

Omalizumab can inhibit respiratory reaction during aspirin desensitization



David M. Lang, MD ^{*}; Mark A. Aronica, MD ^{*}; Elizabeth S. Maieron, BA, RRT ^{*}; Xiao-Feng Wang, PhD [†]; Dorothy C. Vasas, RN, BSN ^{*}; Stanley L. Hazen, MD, PhD [‡]

^{*} Respiratory Institute, Department of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, Ohio

[†] Lerner Research Institute, Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio

[‡] Lerner Research Institute, Department of Cellular and Molecular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio

ARTICLE INFO

Article history:

Received for publication March 20, 2018.

Received in revised form May 2, 2018.

Accepted for publication May 8, 2018.

ABSTRACT

Background: Aspirin desensitization has been associated with benefit in management of aspirin-exacerbated respiratory disease (AERD). An intervention that would encourage aspirin desensitization to be performed more frequently has substantial potential for improving outcomes and quality of life in patients with AERD.

Objective: We investigated whether omalizumab administration would be associated with attenuation of aspirin-provoked bronchospasm in patients with AERD undergoing aspirin desensitization.

Methods: We carried out a randomized, double-blind, placebo-controlled study in which subjects with AERD who fulfilled label criteria for omalizumab received omalizumab or placebo for 16 weeks, and then underwent aspirin desensitization.

Results: Eleven subjects completed aspirin desensitization. Of the 7 who were randomized to omalizumab, 5 had no respiratory reaction during aspirin desensitization. Compared with placebo, omalizumab was associated with a significantly greater likelihood for subjects with AERD to have no respiratory reaction during desensitization ($P = .04$, Fisher exact test). There was an overall difference in urinary leukotriene E4 (LTE4) levels in subjects who received omalizumab and did not have a respiratory reaction during desensitization compared with subjects randomized to placebo ($P = .035$, mixed model with interaction). Urinary LTE4 levels were significantly higher with respiratory reaction in placebo subjects compared with levels obtained after the 100-mg dose in AERD subjects who had no respiratory reaction ($P < .001$, mixed model with interaction).

Conclusion: In atopic AERD subjects, omalizumab administration for 16 weeks was associated with “clinically silent” desensitization. Further studies to investigate the therapeutic utility of omalizumab in patients with AERD who are candidates for aspirin desensitization are warranted based on these findings.

Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00555971) Identifier NCT00555971.

© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Patients with aspirin-exacerbated respiratory disease (AERD) exhibit a “tetrad” of chronic rhinosinusitis, nasal polyposis, asthma, and respiratory reaction after ingestion of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).¹ Despite avoidance of aspirin and NSAIDs, AERD patients frequently experience refractory rhinosinusitis and asthma—in some cases requiring numerous sinus surgery procedures. In as many as 50% of AERD patients, asthma

is severe and steroid dependent.² Aspirin-exacerbated respiratory disease affects an estimated 7% of adults with asthma.³

The aspirin desensitization procedure, in which a state of “tolerance” is induced and maintained, entails administration of incremental doses of aspirin, until 325 mg can be taken without reaction.⁴ Aspirin-induced bronchospasm has been lessened in AERD patients by pretreatment with cromolyn,^{5,6} nedocromil,⁶ salmeterol,⁷ clemastine,⁸ and tacrolimus.⁹ Administration of anti-leukotriene drugs has been shown to attenuate aspirin-provoked bronchospasm¹⁰; however, as is the case with the other mentioned agents, protection is not complete, and response is heterogeneous.¹¹ The anti-leukotrienes shift the dose response curve to the right, combined with a tendency to transfer aspirin-provoked reaction to the upper airway.¹² The blocking influence of anti-leukotrienes has been associated with “clinically silent” aspirin desensitization, but this is infrequent and has not been well characterized.¹³ Despite use of combination “controller” therapy

Reprints: David M. Lang, MD, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A90, Cleveland, OH 44195; E-mail: langd@ccf.org.

Disclosures: David M. Lang has carried out clinical research with, has received honoraria from, and/or has served as a consultant for: Astra Zeneca, Genentech/Novartis, and Hycor. Mark A. Aronica, Elizabeth S. Maieron, Dottie C. Vasas, Xiao-Feng Wang, and Stanley L. Hazen have no conflicts of interest to declare.

Funding Sources: Genentech/Novartis.

<https://doi.org/10.1016/j.anaai.2018.05.007>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

including anti-leukotrienes, and ensuring that asthma is well controlled, aspirin-provoked reactions can be volatile and entail serious bronchospasm.

