

Letter to the Editor

Omalizumab reduces cysteinyl leukotriene and 9 α ,11 β -prostaglandin F₂ overproduction in aspirin-exacerbated respiratory disease

To the Editor:

Aspirin-exacerbated respiratory disease (AERD) is a distinct phenotype of asthma characterized by sensitivity to aspirin and nonsteroidal anti-inflammatory drugs, nasal polyposis, mast cell activation,¹ and overproduction of cysteinyl leukotrienes.^{2,3} AERD is an important clinical issue because it is strongly related to severe asthma.⁴

Some studies suggest that omalizumab is efficacious in patients with severe allergic asthma and other allergic diseases.⁵ Markers of T_H2-driven inflammation, including fractional exhaled nitric oxide, peripheral blood eosinophil counts, and serum periostin, have been identified as candidate predictors of omalizumab treatment⁶; however, data demonstrating that omalizumab improves other inflammatory biomarkers are scarce. Because AERD causes mast cell activation⁷ and serious eosinophilic airway inflammation,⁸ the effects of omalizumab may be different from those usually observed in severe asthma. Here, the clinical efficacy of omalizumab against AERD is described, and urinary markers of mast cell activation, leukotriene E₄ (LTE₄) and prostaglandin D₂ metabolite 9 α ,11 β -prostaglandin F₂ (PGD₂M), were evaluated.

A total of 21 adults with AERD initiated omalizumab treatment at Sagami National Hospital in Japan between July 2009 and September 2013. The Ethics Committee of Sagami National Hospital approved this study. All patients provided written informed consent. AERD was diagnosed by a systemic aspirin provocation test. All patients had 1 or more positive results in skin or serum-specific IgE tests for common environmental allergens. Patients had been on their usual asthma treatment for at least 12 months before enrollment, but had not previously received omalizumab.

Urinary concentrations of LTE₄ and PGD₂M, peripheral blood eosinophil counts, respiratory function, and scores for nasal (congestion, anterior rhinorrhea, and anosmia) and asthma-related (dyspnea, wheezing, and cough) symptoms were assessed at enrollment and after 12 months of omalizumab. The number of exacerbations and hospitalizations, and daily corticosteroid dose during the 12 months before enrollment, was compared with those after 12 months of omalizumab treatment. LTE₄ and PGD₂M were quantified from spot urine samples using enzyme immunoassay after purification with high-performance liquid chromatography, as described previously.⁹ The visual analog scale was used to evaluate nasal and asthma-related symptoms. Asthma exacerbation was defined as emergency medical visits, unscheduled doctor's visits, or the need for additional oral or intravenous steroid therapy. After 12 months of omalizumab treatment, physicians used the Global Evaluation of Treatment Effectiveness to classify responders and nonresponders. Omalizumab dosages were individualized according to body weight and serum IgE level, with administration at 2- or 4-week intervals for a minimum dose of 0.016 mg/kg/IgE (IU/mL). Significance testing was performed using the Wilcoxon signed rank test or Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables.

The study population comprised 21 patients, 3 men and 18 women, with a median age of 60.0 years (interquartile range [IQR], 49.0-64.0 years), a median asthma onset age of 38.0 years (IQR, 23.5-46.5 years), and a median serum IgE level of 77.3 IU/mL (IQR, 53.9-195.0 IU/mL) (see Table E1 in this article's Online Repository at www.jacionline.org). Among the 21 patients, 16 (76.2%) had received systemic corticosteroid therapy at the time of enrollment. During the 12 months before omalizumab treatment, 14 of 21 patients (66.7%) experienced 3 or more asthma exacerbations (median, 5.0 [IQR, 2.0-7.5]) and 6 of 21 patients (28.6%) had at least 1 hospital admission because of an exacerbation (median, 0 [IQR, 0-1.0]).

None of the patients underwent nasal polyp surgery during the study. According to the Global Evaluation of Treatment Effectiveness, 18 of 21 patients were responders (response rate, 85.7%), whereas 3 of 21 were nonresponders (see Fig E1 in this article's Online Repository at www.jacionline.org). Omalizumab was discontinued by 3 of the 21 patients, and all 3 were nonresponders. The primary reason for discontinuation was high out-of-pocket treatment costs relative to efficacy. Baseline characteristics of responders and nonresponders are presented in Table E2 in this article's Online Repository at www.jacionline.org. Before omalizumab treatment, systemic corticosteroid doses and visual analog scale scores for anterior rhinorrhea and anosmia were significantly lower in nonresponders, implying that this subset of patients had less severe disease.

