

Effect of omalizumab on outcomes in patients with aspirin-exacerbated respiratory disease

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ABSTRACT

Background: The current treatment for patients with aspirin-exacerbated respiratory disease (AERD) who have uncontrolled asthma or chronic rhinosinusitis is aspirin desensitization. For patients who are unable to undergo or do not benefit from aspirin desensitization, treatment with biologics is an option, although efficacy data for AERD is scarce.

Objective: We reported a series of patients with AERD who were started on omalizumab and measured the outcomes to assess improvement.

Methods: Adult patients with AERD who were initiated on omalizumab from January 2007 to January 2018 were included. We compared outcomes 6–12 months before initiating biologic therapy and during the last 6–12 months while they were on biologic therapy. Our study investigated the number of oral steroid courses, short-acting beta-agonists (SABA), antibiotics for sinusitis or pneumonia, emergency department visits, hospitalizations, pulmonary function tests, and changes in controller medications.

Results: Twenty-nine patients were placed on omalizumab. Sixty-two percent demonstrated a reduction in the number of steroid courses ($p = 0.0014$) and number of SABA canisters used ($p = 0.0005$) during their last 12 months while on omalizumab. Eighty-six percent of the patients with AERD and on omalizumab demonstrated either a decrease in the number of steroid courses or number of SABA canisters used in the last year of the study. The patients with AERD and with concomitant immunoglobulin E (IgE) mediated respiratory disease showed a statistically significant reduction in the number of steroid courses and number of SABA canisters used while on omalizumab for 1 year ($p = 0.002$ and $p = 0.005$, respectively), whereas those without concomitant IgE-mediated respiratory disease did not have a substantial reduction in steroids or SABA canisters used.

Conclusion: Our case series reported that omalizumab could effectively be used as an adjunct treatment for AERD, but additional larger and longitudinal studies are needed to corroborate these findings.

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Management of aspirin-exacerbated respiratory disease (AERD) is challenging, and patients often have poor quality of life, with a high disease burden.¹ The prevalence of AERD is 7.2% in patients with asthma and 15% in patients with severe asthma, which affects ~1.4 million patients.² Current treatment for uncontrolled AERD despite standard medical care is aspirin desensitization, followed by daily aspirin treatment.^{2–4} However, the response rate is ~73%, which includes patients eliminated due to adverse effects.⁴ Those who have uncontrolled asthma despite maximum treatment, pregnancy, gastritis, bleeding disorder, renal failure, or anticoagulant therapy may be unable to tolerate high-dose aspirin.^{5,6} For patients

who cannot receive or for whom aspirin desensitization fails, treatment with biologics is an option, although efficacy data for AERD are scarce. Results of studies indicate that omalizumab can decrease nasal polyps. However, there is controversy with regard to its contribution to nonsteroidal anti-inflammatory drug (NSAID) tolerance during desensitization. Previous studies describe omalizumab inhibiting respiratory reactions during aspirin desensitization, whereas other studies dispute this association.^{7–9} Our study focused on examining the outcomes of patients with AERD who were placed on omalizumab for their asthma.

METHODS

We performed a retrospective analysis on adult patients with AERD who were placed on omalizumab for severe persistent asthma. The study protocol was approved by Kaiser Permanente Southern California Institutional Review Board (11357). Data were obtained through electronic medical records of patients in all Kaiser Permanente Southern California medical centers. The electronic medical record identified probable patients with AERD via the SNOMED CT Identifier (SNOMED SCTID) code specific for AERD or who met at least two of three International Classification of Dis-

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eases, Ninth and Tenth Revisions (ICD 9/10) codes for asthma, nasal polyps, and aspirin sensitivity, and started omalizumab from January 2007 to January 2018. These charts were then manually reviewed to confirm the AERD diagnosis. We included 16 patients who were confirmed with NSAID challenges and 15 patients with a clinical history of aspirin allergy elicited by allergists. The patients who did not attain adequate symptom control with aspirin by history were confirmed with equivalent or increasing numbers of steroid courses, SABA canisters used, emergency department visits, and hospitalizations.