More than 2 decades ago, the first double-blind, placebo-controlled, crossover study of aspirin desensitization treatment was reported.¹⁴ In two thirds of AERD subjects, statistically significant improvement was observed in symptoms and medication reliance in association with aspirin desensitization treatment. Sweet et al¹⁵ described results of a long-term assessment of the therapeutic utility of aspirin desensitization in 35 AERD patients followed up for an average of 3.7 years and compared their outcomes with 42 AERD “controls” who were not desensitized and avoided aspirin. Aspirin desensitization was associated with statistically significant reduction in hospitalization rates and emergency department use, annual numbers of outpatient visits, episodes of sinusitis and antibiotics required, and the need for polypectomy and sinus surgery procedures. This study may have entailed bias associated with its observational nature; however, statistically significant improvement in a randomized controlled trial of aspirin desensitization treatment was also recently reported in patients with AERD, with no benefit observed in a comparator group of aspirin-tolerant patients with asthma.¹⁶ The economic savings associated with aspirin desensitization treatment accrue from reduced rates of hospitalization and sinus surgery procedures; reoperative intervention can be reduced from an average of once every 3 years (before desensitization) to once every 10 years during long-term aspirin desensitization treatment.^{17,18} A recent American Academy of Allergy, Asthma, and Immunology survey of Allergy/Immunology physicians found that only 62.5% of respondents perform challenge/desensitization procedures for patients with AERD; safety concerns were cited as the most frequent obstacle to performing aspirin desensitization.¹⁹ An intervention that would make aspirin desensitization more widely available, by reducing risk (for severe bronchospasm) associated with this procedure, has substantial potential for improving health care outcomes and quality of life for AERD patients.

Omalizumab is a chimeric human–mouse recombinant antibody, which binds to the domain at which immunoglobulin E (IgE) binds to the high-affinity IgE receptor on mast cells and basophils.²⁰ The salutary effects of omalizumab reported in properly selected patients with asthma include reduced eosinophils in serum²¹ and

sputum.²² Djukanovic et al²³ performed a randomized, double-blind, placebo-controlled trial in which markers of inflammation were assessed in induced sputum, and biopsies were performed via bronchoscopy before and after 16 weeks of treatment with omalizumab. Subjects with mild to moderate asthma who fulfilled label criteria for omalizumab, who had more than 2% eosinophils in sputum, were enrolled. Omalizumab was associated with not only depletion of IgE from the airway and reductions in high-affinity IgE receptor, interleukin (IL)-4, and T and B lymphocytes, but also a dramatic reduction in tissue eosinophilia. Respiratory reaction in AERD has been associated with enhanced release of leukotrienes provoked by aspirin,²⁴ in combination with greater target organ sensitivity to leukotrienes.²⁵ Levels of urinary leukotriene E4 (LTE4), the end metabolite of cysteinyl leukotrienes, are higher in patients with AERD and increase in association with aspirin-provoked respiratory reaction. Recent studies of the pathogenesis of aspirin-provoked respiratory reaction have implicated overproduction of not only leukotrienes but also PGD₂, and have demonstrated a role for prominent eosinophilic inflammation in the lower and upper airway as well as mast cell and platelet activation.²⁶ Because omalizumab administration for 16 weeks was associated with a significant decline in eosinophils and other inflammatory cells in epithelium and submucosa,²³ we hypothesized that a substantial and clinically significant reduction in the capacity for mediator release would be fostered by administration of omalizumab, and that on this basis in subjects with AERD who received omalizumab for 16 weeks, respiratory reaction during aspirin desensitization would be significantly attenuated.

Methods

The study protocol is shown in Figure 1. Patients referred to the Department of Allergy and Clinical Immunology for aspirin desensitization were recruited for participation. Subjects 18 years of age and older were evaluated to determine whether their history, clinical course, and additional evaluation fulfilled criteria consistent with: (1) AERD: a history of moderate to severe persistent asthma and chronic polypoid rhinosinusitis requiring previous sinus surgery procedures, combined with a convincing history of respiratory reaction(s) to aspirin or NSAIDs; (2) label criteria for omalizumab²⁰: serum IgE level 30 to 700 IU/mL, and allergy to a perennial

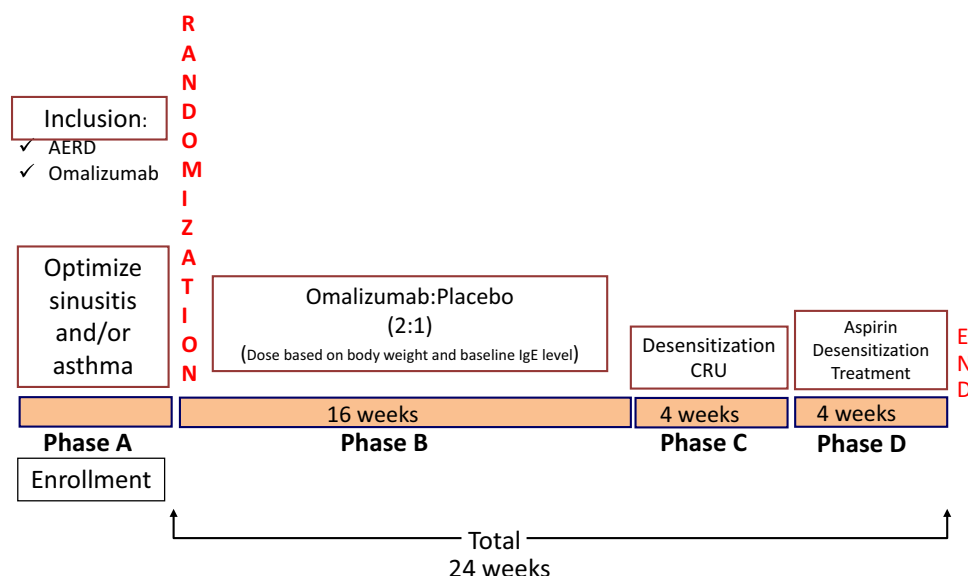


Figure 1. The 4 phases of study participation. AERD, aspirin desensitization; CRU, Clinical Research Unit.

aeroallergen confirmed by wheal/flare reaction on skin testing or in vitro serum specific IgE. Phase A of this study also entailed management to optimize rhinosinusitis and asthma.