Table 1 presents urine biomarker concentrations, peripheral blood eosinophil counts, respiratory function, nasal and asthma-related symptom scores, the number of exacerbations and hospitalizations, and daily corticosteroid doses assessed before and after omalizumab treatment. Omalizumab was associated with a marked reduction in urinary concentrations of LTE₄ (76.2%; *P* < .001) and PGD₂M (89.0%; *P* = .002) (Fig 1). The number of exacerbations and hospitalizations, daily doses of systemic corticosteroid, and all nasal and asthma-related symptom scores were also significantly reduced. Unexpectedly, rapid symptomatic improvement occurred in 11 of 21 patients (52.4%) within the first week of omalizumab treatment. Furthermore, all 18 responders experienced symptomatic improvement within the 3-month treatment period.

To the authors' knowledge, this is the first report to demonstrate that omalizumab displayed rapid clinical effectiveness and inhibited mast cell activation and leukotriene overproduction in AERD. Gevaert et al¹⁰ documented the clinical efficacy of omalizumab for nasal polyps with comorbid asthma,¹⁰ which may be attributed to suppression of local tissue IgE. Our previous study demonstrated a significant decrease in urinary LTE₄ concentrations after surgery for nasal polyposis in patients with AERD.¹¹ Because omalizumab reduces the expression of high-affinity IgE Fc receptors on mast cells,^{5,12} it may suppress mast cell activation. In this report, omalizumab treatment ameliorated both upper and lower respiratory tract symptoms, with a significant reduction in urinary LTE₄ and PGD₂M concentrations, suggesting that omalizumab may stabilize AERD by suppressing mast cell activation and eosinophil-related inflammation. Furthermore, no moderate-to-severe adverse events such as anaphylaxis occurred.

TABLE I. Urine biomarkers, asthma treatments, and symptoms before and after omalizumab treatment

Parameter* (n = 21)	Before	After	Difference†	P value
Urine biomarkers (pg/mg of creatinine)				
LTE ₄	703.2 (234.9-2245.4)	167.7 (72.3-296.5)	-620.5 (-1857.8 to -58.2)	<.001
PGD ₂ M‡	55.5 (14.8-96.5)	6.1 (4.3-13.6)	-44.2 (-89.7 to -9.7)	.002
Eosinophil count (per μ L)	550.0 (230.0-820.0)	340.0 (70.0-575.0)	-200.0 (-390.0 to -30.0)	.002
Exacerbations (no. per 12 mo)	5.0 (2.0-7.5)	0.0 (0.0-2.5)	-2.0 (-6.5 to -1.0)	.001
Hospitalizations (no. per 12 mo)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (-1.0 to 0.0)	.024
Systemic corticosteroids (mg/d) (prednisolone equivalents)	5.0 (2.5-7.5)	0.0 (0.0-3.3)	-5.0 (-5.0 to 0.0)	.001
Inhaled corticosteroid dose (μ g/d) (fluticasone equivalents)	480.0 (320.0-760.0)	400.0 (285.0-800.0)	0.0 (-160.0 to 0.0)	.092
VAS for symptoms§ (cm)				
Nasal congestion	4.0 (2.5-7.9)	1.1 (0.1-3.6)	-2.8 (-5.0 to -1.0)	<.001
Anterior rhinorrhea	4.5 (2.9-8.5)	1.2 (0.0-3.5)	-2.7 (-4.7 to -0.2)	<.001
Anosmia	8.8 (4.6-10.0)	3.0 (0.9-7.4)	-3.1 (-5.2 to -0.4)	<.001
Dyspnea	6.1 (2.1-8.3)	1.2 (0.1-2.4)	-4.3 (-5.3 to -1.4)	<.001
Wheezing	6.2 (3.2-8.6)	1.3 (0.4-2.9)	-3.8 (-6.6 to -1.2)	<.001
Cough	5.9 (1.6-8.2)	0.9 (0.0-2.1)	-3.8 (-6.7 to -0.1)	<.001
FEV ₁ (% predicted)	86.7 (65.6-96.8)	88.5 (69.3-101.0)	4.6 (-2.4 to -15.6)	.079
FVC (%)	103.0 (91.2-122.4)	107.7 (94.6-122.4)	1.3 (-4.6 to -12.7)	.149

Significance testing was performed using the Wilcoxon signed rank test for continuous variables.

FVC, Forced vital capacity; VAS, visual analog scale.

*Data are expressed as median (IQR).

†Median (IQR) difference (post-pre omalizumab treatment).

‡Urine samples for this measurement were available in 13 patients (10 responders and 3 nonresponders).