Outcomes of the patients with AERD and on omalizumab were compared between 6 and 12 months before starting and during the last 6 and 12 months on omalizumab. Outcomes consisted of the number of oral steroid courses, short-acting β -agonist (SABA) canisters used, emergency department visits, hospitalizations, antibiotics for sinusitis or pneumonia, pulmonary function tests (PFTs: FEV₁, FEV₁/FVC), and changes in controller medications. Evaluation of sociodemographic characteristics and potential contributing factors consisted of the following: age, sex, immunoglobulin E (IgE) level, eosinophilia, allergen sensitization, and biologic dose with duration. Statistical analysis was conducted on the omalizumab use to assess the mean difference in both the number of steroid courses and the number of SABA canisters used. All statistical analyses were performed by using SAS Enterprise Guide, (Cary, NC); version 9.3. Paired *t*-tests were used to compare the mean difference of the number of steroid courses and SABA canisters used before and during omalizumab treatment. A logistic regression model was used to assess the factors that were associated with an improved response to omalizumab, with emphasis on the reduction in steroids or SABA. In addition, *p* values were generated by using the Wilcoxon rank sum test for continuous variables.

RESULTS

A total of 29 patients were treated with omalizumab. The median age was 57 years (interquartile range, 42–64 years), and 45% of our study population (13/29) were men. The median total IgE value was 218 kU/L. The mean duration of omalizumab use was 27 months and the median was 16 months. Patient characteristics with pretreatment levels of IgE, peripheral eosinophils, environmental allergen sensitization, and outcomes are shown in Table 1. Adequate respiratory or sinus symptom improvement after aspirin desensitization was not achieved in 15 patients. Twelve of these 15 patients had environmental allergen sensitization demonstrated by skin testing. Eight of the 12 patients with environmental sensitization (67%) showed steroid reduction with omalizumab. Among the three patients who were not

sensitized to any environmental allergens, only one showed improvement with steroid reduction (33%). Therefore, more patients with AERD and with perennial environmental allergen sensitization had steroid reduction while on omalizumab, but the improvement was not unanimous.

Among the 15 patients in the omalizumab group for whom sufficient symptom control with aspirin failed, 7 had mild symptom improvement with aspirin, and thus aspirin was continued before initiation of omalizumab (Table 1). These patients were on aspirin for at least 1 year before they received omalizumab. Among the seven patients who continued using aspirin, five patients had perennial environmental allergen sensitization. Two of these five patients (40%) had steroid reduction with omalizumab. In this subset of patients with IgE-mediated respiratory disease who partially responded to aspirin, our data did not show as much improvement with steroid reduction from omalizumab. Eight patients who had no symptom improvement after aspirin desensitization discontinued their aspirin treatment before starting omalizumab. All of these eight patients had perennial environmental allergen sensitization. In contrast to the subset earlier, 75% of these patients (6/8) had steroid reduction with omalizumab. This suggested that omalizumab may be more effective for patients with AERD and with environmental sensitization who do not respond to aspirin treatment compared with those with partial response to aspirin. The mechanism behind unresponsiveness to aspirin was unclear but may have been due to the large burden of IgE-mediated disease.

The participants who did not undergo aspirin desensitization had unstable asthma (8), chronic kidney disease (CKD) (3), or gastritis (2). One patient declined aspirin desensitization. Among the eight patients who had unstable asthma, four had FEV₁ consistently 40%–50% at baseline is in very severe asthma, two were on chronic daily prednisone for more than 6 months (5–10 mg/day), and two had frequent exacerbations that required emergency department visits or urgent care visits every 1–2 months. All of these patients were on maximum asthma treatment. Given that all of these patients were at extremely high risk for NSAID challenge and aspirin desensitization, a full discussion with the patients and their treating allergists on the benefits and risks was conducted, and the decision was to avoid NSAIDs at that time.

The patients with AERD and on omalizumab showed a reduction in the number of oral steroid courses and SABA canisters used. Results are delineated in Table 2. Sixty-two percent of the patients (18/29) demonstrated a statistically significant decrease in the number of oral steroid courses in their last year compared with the year before initiating omalizumab (*p* = 0.0014). Sixty-six percent (19/29) had a decrease in the number of oral

Table 1 Patient characteristics and differences in steroid courses and SABA canisters used