In Phase B, block randomization with allocation concealment was performed such that subjects fulfilling inclusion criteria received either omalizumab or identical placebo, injected every 2 or 4 weeks, based on serum IgE and body weight, for 16 weeks. Assignment of subjects to omalizumab or placebo was randomized in a 2:1 fashion. One investigator (MAA) was unblinded and served as safety monitor. The unblinded investigator did not interact with subjects during their participation, nor participate in adjudicating the type of respiratory reaction that subjects exhibited. All other investigators, research personnel, and outcome adjudicators were blinded to treatment assignment.

In phase C, within 4 weeks after receiving study drug, aspirin desensitization was performed in the Cleveland Clinic Clinical Research Unit. Subjects then entered phase D, in which they took aspirin daily to perpetuate the desensitized state, either at a dosage of 650 mg twice daily or 325 mg twice daily if gastroesophageal reflux was present.

Aspirin desensitization was performed in accordance with previously established protocols, beginning at 30 mg and advancing with serial dosing to 650 mg,²⁷ as shown in Table 1. Subjects were categorized into 5 groups based on the type of respiratory reaction to aspirin: (1) combined upper and lower respiratory reaction (decline in forced expiratory volume in 1 second [FEV₁] > 20%); (2) upper airway reaction with partial lower respiratory reaction (sub-threshold decline in FEV₁ = 15%–20%); (3) isolated lower respiratory reaction; (4) isolated upper respiratory reaction; (5) no respiratory reaction. Day 1 entailed administration of 2 placebos to confirm stability of asthma and rhinosinusitis, before proceeding with aspirin dosing. Spirometry was performed at baseline each day, every hour, and in association with respiratory symptoms. Urine was obtained for measurements of LTE₄: at baseline, before randomization; at baseline, before aspirin desensitization procedure; 3 hours after aspirin doses 1 through 3, as shown in Table 1; 3 hours after respiratory reaction; after completion of aspirin desensitization, 3 hours after the 650-mg aspirin dose; at the 1-month follow-up visit while taking aspirin desensitization treatment. Urine was collected, aliquoted, and immediately frozen; samples were maintained at –70°C and were analyzed using enzyme immunoassay²⁸ in accordance with the manufacturer's instructions (Cayman Chemical, Ann Arbor, MI), with LTE₄ levels expressed as picograms per milligram of creatinine.

Medications as appropriate for management of AERD, including agents to treat both asthma and rhinosinusitis, were maintained throughout study participation. Efforts were made to maintain medications at constant doses during participation, and to avoid adding additional medications, unless required for exacerbation of asthma or rhinosinusitis.

Subjects with the following features were excluded from participation: women of childbearing potential not using appropriate contraception methods or currently breastfeeding, women who desired to become pregnant, men who desired to get someone pregnant, individuals with known sensitivity to omalizumab, who had

received omalizumab or another biologic agent in the previous 12 months, with current tobacco habituation, with chronic obstructive pulmonary disease, alcohol or drug abuse within last 12 months, who had a significant medical condition including neurologic, kidney, gastrointestinal, liver, or cardiovascular disease, or who had a contraindication for aspirin administration, including severe anemia, thrombocytopenia, or recent gastrointestinal hemorrhage.

This protocol was approved by the Cleveland Clinic Institutional Review Board, and for the Investigational New Drug Program by the United States Food and Drug Administration. Informed consent was obtained from all subjects in writing. Genentech/Novartis provided financial support but had no role in the design of this study, data tabulation, analysis, or interpretation.

Statistical Analysis

The study variables were described using mean with standard deviation or using proportions as appropriate. Continuous variables were compared using the *t* test or Mann–Whitney *U* test. Categorical variables were compared using Pearson's χ^2 test or Fisher exact test. Nonparametric comparisons were used to analyze differences between groups and patterns of reaction during aspirin desensitization. Linear mixed models were employed to test differences in levels of urinary LTE₄ over time, when adjusted by time effects and the interaction between urinary LTE₄ and time. All *P* values are reported as 2-tailed; *P* < .05 was considered statistically significant. Statistical analyses were performed using SAS software (Version 9.4, SAS Institute, Cary, NC).

Results

As shown in Figure 2, 72 subjects were considered for participation; 56 were excluded, in most cases because of a history not convincing for AERD¹ or criteria for receiving omalizumab²⁰ not being fulfilled. Sixteen subjects who fulfilled inclusion criteria were enrolled. All had moderate to severe persistent asthma, chronic polypoid rhinosinusitis, more than 1 respiratory reaction, or a single severe respiratory reaction to aspirin or NSAIDs. Three subjects, a 42-year-old woman who had a serious relapse of chronic urticaria, a 58-year-old woman with persisting severe ventilatory impairment despite maximal pharmacotherapy, and a 40-year-old woman lost to follow-up after informed consent was signed, were not randomized. In 2 cases, study drug was administered for 16 weeks, then before undergoing desensitization, a 57-year-old woman randomized to omalizumab fell and had a cervical spine fracture, and a 52-year-old woman who received placebo had a left cerebellar stroke. Study blind was broken in the latter case, to inform this subject that she had received placebo.