§VAS incorporates quantitative and objective measures to assess the severity of asthma and nasal symptoms as well as the efficacy of treatment. VAS scores ranged from "not at all bothersome" (0 cm) to "extremely bothersome" (10 cm).

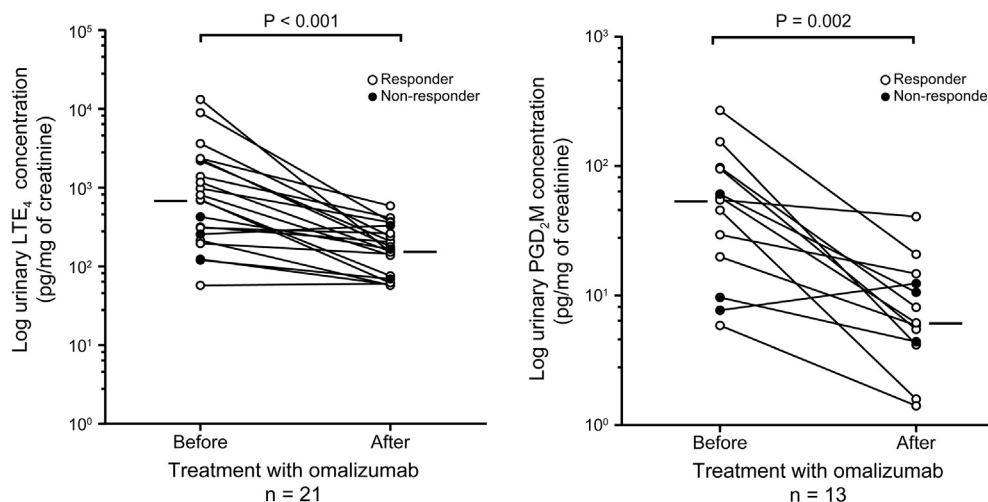


FIG 1. Urinary concentrations of LTE₄ and PGD₂M before and after omalizumab treatment in responders and nonresponders. Data on PGD₂M concentrations are missing from 8 patients. Urinary LTE₄ and PGD₂M concentrations are expressed using a log scale. Horizontal bars indicate median values.

Limitations of this study include the non-placebo-controlled and nonrandomized design. Also, it was unclear whether reductions in urinary LTE₄ and PGD₂M concentrations were direct or indirect effects of omalizumab, in addition to the lack of data on PGD₂M concentration for 8 patients.

In conclusion, omalizumab produced rapid and significant clinical effectiveness in patients with severe AERD who continued treatment for at least 12 months, and induced a remarkable reduction in urinary LTE₄ and PGD₂M concentrations. Omalizumab may be a potential therapeutic approach for AERD. Prospective, multicenter, randomized, double-blind, and

placebo-controlled studies are needed to verify the effectiveness of omalizumab against AERD.

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Hiroaki Hayashi, MD^{a,b}
 Chihiro Mitsui, MD^a
 Eiji Nakatani, MS^c
 Yuma Fukutomi, MD, PhD^d
 Keiichi Kajiwaru, BSc^a
 Kentaro Watai, MD^{a,d}

Kiyoshi Sekiya, MD^a
Takahiro Tsuburai, MD, PhD^a
Kazuo Akiyama, MD^a
Yoshinori Hasegawa, MD, PhD^b
Masami Taniguchi, MD, PhD^a

From ^athe Clinical Research Center for Allergy and Rheumatology, Sagami Hospital, Sagami, Kanagawa, Japan; ^bthe Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan; ^cTranslational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan; and ^dthe Department of Allergy and Clinical Immunology, Juntendo University Graduate School of Medicine, Tokyo, Japan. E-mail: m-taniguchi@sagami-hosp.gr.jp.

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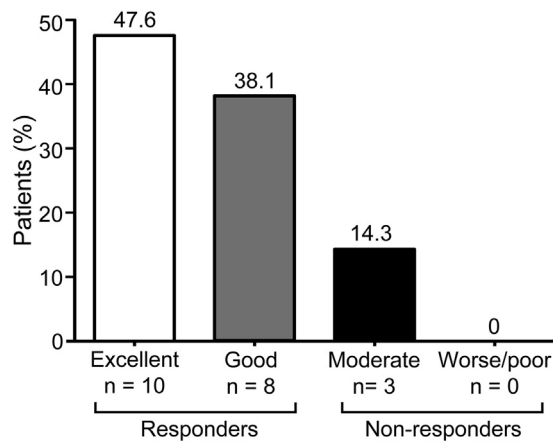


