjusted FE_{NO}. AUC for each subject then was calculated by the trapezoidal rule using the adjusted FE_{NO} values as follows:

$$\text{AUC} = \left\{ (t_1 - t_0) \cdot \frac{yt_0 + yt_1}{2} + (t_2 - t_1) \frac{yt_1 + yt_2}{2} \ldots + (t_L - t_{L-1}) \frac{yt_{L-1} + yt_L}{2} \right\}, \quad (2)$$

where y_{ti} = adjusted FE_{NO} at time point t_i with $i = 1, 2, 3 \ldots L$ (final time point), with time in units of weeks.

Finally, the AUC was standardized by time period (weeks), ie, it was divided by 12 in the primary analysis and 16 in the secondary analysis. All analyses were performed using SAS 8.2 (Cary, NC).

RESULTS

Subjects

A total of 29 subjects participated and were randomized to omalizumab ($n = 18$) and placebo ($n = 11$) treatment groups in a 2:1 ratio, as dictated by the main study. The only significant difference between the groups was age, resulting in a difference in absolute FEV_1. However, the 2 groups were comparable in terms of mean FEV_1 percent predicted, indicating that asthma severity was similar for both patient groups (Table 2). Baseline BDP dose was also comparable between groups (Table 2), as were baseline (randomization) values of mean FE_{NO} (active: 38.6 ± 25.6 ppb; placebo: 52.7 ± 52.9 ppb [$P = .44$]).

ICS Dose Reduction

The degree and pattern of BDP dose reduction during the steroid-reduction and open-label phases were equivalent between the omalizumab- and placebo-treated groups (Table 3). Subjects in the omalizumab- and placebo-treated groups had reduced their BDP dose by an average of 51% and 60%, respectively, at the end of the steroid-reduction phase and by 68% and 94%, respectively, by the end of the open-label period. In the active and placebo groups, 44% and 27% of the subjects, respectively, had stopped use of ICS at the end of the steroid-reduction phase. Corresponding values at the end of the open-label period were 75% and 73%, respectively.

Exhaled NO

Change in FE_{NO} During Steroid-Stable Phase (Secondary Outcome Variable)

AUC for adjusted FE_{NO} was calculated from baseline to week 16 (end of steroid-stable phase) after

TABLE 2. Demographic and Baseline Characteristics

	Omalizumab ($n = 18$)	Placebo ($n = 11$)	*P* Value
Gender	15 males 3 females	5 males 6 females	
Age, y	8.8 ± 1.8	10.8 ± 0.8	<.001
Height, cm	137.2 ± 14.2	145.9 ± 9.1	NS
Weight, kg	36.2 ± 13.4	40.8 ± 14.5	NS
Serum IgE, IU/mL	315.6 ± 279.7	301.7 ± 213.0	NS
FEV_1, mL	1665.6 ± 411.2	2023.6 ± 355.5	.02
FEV_1, % predicted	87.7 ± 15.4	91.1 ± 14.3	NS
FVC, mL	2251.7 ± 558.1	2592.7 ± 376.2	NS
Daily BDP dose, μg	261.3 ± 114.8	282.5 ± 120.4	NS

Values are mean ± SD. NS indicates not significant; FVC, forced vital capacity.

TABLE 3. Percent Reduction of Dose of Inhaled Beclomethasone Dipropionate, Relative to Baseline, During the Steroid-Reduction and Open-Label Phases

Week	Omalizumab			Placebo			
	n	Mean	SD	*n*	Mean	SD	*P* Value
18	15	16.2	12.6	7	18.4	22.8	.76
20	17	32.5	21.7	9	37.5	27.4	.77
22	10	46.7	26.9	8	47.1	28.3	.55
24	15	55.7	30.0	9	64.5	27.0	.56
26	11	68.7	29.4	8	61.7	35.4	.61
28*	11	50.7	64.8	9	59.1	36.3	.48
36	13	57.2	38.5	7	76.2	34.8	.82
52	13	67.4	65.7	7	94.16	15.4	.75

* End of steroid-reduction phase. At this time point, all placebo-treated patients were switched to omalizumab therapy.

imputation. There was no significant difference between the active and placebo groups for AUC for adjusted NO during this time period (1.31 ± 1.511 vs 1.45 ± 0.736 [$P = .732$]).

Change in FE_{NO} During Steroid-Reduction Phase (Primary Outcome Variable)

The variability of FE_{NO} in the placebo-treated group was greater than that of the omalizumab-treated group at most visits during the double-blind, steroid-reduction period (Fig 1). Overall, there was a significant difference between active and placebo groups for AUC for adjusted FE_{NO} during this phase (0.88 ± 0.69 vs 1.65 ± 1.06 [$P = .031$]).

Change in FE_{NO} During Open-Label Period in Placebo Group

During the 24-week, open-label extension phase, all patients in the placebo group were switched to omalizumab treatment. In the placebo group, FE_{NO} fell from 82.1 ± 55.6 ppm at the end of the steroid-reduction phase to 33.3 ± 21.6 ppb at the end of the open-label period ($P = .076$). This decrease occurred while the mean dose of BDP remained very low (Table 3), accompanied by a reduction in the variability of FE_{NO} that was seen among placebo-treated subjects during the steroid-reduction phase (Fig 1).