Eleven subjects completed aspirin desensitization: 7 were randomized to receive omalizumab, 4 to placebo. Demographic characteristics of these subjects are described in Table 2. No statistically significant differences were seen at baseline in age, body mass index, number of sinus surgeries, or FEV₁; however, subjects randomized to receive placebo were all women, whereas 4 women and 3 men were randomized to the omalizumab arm. All subjects were white, except for a 20-year-old African-American man who was randomized to omalizumab. A difference in mean IgE level, which was statistically significantly higher in subjects randomized to omalizumab (120.5 IU/mL vs 64.6 IU/mL; *P* = .02, Mann–Whitney *U* test) was seen. All 11 subjects had moderate to severe persistent asthma and were receiving combination controller therapy. All subjects were taking montelukast 10 mg daily; all were receiving inhaled corticosteroids combined with long-acting beta agonists, except for a 58-year-old man whose asthma was well controlled on medium-dose inhaled steroid combined with montelukast.

Table 1
Desensitization Protocol

	Day 1	Day 2	Day 3
8:00 AM	Placebo	60 mg	325 mg
11:00 AM	Placebo	100 mg	650 mg
2:00 PM	30 mg	150 mg	

NOTE. Aspirin desensitization protocol, with the first day including 2 placebos to confirm stability of asthma and rhinosinusitis symptoms before proceeding with aspirin dosing.

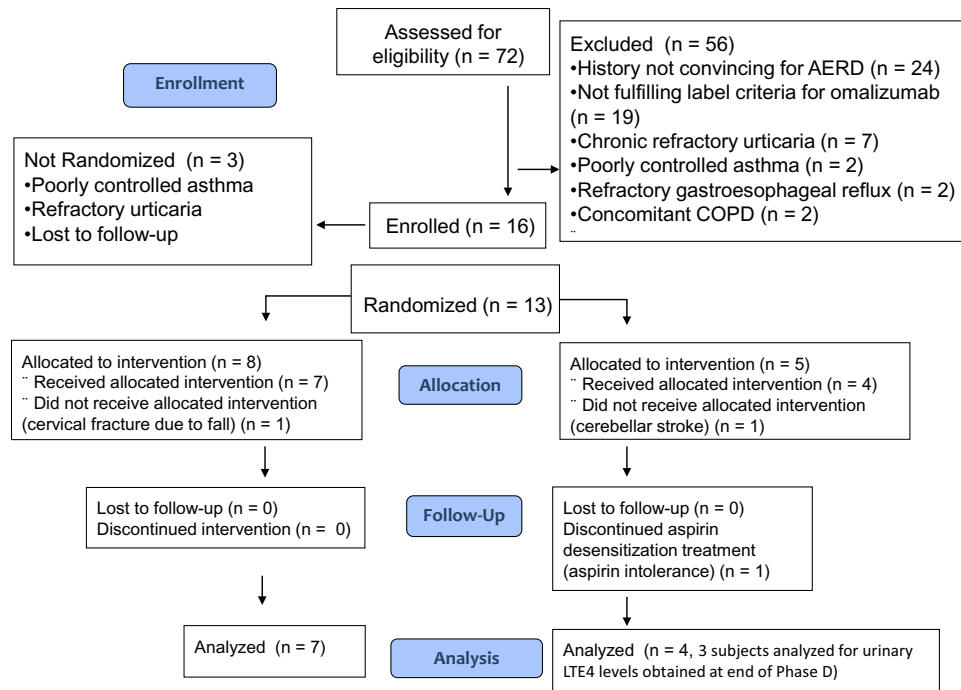


Figure 2. Study flowchart.

Of the 11 subjects who underwent aspirin desensitization, 2 had combined upper and lower airway reactions with declines in FEV₁ exceeding 20% of baseline, 4 had isolated upper airway reactions, and 5 subjects completed aspirin desensitization without respiratory reaction. Four reactions were observed at the 100-mg aspirin challenge dose, with one combined reaction and one upper airway reaction at 60 mg and 150 mg, respectively.

When the blind was broken after completion of the study, when the last subject completed phase D, as shown in Table 3, we found that the subjects with combined reactions had received placebo, 2 in each group had exhibited upper airway reactions, and the 5 subjects who completed aspirin desensitization with no respiratory reaction had all been randomized to omalizumab. The difference in patterns of respiratory reaction during aspirin desensitization that

we observed was statistically significant ($P = .04$, Fisher exact test), indicating that randomization to omalizumab compared with placebo was associated with a statistically significant increase in the likelihood for subjects to exhibit no respiratory reaction to aspirin during desensitization.

As illustrated in Figure 3, subjects who did not subsequently react to aspirin had a lower mean level of urinary LTE4 after 16 weeks of omalizumab compared with placebo; however, this was not statistically significant ($P = .37$, mixed model with interaction). In the 5 nonreactors, mean urinary LTE4 levels remained relatively low during aspirin desensitization. A statistically significant overall difference was seen comparing LTE4 levels in subjects receiving omalizumab who did not have respiratory reaction and those randomized to placebo ($P = .035$, mixed model with interaction).