Patient No.	Pretreatment IgE level, kU/L	Environmental Sensitization	Pretreatment Peripheral Eosinophils, cells/ μ L	Aspirin Desensitization*	Current Aspirin Therapy	Steroid Difference#	SABA Difference#
1	749	Grasses, dust mite	124	No	N/A	2	1
2	361	Cat, dust mite	340	Yes	No	3	0
3	505	Mold, trees, cockroach	220	No	N/A	4	-1
4	88	Dust mite, cockroach	110	Yes	No	9	0
5	176	Mold, dog, dust mite	500	No	N/A	0	4
6	55	None	300	No	N/A	3	1
7	87	None	240	No	N/A	3	3
8	167	Grasses, weeds, trees, dog	600	No	N/A	4	1
9	460	Grasses, weeds, trees, mold, cat	1500	Yes	Yes	0	4
10	221	Mold, cat, dust mite	400	Yes	Yes	9	0
11	242	Mold, cat, dog, dust mite	517	Yes	Yes	0	2
12	284	None	220	No	N/A	4	0
13	351	Cat, dust mite	792	Yes	Yes	-1	-1
14	282	Grasses, trees, mold, dog, cat, dust mite, cockroach	1400	Yes	No	1	2
15	533	Grasses, weeds, trees, dog, cat, dust mite, cockroach	2000	Yes	Yes	2	1
16	150	Grasses	621	No	N/A	2	2
17	5	None	110	Yes	Yes	0	0
18	59	Mold	650	No	N/A	3	2
19	182	Grasses, weeds, trees, mold, cat, dog, dust mite	405	No	N/A	2	1
20	4	None	255	Yes	Yes	3	0
21	177	Grasses, weeds, trees, mold, cat, dog	151	No	N/A	-2	-1
22	368	Grasses, trees, cat, dog, dust mite, cockroach	1172	Yes	No	1	1
23	224	Grasses, weeds, trees, mold, cat	230	Yes	No	4	1
24	45	None	130	No	N/A	-6	0
25	218	Grasses, mold, cat	1199	Yes	No	0	3
26	219	Cockroach	1100	No	N/A	9	10
27	79	Trees, cockroach	383	Yes	No	3	2
28	94	None	563	Yes	No	0	1
29	244	Cat, dust mite	720	No	N/A	-2	1

SABA = Short-acting β -agonist; IgE = immunoglobulin E; N/A = not applicable

*The patients who received aspirin desensitization had aspirin challenges, whereas patients who did not undergo aspirin desensitization did not receive aspirin challenge.

#Comparisons for omalizumab were done with 1 year before and the last year while on omalizumab; the difference is calculated by pretreatment steroids/SABAs – posttreatment steroids/SABAs; the positive numbers reflect steroid or SABA reduction, whereas negative numbers reflect an increase in steroids or SABA canisters.

Table 2 The mean difference of the number of steroid courses and number of SABA canisters used before and during omalizumab*

	Omalizumab Use					
	6 mo Before	6 mo After	p#	1 y Before	1 y After	p#
Steroid courses, no. mean ± SD	2.39 ± 1.97	1.25 ± 1.34	0.006	4.09 ± 2.98	2.00 ± 2.03	0.0014
SABA canisters, no. mean ± SD	1.33 ± 1.14	0.76 ± 0.83	0.024	2.70 ± 2.14	1.24 ± 1.15	0.0005

SABA = Short-acting β-agonist; SD = standard deviation.
*Mean values were calculated from post-omalizumab reduction of the number of steroid courses and SABA canisters used.
#The p values were generated by using the paired t-test.

Table 3 Association of environmental sensitization with mean difference in number of steroid courses and SABA canisters used

Difference	Patients with No Environmental Sensitization (n = 7)	p#	Patients with Environmental Sensitization (n = 22)	p#
Steroid courses, mean ± SD*	1.00 ± 3.46	0.47	2.41 ± 3.22	0.002
SABA canisters, mean ± SD*	0.71 ± 1.11	0.14	1.59 ± 2.34	0.005

SABA = Short-acting β-agonist; SD = standard deviation.
*Mean values were calculated from post-omalizumab reduction of steroid courses and SABA canisters used.
#The p values were generated by using the paired t-test.

steroid courses compared with 6 months before therapy and their last 6 months on omalizumab ($p = 0.006$). In addition, 62% of the patients with AERD (18/29) exhibited a reduction in SABA use in their last year when compared with the year before starting omalizumab ($p = 0.0005$). Approximately half had a reduction in SABAs in their last 6 months in comparison with 6 months before starting omalizumab ($p = 0.024$). Also, 86% of the patients with AERD (25/29) and on omalizumab demonstrated either a decrease in the number of steroid courses or number of SABA canisters used in their last year (Table 1). Other outcomes, including the number of emergency department visits, hospitalizations, antibiotics for sinusitis or pneumonia, pulmonary function tests, and controller medications were not statistically significant (analysis not shown).

