

Aspirin tolerance in patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease following treatment with omalizumab



Elsa Phillips-Angles, MD^a, Pilar Barranco, MD, PhD^{a,b},
Magdalena Lluch-Bernal, MD, PhD^a,
Javier Dominguez-Ortega, MD, PhD^{a,b},
Valentín López-Carrasco, NP^a, and
Santiago Quirce, MD, PhD^{a,b}

Clinical Implications

- Patients with severe allergic asthma and hypersensitivity to nonsteroidal anti-inflammatory drugs acquire aspirin and nonsteroidal anti-inflammatory drug tolerance after treatment with omalizumab.

TO THE EDITOR:

Aspirin-exacerbated respiratory disease (AERD) is characterized by the coexistence of nasal polyps, rhinosinusitis, and asthma, which is exacerbated after the diagnostic or therapeutic exposure to nonsteroidal anti-inflammatory drugs (NSAIDs).¹ These patients have very limited analgesic and anti-inflammatory therapeutic alternatives, thus confined to the use of opioids and steroids. These drugs have frequent adverse effects when taken for long periods in chronic diseases.

AERD presents with a high production of leukotrienes due to an alteration in the production of eicosanoids, which affects the cyclo-oxygenase pathway, through an IgE-independent mechanism.¹ Clinical evaluation and treatment of AERD can be complex and it can comprise aspirin desensitization when asthma is uncontrolled or the use of NSAIDs is needed to treat another illness, for example, because of its antiplatelet effect.¹

Omalizumab is a humanized recombinant mAb that blocks IgE from binding to its high-affinity receptor (FcεRI) and it has been approved for the treatment of moderate to severe persistent asthma and chronic idiopathic urticaria. Omalizumab has also proven to be effective in the treatment of patients with nasal polyps and asthma, both allergic and nonallergic.² Moreover, 3 cases of patients with AERD who were successfully treated with omalizumab have been published.³⁻⁵

Our aim was to evaluate NSAID tolerance in patients with severe asthma⁶ treated with omalizumab, and previous clinical history of AERD. The study took place after receiving approval by our institutional ethics committee, and a written informed consent was obtained from all patients. We recruited adult patients (≥18 years of age) with severe allergic asthma undergoing treatment with omalizumab with a history of AERD. All the patients included in the study were under treatment with high doses of inhaled steroids combined with long-acting beta agonists and montelukast for more than a year. Nasal, bronchial, and/or oral challenges had been performed before starting treatment with omalizumab to confirm NSAID intolerance (worsening of nasal and/or bronchial symptoms). Nasal challenge test was performed

with ketorolac, bronchial challenge with lysine acetylsalicylate, and the oral challenge with aspirin. Maximum accumulated doses were 16.38 mg⁷ of ketorolac in the nasal challenge and 30.78 mg⁸ of lysine acetylsalicylate in the bronchial challenge. Maximum dose of aspirin in the oral challenge was 500 mg.⁸

We excluded patients in whom provocation challenge tests were contraindicated and those who rejected them. After 6 months⁶ of treatment with omalizumab, we evaluated asthma control and quality of life (number of exacerbations, Asthma Control Test, Asthma Quality of Life Questionnaire [AQLQ], FEV₁, fractional exhaled nitric oxide) and persistence of NSAID hypersensitivity. Seven patients (5 females) with a median age of 45 years were included. Their clinical and analytical characteristics are presented in Table I. They all presented a history of AERD after the intake of NSAIDs with the exception of patient 7 who was recommended not to take NSAIDs as a preventive measure. Table II presents the changes observed before and after 6 months of treatment with omalizumab at different doses according to weight and IgE levels. A statistical analysis was performed applying Wilcoxon test for paired samples, obtaining a significant decrease in the number of severe exacerbations (mean number of severe exacerbations/patient/year before treatment, 2.14; after treatment, 0.00; $P = .026$) and patients' improved quality of life measured by AQLQ (mean AQLQ score before treatment, 5.76; after treatment, 6.36; $P = .018$) after 6 months of treatment with omalizumab. No significant differences were seen in visual analog scale score or FEV₁. All but 1 of the patients completed nasal and oral challenges without experiencing any symptoms, and subsequently 4 out of 6 have a frequent intake of ibuprofen. The patient who had a positive result in the nasal challenge suffered from rhinitis after the administration of 8.82 mg of intranasal ketorolac, whereas in the previous challenge performed before treatment with omalizumab he had suffered from rhinoconjunctivitis and a bronchospasm.