Table 2
Demographic Data for Subjects Randomized to Omalizumab or Placebo

Omalizumab	Sex	Race	Age	Body mass index	Number of sinus surgeries	FEV1 (% predicted)	Total serum IgE level	Medications
01	M	B	20	32	1	65	213	High-dose ICS/LABA, M
02	F	W	42	19	2	80	100	High-dose ICS/LABA, M
03	F	W	49	29	4	113	38	Medium-dose ICS/LABA, M
04	F	W	48	30	3	95	74	High-dose ICS/LABA, M
05	F	W	58	23	2	98	127	Medium-dose ICS/LABA, M
06	M	W	58	31	1	98	251	Medium-dose ICS, M
07	M	W	45	26	3	99	41	Medium-dose ICS/LABA, M
		Mean	45.7 ^a	27.1 ^a	2.29 ^a	92.6 ^a	120.5 ^b	
		SD	11.9	4.7	1.1	14.4	76.7	
Placebo	Sex	Race	Age	Body mass index	Number of sinus surgeries	FEV1 (% predicted)	Total serum IgE level	Medications
P1	F	W	40	27	2	113	33	High-dose ICS/LABA, M
P2	F	W	50	38	2	66	126	Medium-dose ICS/LABA, M
P3	F	W	46	26	2	79	40	High-dose ICS/LABA, M
P4	F	W	31	32	1	102	60	Medium-dose ICS/LABA, M
		Mean	41.8 ^a	30.75 ^a	1.75 ^a	90.0 ^a	64.6 ^b	
		SD	7.2	5.5	0.5	18.5	36.6	

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta-agonist; M, montelukast.

^a $P = NS$.

^b $P = .02$.

Table 3
Respiratory Reactions

	Lower airway reaction (decline in FEV ₁ ≥ 20%)	Upper airway reaction	No respiratory reaction
Placebo	2	2	0
Omalizumab	0	2	5

NOTE. Patterns of respiratory reaction observed during aspirin desensitization (Phase C of study participation) are displayed. Randomization to omalizumab was associated with a statistically significant increase in the likelihood for no respiratory reaction to aspirin during desensitization compared with placebo ($P = .04$).

Compared with levels obtained after the 100-mg dose in nonreactors, urinary LTE₄ levels were significantly higher with reaction in placebo subjects (Mean $\pm$ SE = $1,852 \pm 280$ vs $17,489 \pm 7,102$, $P < .001$, mixed model with interaction).

Omalizumab was tolerated without untoward effect. One subject who received placebo developed gastrointestinal intolerance and suspended aspirin during the 4 weeks of aspirin desensitization treatment; she did not complete participation.

Discussion

Aspirin desensitization offers patients with AERD opportunity for benefit, including reduced symptoms, lower medication reliance, and improved quality of life^{16,18}; however, primarily because of risk for serious bronchospasm, aspirin desensitization is not commonly performed by many allergy/immunology physicians.¹⁹ The Centers for Disease Control estimates that 17.7 million adult Americans currently have asthma.²⁹ The corresponding estimate based on these data is that as many as 1.24 million adult Americans have AERD.³ We found that in subjects with AERD who fulfilled criteria for anti-IgE therapy and who were randomized to omalizumab,

respiratory reactions were statistically significantly less likely to occur during aspirin desensitization. Our data imply that omalizumab has substantial utility for management of this subgroup of patients with AERD and could lead to aspirin desensitization being performed more frequently.

The strengths of our study include its randomized double-blind, placebo-controlled design. Randomization and blinding minimize bias and enhance the likelihood that intervention and control groups are similar at enrollment and during study participation. In a randomized, double-blind trial, the control subjects, who in our study received placebo that contained the vehicle for omalizumab without active drug, are enrolled to determine whether an observed effect is truly related to the intervention. Observing outcomes in the control group permits an assessment of the outcomes that would have occurred had the treated subjects not received the intervention. In our study, subjects were randomized to receive either omalizumab or placebo in a double-blind fashion such that neither subjects nor investigators were aware of treatment assignment. Five of our seven subjects randomized to omalizumab exhibited no respiratory reaction during desensitization.

Another strength is our study protocol, which included a challenge dose of 650 mg. In patients with AERD, initial reaction to aspirin at a dosage of 650 mg is not commonly observed, and for this reason omitting this dose in a patient undergoing aspirin challenge who has not reacted to this point has been recommended.³⁰ Inclusion of the 650-mg dose confirmed that “silent desensitization” had occurred.

Our findings demonstrating the utility of omalizumab in the setting of AERD are supported by a number of case reports in which omalizumab administration was associated with induction of aspirin tolerance in patients with AERD.^{31–34}

In one of these reports,³⁴ aspirin desensitization was successfully performed in a patient who also had aspirin-exacerbated