FIG E1. Physicians' Global Evaluations of Treatment Effectiveness (GETE) at study end. GETE was used to assess control of asthma symptoms in response to the omalizumab treatment, as excellent (complete control), good (marked improvement), moderate (discernible, but limited improvement), poor (no appreciable change), or worsening. Patients with an "excellent" or "good" response were classified as responders, whereas those with a "moderate," "poor," or "worsening" response were classified as nonresponders. ^{E1-E3}

TABLE E1. Characteristics of patients with AERD (n = 21)

Characteristic	Value
Age (y)	60.0 (49.0-64.0)
Sex, n (%)	
Male	3 (14.3)
Female	18 (85.7)
Body weight (kg)	53.0 (47.0-64.0)
Body mass index (kg/m ²)	21.4 (19.3-26.6)
Smoking status (never/past/current), n (%)	11 (52.4)/9 (42.9)/1 (4.7)
Pack-year (among smokers)	8.8 (4.0-26.8)
The status for sinus surgery and polypectomy	
History of sinus surgery and polypectomy*, n (%)	13 (62.0)
The median number of lifetime nasal polyp surgeries†	1.0 (1.0-2.0)
The median time since last nasal polyp surgery† (y)	7.0 (2.5-12.0)

Data are expressed as median (IQR) or n (%).

*None of the patients who had sinus surgery and polypectomy during omalizumab treatment.

†Among the 13 patients who had a history of sinus surgery and polypectomy.

TABLE E2. Comparison of characteristics between responders and nonresponders for omalizumab

Variable before omalizumab treatment*	Responders (n = 18)	Nonresponders (n = 3)	P value
Age (y)	54.9 ± 12.4	69.0 ± 13.0	.086
Sex, n (%)			.386
Male	2 (11.1)	1 (33.3)	
Female	16 (88.9)	2 (66.7)	
Body weight (kg)	55.2 ± 11.7	52.7 ± 17.0	.749
Body mass index (kg/m ²)	22.5 ± 3.7	20.5 ± 6.2	.436
Smoking status (never/past/current), n (%)	10 (55.6)/7 (38.9)/1 (5.5)	1 (33.3)/2 (66.7)/0 (0.0)	.647
Pack-year (among smokers)	16.1 ± 16.4	7.5 ± 3.5	.500
Asthma onset age (y)	34.9 ± 14.9	45.7 ± 21.1	.286
History of sinus surgery and polypectomy, n (%)	11 (61.1)	2 (66.7)	.684
The mean number of lifetime nasal polyp surgeries	1.1 ± 1.2	0.7 ± 0.6	.553
The mean time since last nasal polyp surgery (y)	9.8 ± 7.8	4.0 ± 2.8	.332
Urine biomarkers (pg/mg of creatinine)			
LTE ₄	2198.5 ± 3456.9	268.7 ± 153.5	.356
PGD ₂ M†	83.0 ± 78.5	26.1 ± 30.1	.256
IgE (IU/mL)	184.5 ± 224.6	73.1 ± 44.5	.412
Eosinophil count (per μL)	594.4 ± 375.5	393.3 ± 371.7	.401
Exacerbations (no. per 12 mo)	5.4 ± 3.4	2.7 ± 2.9	.208
Hospitalizations (no. per 12 mo)	0.6 ± 1.0	0.3 ± 0.6	.726
Systemic corticosteroids (mg/d) (prednisolone equivalents)	6.1 ± 3.6	0.0 ± 0.0	.009
Inhaled corticosteroid dose (μg/d) (fluticasone equivalents)	555.6 ± 269.2	430.0 ± 196.7	.452
VAS for symptoms‡ (cm)			
Nasal congestion	5.8 ± 3.2	2.1 ± 1.7	.072
Anterior rhinorrhea	5.6 ± 3.4	3.1 ± 0.8	.019
Anosmia	8.1 ± 2.7	2.5 ± 1.9	.003
Dyspnea	5.9 ± 3.2	2.4 ± 2.6	.093
Wheezing	6.2 ± 3.0	2.8 ± 1.9	.075
Cough	5.8 ± 3.4	1.6 ± 2.0	.060
FEV ₁ (% predicted)	79.8 ± 27.1	91.0 ± 14.1	.500
FVC (%)	99.3 ± 25.6	110.9 ± 14.1	.460

Significance testing was performed using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables.

FVC, Forced vital capacity; VAS, visual analog scale.

*Data are expressed as mean ± SD.

†Urine samples for this measurement were available in 13 patients (10 responders and 3 nonresponders).

‡VAS incorporates quantitative and objective measures to assess the severity of asthma and nasal symptoms as well as the efficacy of treatment. VAS scores ranged from “not at all bothersome” (0 cm) to “extremely bothersome” (10 cm).