The pathogenetic mechanisms underlying AERD have not yet been fully elucidated. However, it is known that patients with AERD have a high count of platelet-adherent neutrophils, monocytes, and eosinophils in blood and sinonasal tissues. They also suffer from a dysregulation of the 5-lipoxygenase-LTC₄ synthase pathway, which contributes to an increase in the production of cysteinyl leukotrienes.¹ Supporting this theory, Serrano-Candela et al⁹ performed a study in patients with chronic urticaria, in whom they proved that omalizumab acts by binding free IgE and also by dissociating prebound IgE from FcεRI in mast cells and basophils. They also demonstrate that omalizumab can directly inhibit IgE-dependent phosphorylation events, thus inhibiting mast cell and basophil activation and provoking a decrease in mediators. A reduction in extracellular signal-regulated kinase phosphorylation and an overthrow in following events such as leukotriene synthesis, in both mast cells and basophils, might explain the effects of omalizumab on sustained inflammation in patients with severe asthma. Furthermore, the action of omalizumab as a mast cell stabilizer could also contribute to its action over the tolerance of NSAIDs in our patients.

Even though the exact mechanisms of action of omalizumab in patients with AERD is yet to be proven, it is clear that it

TABLE I. Clinical and demographic characteristics of population

Characteristic	Patient no.						
	1	2	3	4	5	6	7
Age (y)	23	47	60	52	34	45	45
Sex	F	F	F	F	M	F	M
Allergen sensitization	Pollen, pet	Pollen, pet, HDM	HDM	Pollen, pet	Pollen, pet	Pet	Pollen, HDM
Age of onset of asthma symptoms (y)	15	30	36	48	31	22	17
Age of asthma diagnosis (y)	15	30	39	49	31	22	17
Age of onset of rhinosinusitis symptoms (y)	15	30	25	48	31	22	27
Age of rhinosinusitis diagnosis (y)	15	36	35	49	31	23	27
No. of polyp surgeries	1	1	1	2	1	6	6
Age of last surgery (y)	17	37	49	50	32	44	44
Age of first episode of AERD (y)	15	14	39	50	31	28	0
First episode of AERD (symptoms)	Asthma	Rhinitis + asthma	Asthma	Rhinitis + asthma	Asthma	Rhinitis + asthma	Asthma
NSAID that elicited symptoms	Ibuprofen + paracetamol	Aspirin + metamizole	Aspirin + metamizole + paracetamol		Ibuprofen + metamizole	Ibuprofen + metamizole	Aspirin + ibuprofen + metamizole
Age of AERD diagnosis (y)	15	43	44	50	31	29	44
Total serum IgE (UI/mL)	441	268	192	818	34.9	57.3	1772
Eosinophil blood count (cells/ μ L)	480	470	230	810	630	540	380
Follow-up since	2006	2009	2000	2005	2014	2013	2001

F, Female; *HDM*, house dust mite; *M*, male.

TABLE II. Clinical characteristics and nasal/bronchial/oral challenges before and after 6 mo of treatment with omalizumab

Characteristic	Patient no.													
	1		2		3		4		5		6		7	
Omalizumab doses	225 mg/2 wk		300 mg/4 wk		300 mg/4 wk		600 mg/2 wk		150 mg/4 wk		150 mg/4 wk		600 mg/2 wk	
Before/after omalizumab	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
No. of severe asthmatic exacerbations*	6	0	3	0	1	0	3	0	1	0	1	0	0	0
FEV ₁ (L, % predicted)	2.89 (121.7%)	2.93 (119%)	2.38 (92.6%)	2.33 (91%)	1.96 (90.4%)	2.13 (98.2%)	2.62 (102.5%)	2.5 (102%)	4.59 (102%)	4.77 (107%)	3.02 (115.9%)	3.09 (119.7%)	2.85 (68%)	3.51 (86%)
FENO (ppb)	92	50	19	18	64	28	43	28	42	216	29	35	36	36
ACT score	25	25	23	24	22	23	21	23	20	23	23	25	20	22
AQLQ score	6.375	6.5	5.375	6.4	4.65	5	5.6	6.7	6.187	6.34	6.37	7	5.8	6.6
VAS score	0	1	2	0	0	0.5	0	1	0	0	0	1	2	3
PNIF (L/min)	90	90	110	80	80	80	90	110	160	60	60	130	110	150
Challenges														
Type	Nasal	Nasal and oral	Nasal	Nasal and oral	Nasal	Nasal	Bronchial	Nasal and oral	Nasal	Nasal and oral	Oral	Nasal and oral	Nasal	Nasal and oral
Result	3.78 mg	Negative	1.26 mg	Negative	8.82 mg	8.82 mg	30.78 mg	Negative	16.38 mg	Negative	75 mg	Negative	16.38 mg	Negative
Symptoms	Rhinitis	None	Rhinitis	None	Rhinoconjunctivitis and bronchospasm	Nasal	Bronchospasm	None	Rhinitis	None	Rhinoconjunctivitis	None	Bronchospasm	None
NSAID currently tolerated	Ibuprofen		Ibuprofen		None		Ibuprofen		None		Ibuprofen		None	