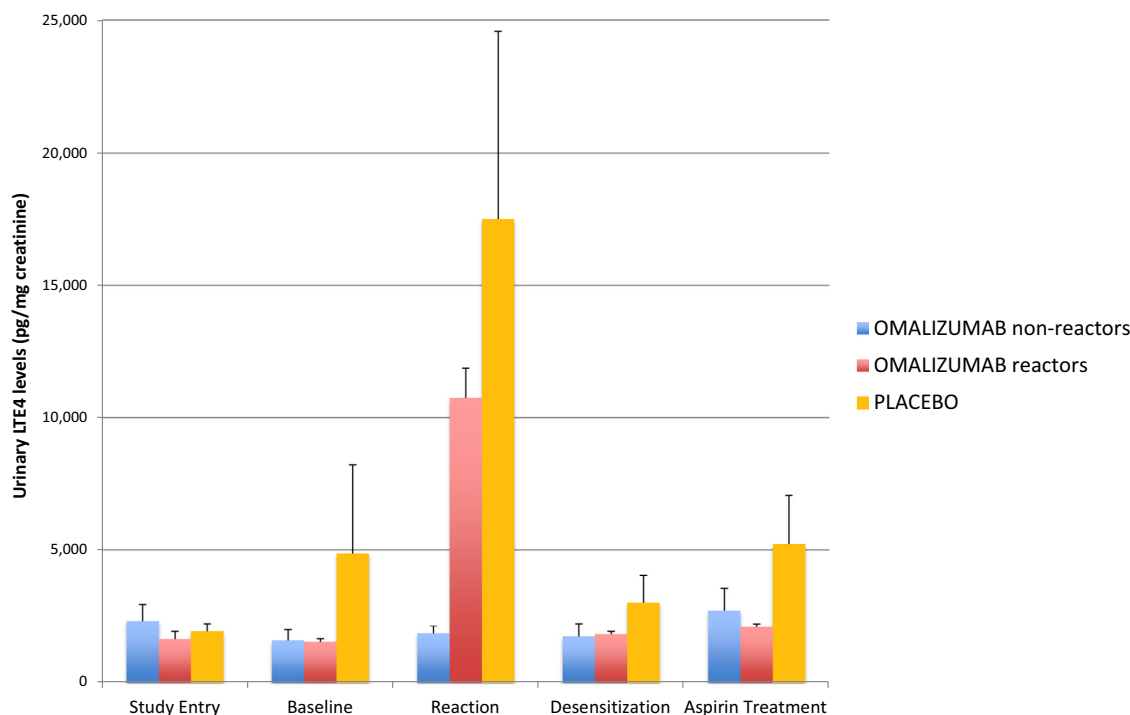


Figure 3. Means of urinary LTE₄ levels are displayed for 5 time points during study participation: (1) Study entry, (2) Baseline, after 16 weeks of study drug and before aspirin exposure; (3) After respiratory reaction or 100-mg dose in subjects without respiratory reaction; (4) After administration of 650 mg aspirin; (5) After 1 month of aspirin desensitization treatment. Error bars indicate standard error (SE). In subjects receiving omalizumab who did not have respiratory reaction, levels were statistically significantly different compared with subjects randomized to placebo ($P = .035$). Compared with urinary LTE₄ levels obtained after the 100-mg dose in nonreactors randomized to omalizumab, levels were significantly higher with reaction in placebo subjects (Mean $\pm$ SE = $1,852 \pm 280$ vs $17,489 \pm 7,102$, $P < .001$).

urticaria/angioedema. In 1 of our subjects, a 45-year-old man in whom AERD was confirmed by respiratory reaction during aspirin desensitization several years earlier, the procedure was aborted because of development of generalized urticaria for which oral corticosteroids were required. However, in association with being randomized to omalizumab in this study, he exhibited no respiratory or cutaneous reaction, and he continues to benefit on aspirin desensitization treatment.

In contrast to our findings and previous reports,^{31–34} Waldram et al³⁵ described respiratory reactions, none of which was severe, during aspirin desensitization in 8 of 9 patients receiving omalizumab. The duration of omalizumab administration was not specified in this study. Possibly several doses, as administered in our study, or a larger dose, are required for a clinically significant effect to occur. For patients with moderate to severe persistent asthma, omalizumab is dosed according to total serum IgE and body weight. Omalizumab dosing for patients with chronic urticaria differs from the algorithm used for asthma.²⁰ Possibly optimal dosing of omalizumab for inhibition of respiratory reaction in AERD patients may also need to differ from the algorithm used for treatment of patients with asthma.

In properly selected patients with moderate to severe asthma who receive omalizumab, no criteria are established for predicting whether a favorable response will occur. Hanania et al³⁶ found that a salutary effect of omalizumab was more likely in subjects with higher levels of exhaled nitric oxide, peripheral eosinophils, and serum periostin—biomarkers reflecting Th2-driven inflammation. The heterogeneity in outcomes observed with omalizumab treatment likely reflects the diversity of inflammatory and immunologic asthma phenotypes that influence therapeutic response. Our data, taken together with the findings of recent case reports^{31–34} and Waldram et al³⁵ imply that heterogeneity of response to omalizumab also may exist in patients with AERD. Further studies will be required to achieve a clearer understanding of the mechanism of the anti-inflammatory effect of omalizumab in AERD, the factors that predispose to a salutary response, and its potential therapeutic role in AERD patients who do or do not fulfill label criteria and are candidates for aspirin desensitization.

An alternative interpretation for our findings is possible. The diagnosis of AERD is suspected by history, and it can be confirmed only by aspirin challenge. Pleskow et al reported more than 30 years ago that in patients who fulfill diagnostic criteria for AERD according to history, the rate of “false positive” diagnosis based on aspirin challenge as reference standard is 16%.³⁷ We reviewed 50 randomly selected patients who underwent aspirin desensitization during the past 7 years at Cleveland Clinic (data not shown) and found that in 8 cases (16%), no respiratory reaction to aspirin was observed. Using 16% as an estimate for the rate of what one would expect for a “false positive” diagnosis of AERD based on history, the probability that this alternative hypothesis explains our observations, that is, that all 5 of our subjects who did not react to aspirin did not have AERD and by chance were all randomized to receive omalizumab, is associated with a calculated probability of less than 1 in 500 ($P < .002$, exact binomial test); the chance that 4 of the 5 nonreactors did not have AERD and were all randomized to the treatment arm is also unlikely ($P = .015$, exact binomial test).