Our study also examined whether outcomes were different between the patients with AERD and with environmental sensitization and those without allergic sensitization (Table 3). Twenty-two patients had environmental sensitization documented by skin testing, and seven patients had negative environmental allergen skin testing results. The patients with AERD and with environmental sensitization showed statistically significant reduction in the number of steroid courses and number of SABA canisters used while on omalizumab for 1 year ($p = 0.002$ and $p = 0.005$, respectively). However, patients with AERD who did not have environmental sensitization did not have a substantial reduction in the number of steroid courses or

SABA canisters used ($p = 0.47$ and $p = 0.14$, respectively) (Table 3).

With regard to omalizumab use, we further investigated factors associated with increased reduction of steroids or SABA canisters used. Peripheral eosinophilia, with an eosinophil level of $\geq 500/\mu\text{L}$, was associated with a decrease in steroids and SABAs in the last year compared with the year before initiating omalizumab ($p = 0.047$ and $p = 0.02$, respectively). This aligned with a previous study that showed that patients with a higher eosinophil count, of $\geq 300/\mu\text{L}$, resulted in a greater reduction of exacerbations with omalizumab compared with those with lower eosinophil counts.¹⁰ The level of baseline total IgE and a longer duration of omalizumab (12, 16, 24 months) were not associated with differences in steroid or SABA use reduction. There was no correlation between specific allergen sensitization with improved outcomes.

DISCUSSION

This study revealed that omalizumab treatment was associated with a significant decrease in the use of corticosteroids and SABAs if the patients with AERD had concomitant allergic rhinitis and asthma. If the patients with AERD did not have concomitant allergic respiratory disease, then omalizumab had no significant effect on the patients with AERD with respect to their use of corticosteroids or number of rescue SABA canisters used. In addition, omalizumab seemed to

have a greater impact on decreasing the number of steroid courses in a subgroup of patients with AERD who had perennial environmental sensitization and no symptom improvement with aspirin compared with those who had partial improvement with aspirin. The failure of aspirin desensitization and daily aspirin may be due to concomitant IgE-mediated disease.

Given the retrospective nature, this was a real-world study that followed up the patients longitudinally. Limitations include selection bias because this was a non-placebo controlled and nonrandomized design. Based on a history of asthma, chronic sinusitis with nasal polyps, and respiratory symptoms after NSAID ingestion, the likelihood of having AERD is 80%–100%.^{2,11} Therefore, it was possible that 2 or 3 of the 15 patients who were diagnosed by history may not have had AERD because aspirin challenges were not performed. Evaluation of sinus outcomes was limited because Lund-McKay sinus scores were not available in the retrospective review and our study did not track sinus surgeries over several years. Omalizumab may act on AERD through several mechanisms. Omalizumab treats allergic rhinitis and asthma by reducing free IgE and downregulating IgE receptors on mast cells, basophils, and dendritic cells in patients who have specific IgE-mediated allergies.^{12,13}

Because omalizumab did not completely correlate with steroid reduction in all the patients with AERD and with perennial sensitization, omalizumab may also have stabilized mast cells by decreasing mast cell activation and inhibiting cysteinyl leukotriene and prostaglandin D2 (PGD2) production, which is another possible mechanism of its efficacy in AERD.¹⁴ Although the eight patients with AERD and without environmental sensitization in our study did not show statistically significant improvement with omalizumab, a larger study may show improvement. Analysis of our results indicated that patients with AERD who have higher eosinophil counts, $\geq 500/\mu\text{L}$, compared with those with lower eosinophil counts may benefit more from omalizumab. Omalizumab has been shown to significantly reduce sputum and bronchial eosinophils, which suggests that anti-IgE downregulates overall T helper type 2 expression.¹⁵

CONCLUSION

Overall, our study showed that anti-IgE treatment is efficacious in assisting with greater control of AERD, and this corroborated the findings of limited studies on omalizumab. Eosinophilia (eosinophils $\geq 500/\mu\text{L}$) was associated with greater improvement of steroid and SABA reduction in patients with AERD who were on omalizumab. Although our case series was retrospective, to our knowledge, this was the largest study to investigate the effects of an anti-IgE on symptom control of patients with AERD. Prospective double-blind and randomized

studies will be needed to confirm the observed positive effects. Given the cost of omalizumab, use of omalizumab may be restricted to patients who are refractory to a multidisciplinary approach, including asthma medications, aspirin desensitization, and sinus surgeries. Further studies will be important to examine the specific phenotypes to benefit from anti-IgE or interleukin-5 biologic therapy. It is also essential to further investigate the demographics of AERD to compare characteristics of patients who do well on aspirin with those who need biologic treatment.

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