Change in FE_{NO} in Active Group During 52 Weeks of Treatment With Omalizumab

Analysis of FE_{NO} over 52 weeks of omalizumab treatment in the active group demonstrated that there was a significant reduction from baseline to the end of the open-label period (41.9 ± 29.0 to 18.0 ± 21.8 ppb [$P = .032$]) despite a high degree of steroid reduction (Table 3).

DISCUSSION

This is the first study to evaluate FE_{NO} via a noninvasive measure of airway inflammation during therapy with an anti-IgE antibody. The main findings were a significant elevation in FE_{NO} in the placebo group versus omalizumab during steroid reduction, whereas FE_{NO} remained stable in the active group relative to baseline. This occurred despite a profound and comparable reduction in BDP dosage in both groups.

Furthermore, FE_{NO} fell significantly during 1 year of continuous treatment with omalizumab in the active group despite continuing the profound reduction in corticosteroid therapy. In fact, omalizumab reduced FE_{NO} to a similar degree to that observed with ICSs[12,16] and leukotriene-modifying agents,[24] which suggests antiinflammatory activity for this agent in allergic asthma. In contrast, the observation that the concentration of FE_{NO} showed a significant increase in the placebo-treated group during the steroid-reduction phase suggests that airway inflammation worsened in some subjects as a consequence of an overall decrease in antiinflammatory therapy.

Because BDP doses did not differ between active and placebo groups at any time point, the changes in FE_{NO} were unrelated to a lower degree of steroid-reduction in the active treatment group. This finding strengthens our belief that omalizumab has antiinflammatory effects in allergic asthma. Indeed, a recent study has shown that omalizumab reduces eosinophilic inflammation in induced sputum and mucosal biopsies.[25] Because BDP was reduced to a similar extent in both groups, this study cannot suggest that omalizumab is steroid sparing, although other studies have indicated that this may be so.[4,5]

Examining possible confounding factors, some studies have shown that the concentration of FE_{NO} increases with age in children[26] and with mean predicted FEV_1.[27,28] This may explain the trend to higher concentrations of FE_{NO} at baseline in the placebo-treated group, who were significantly older than

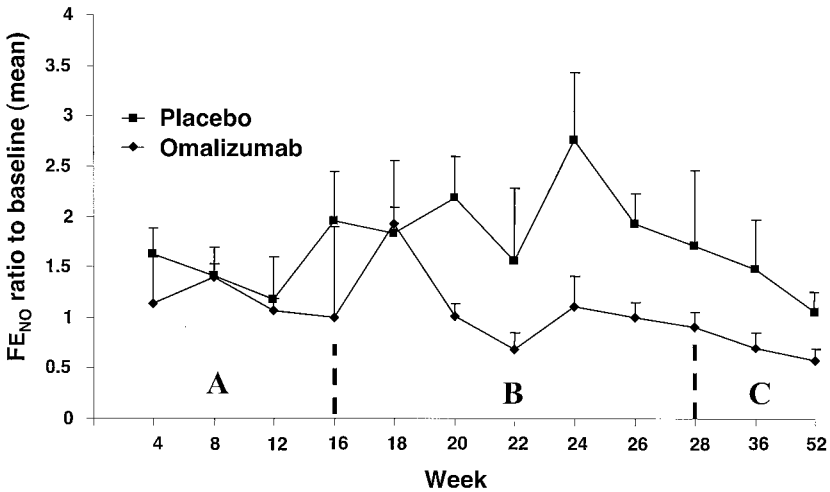

Fig 1. Change in ratio of adjusted FE_{NO}, expressed as mean (± standard error of the mean) in the omalizumab and placebo treatment groups during the study. A, Steroid-stable phase. B, Steroid-reduction phase. C, Open-label phase.

those randomized to omalizumab. The small magnitude of age- and FEV_1-related change in FE_{NO}, however, makes it likely that the differences and dynamic changes in FE_{NO} between omalizumab- and placebo-treated groups were valid.

This study was relatively underpowered, particularly in the placebo group, due to the 2:1 recruitment ratio dictated by the main study. Furthermore, participation declined as the study proceeded, probably due to the length of the protocol. This study therefore should be considered as a preliminary examination of the effect of omalizumab on FE_{NO}, with suggestive findings that should serve as a basis for a more-definitive study.

CONCLUSIONS

The stability of FE_{NO} during profound steroid reduction in children receiving omalizumab suggests that this agent may prevent an increase in airway inflammation that would be expected from ICS reduction. Despite the limitation of a small number of patients, this preliminary study suggests that omalizumab may be useful as a novel long-term, antiinflammatory therapy for treatment of moderate-to-severe allergic asthma in children. Investigations of larger patient groups are required to confirm this finding.

ACKNOWLEDGMENTS

This work was an addendum to a study supported by Genentech Inc (South San Francisco, CA) and Novartis Pharmaceuticals Corporation (East Hanover, NJ). This study was supported by Novartis Pharma AG (Basel, Switzerland) and Genentech Inc.

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