We found that in subjects randomized to omalizumab compared with those who received placebo, as illustrated in Figure 3, after 16 weeks of study drug, LTE4 levels were lower in those who received omalizumab. This difference did not achieve statistical significance; however, Hayashi et al³⁸ recently reported that omalizumab administration was associated with a statistically significant reduction in urinary LTE4 levels in patients with AERD, supporting our hypothesis that the anti-inflammatory effects of omalizumab lead to a lowering of the capacity for leukotriene release with aspirin exposure in patients with AERD.

Several limitations of our study merit comment. The dramatic anti-inflammatory effects of omalizumab documented via endobronchoscopic biopsy were observed in association with omalizumab administration for a period of 16 weeks²³; for this reason, our study was designed for a 16-week duration of omalizumab administration before aspirin desensitization. The findings of our study cannot be generalized to AERD patients who have received omalizumab for less than 16 weeks. The blocking effect of omalizumab on respiratory reaction that we observed also cannot be extended to patients with AERD who do not fulfill label criteria for omalizumab. We believed that, based on their established role for patients with AERD undergoing desensitization,¹² suspension of anti-leukotriene drugs before performing aspirin desensitization would have been unethical. Because all subjects were taking montelukast during study participation, we cannot exclude the possibility that this exposure may have influenced the findings we observed. The benefits of randomization are numerous; however, this design may result in groups that are not comparable in terms of certain covariates. Unexpectedly, baseline mean IgE levels were significantly higher in subjects randomized to omalizumab compared with placebo. In previous studies,³⁹ serum IgE levels have not correlated with response to omalizumab in subjects with moderate to severe allergic asthma. We do not believe the lack of respiratory reaction in 5 of 7 AERD subjects randomized to omalizumab can be explained by this difference. A sex imbalance was seen in our study. The 3 men enrolled were randomized to omalizumab, and all 3 had no respiratory reaction to aspirin. Medication effects can differ based on the influence of sex.⁴⁰ Further studies will be required to determine whether a remarkable difference occurs in response to omalizumab in patients with AERD based on sex. Although the probability that all 5 subjects randomized to omalizumab did not have AERD and were all randomized to omalizumab is less than 1 in 500, because all subjects did not have AERD confirmed by prior aspirin challenge, we cannot exclude the possibility that 1 or more of these subjects did not have AERD. Finally, although this is a small study, the difference in patterns of respiratory response during aspirin desensitization was dramatic and statistically significant; moreover, our study was double-blind and placebo controlled. Our experience is similar to a previous double-blind study of patients with AERD: 11 AERD subjects completed our study, with 72 potential participants screened; in a recently published double-blind, placebo-controlled study of aspirin desensitization treatment in which 109 potential participants were screened, only 15 with AERD and 13 with aspirin-tolerant asthma completed participation.¹⁶

In this study, 5 of 7 AERD patients who fulfilled label criteria for omalizumab, and who were randomized to omalizumab for 16 weeks, exhibited “clinically silent” desensitization to aspirin. As measurements of urinary LTE4 increase dramatically in association with aspirin-provoked respiratory reaction,²⁴ our findings suggest that the protective effect of omalizumab is related to a reduced capacity for leukotriene release with exposure to provocative doses of aspirin. Elucidating the mechanism by which omalizumab can achieve this effect will require additional investigation. Clinicians should be aware that “false negative” aspirin challenges may be observed in patients with AERD in association with omalizumab administration. Based on our findings, further studies to investigate the therapeutic utility of omalizumab in patients with AERD undergoing aspirin desensitization are warranted.

Acknowledgments

We thank Genentech/Novartis for supporting this investigator-initiated study, and also express our appreciation to the subjects with AERD who participated in this study, the Cleveland Clinic Clin-

ical Research Unit staff for their dedicated support, and Sarah Neale and Alan Pratt for performing measurements of urinary LTE4.

References

- [1] Woessner K, White A. Evidence based approach to aspirin desensitization in aspirin exacerbated respiratory disease. *J Allergy Clin Immunol*. 2014;133:286–287.
- [2] Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators: European Network on Aspirin-Induced Asthma. *Eur Respir J*. 2000;16:432–436.
- [3] Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol*. 2015;135:676–681.
- [4] Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin exacerbated respiratory disease: a practice paper. *Ann Allergy Asthma Immunol*. 2007;98:172–174.
- [5] Yoshida S, Amayasu H, Sakamoto H, et al. Cromolyn sodium prevents bronchoconstriction and urinary LTE4 excretion in aspirin-induced asthma. *Ann Allergy Asthma Immunol*. 1998;80:171–176.
- [6] Robuschi M, Gambaro G, Sestini P, et al. Attenuation of aspirin-induced bronchoconstriction by sodium cromoglycate and nedocromil sodium. *Am Rev Respir Crit Care Med*. 1997;155:1461–1464.
- [7] Szczeklik A, Dworski R, Mastalerz L, et al. Salmeterol prevents aspirin-precipitated attacks of asthma and interferes with eicosanoid metabolism. *Am J Respir Crit Care Med*. 1998;158:1168–1172.
- [8] Szczeklik A, Serwonska M. Inhibition of idiosyncratic reactions to aspirin in asthmatic patients by clemastine. *Thorax*. 1979;34:654–657.
- [9] Kawano T, Matsuse H, Kondo Y, et al. Tacrolimus reduces urinary excretion of leukotriene E (4) and inhibits aspirin-induced asthma to threshold dose of aspirin. *J Allergy Clin Immunol*. 2004;114:1278–1281.
- [10] Stevenson DD, Simon RA, Mathison DA, Christiansen SC. Montelukast is only partially effective in inhibiting aspirin responses in aspirin sensitive asthmatics. *Ann Allergy Asthma Immunol*. 2000;85:477.
- [11] Lang DM. Blocking aspirin-induced bronchospasm. *Ann Allergy Asthma Immunol*. 2005;95:307–308.
- [12] Berges-Gimeno M, Simon R, Stevenson D. The effect of leukotriene-modifier drugs on aspirin induced asthma and rhinitis reactions. *Clin Exp Allergy*. 2002;32:1491–1496.
- [13] Lee RU, Stevenson DD. Aspirin exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res*. 2011;3:3–10.
- [14] Stevenson D, Pleskow W, Simon R, et al. Aspirin sensitive rhinosinusitis: a double blind cross over study of treatment with aspirin. *J Allergy Clin Immunol*. 1984;73:500–507.
- [15] Sweet J, Stevenson D, Simon R, Mathison D. Long term effects of aspirin desensitization treatment for aspirin sensitive rhinosinusitis asthma. *J Allergy Clin Immunol*. 1990;85:59–65.
- [16] Swierczynska-Krepa M, Sanak M, Bochenek G, et al. Aspirin desensitization in patients with aspirin induced and aspirin tolerant asthma: a double blind study. *J Allergy Clin Immunol*. 2014;134:883–890.
- [17] Shaker M, Lobb A, Jenkins P, et al. An economic analysis of aspirin desensitization in aspirin exacerbated respiratory disease. *J Allergy Clin Immunol*. 2008;121:81–87.
- [18] Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin sensitive patients with rhinosinusitis-asthma: long term outcomes. *J Allergy Clin Immunol*. 1996;98:751–758.
- [19] Waldram JD, White AA. A survey of aspirin desensitization practices among allergists and fellows in training in the United States. *J Allergy Clin Immunol Pract*. 2016;4:1253–1255.
- [20] Omalizumab, Xolair, label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Accessed November 30, 2016.
- [21] Noga O, Hanf G, Kunkel G. Immunologic and clinical changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol*. 2003;131:46–52.
- [22] 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;155:1828–1834.
- [23] Djukanovic R, Wilson S, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody Omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med*. 2004;170:583–593.
- [24] Christie PE, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143:1025–1029.
- [25] Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis*. 1989;140:148–153.
- [26] Cahill KN, Laidlaw TM. Pathogenesis of aspirin induced reactions in aspirin exacerbated respiratory disease. *Immunol Allergy Clin North Am*. 2016;36:681–691.
- [27] Berges-Gimeno MP, Stevenson DD. Nonsteroidal anti-inflammatory drug-induced reactions and desensitization. *J Asthma*. 2004;41:375–384.
- [28] Kumlin M, Stensvad F, Larsson L, Dahlen B, Dahlen SE. Validation and application of a new simple strategy for measurements of urinary leukotriene E4 in humans. *Clin Exp Allergy*. 1995;25:467–479.
- [29] Asthma. <https://www.cdc.gov/nchs/fastats/asthma.htm>. Accessed March 30, 2017.
- [30] Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol*. 2009;123:406–410.
- [31] Aksu K, Kurt E. Aspirin tolerance following omalizumab therapy in a patient with aspirin exacerbated respiratory disease. *Allergol Immunopathol (Madr)*. 2013;41:208–210.
- [32] Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2015;3:459–460.
- [33] Bobolea I, Barranco P, Fiandor A, Cabañas R, Quirce S. Omalizumab: a potential new therapeutic approach for aspirin exacerbated respiratory disease. *J Invest Allergol Clin Immunol*. 2010;20:446–453.
- [34] Guillen D, Bobolea I, Calderon O, et al. Aspirin desensitization achieved after omalizumab treatment in a patient with aspirin exacerbated urticaria and respiratory disease. *J Invest Allergol Clin Immunol*. 2015;25:133.
- [35] Waldram J, Walters K, Simon R, Woessner K, Waalen J, White A. Safety and outcomes of aspirin desensitization for aspirin exacerbated respiratory disease: a single center study. *J Allergy Clin Immunol*. 2018;141:250–256.
- [36] Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187:804–811.
- [37] Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J Allergy Clin Immunol*. 1983;71:574–579.
- [38] Hayashi H, Mitsui C, Nakatani E, et al. Omalizumab reduces cysteinyl leukotriene and 9a,11b-prostaglandin F2 overproduction in aspirin exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137:1585–1587.
- [39] Wahn U, Martin C, Freeman P, Blogg M, Jimenez P. Relationship between pre-treatment specific IgE and the response to omalizumab therapy. *Allergy*. 2009;64:1780–1787.
- [40] Whitley HP, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician*. 2009;80:1254–1258.