ACT, Asthma Control Test (≥ 20 , controlled; 16-19, partially controlled, < 15 , not controlled); AQLQ, Asthma Quality of Life Questionnaire (7, not impaired; 1, severely impaired); FENO, fractional exhaled nitric oxide; ICS-LABA, high doses of inhaled corticosteroids with long-acting beta agonist; NC, nasal corticosteroid; PNIF, peak nasal inspiratory flow; VAS, visual analog scale in rhinitis (0, complete anosmia; 1, partial intermittent anosmia; 2, maintained intermittent anosmia; 3, intermittent sense of smell; 4, normal sense of smell).

*Timing of observation of severe exacerbations before omalizumab: 1 y and after omalizumab: 6 mo.

contributed to gain control of NSAID-induced symptoms in these patients. Omalizumab can be considered a multi-action treatment in patients with AERD, given its action on polyps, asthma symptoms, and NSAID hypersensitivity.

In summary, we report a case series of development of tolerance to NSAIDs in patients with AERD treated with omalizumab, which expands the results of previously published isolated case reports.³⁻⁵ All but 1 of our patients acquired complete tolerance to NSAIDs after 6 months of treatment with omalizumab. This was an added beneficial effect of omalizumab in this group of patients who have severe allergic asthma treated with omalizumab and also have NSAID-exacerbated respiratory disease. This was an interesting clinical observation we obtained, but it is not to be applied to the general population with AERD. Nevertheless, it might be reasonable in specific individuals with compelling need for aspirin in whom a desensitization is not possible. More studies are needed to clarify the mechanisms of acquisition of tolerance to NSAIDs in patients treated with omalizumab.

^aDepartment of Allergy, Hospital La Paz, Institute for Health Research (IdiPAZ), Madrid, Spain

^bCIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 13, 2016; revised December 7, 2016; accepted for publication December 20, 2016.

Available online January 20, 2017.

Corresponding author: Elsa Phillips-Angles, MD, Department of Allergy, Hospital La Paz, Paseo de la Castellana, 261, 28046 Madrid, Spain. E-mail: e.phillips.angles@gmail.com.

2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.12.013>

REFERENCES

1. Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. *N Engl J Med* 2016;374:484-8.
2. Gevaert P, Calus L, van Zele T, Blomme K, De Reuyck N, Bautters W, et al. Omalizumab is effective in allergic or nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2012;131:110-6.
3. Bobolea I, Barranco P, Fiandor A, Cabañas R, Quirce S. Omalizumab: a potential new therapeutic approach for AERD. *J Invest Allergol Clin Immunol* 2010;20:446-53.
4. Aksu K, Kurt E. Aspirin tolerance following omalizumab therapy in a patient with AERD. *Allergol Immunopathol (Madr)* 2013;41:208-10.
5. Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of AERD. *J Allergy Clin Immunol Pract* 2015;3:459-60.
6. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
7. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010;105:130-5.
8. Barranco P, Bobolea I, Larco JI, López-Serrano MC, Quirce S. Diagnosis of aspirin-induced asthma combining the bronchial and the oral challenge tests: a pilot study. *J Invest Allergol Clin Immunol* 2009;19:446-52.
9. Serrano-Candelas E, Martínez-Aranguren R, Valero A, Bartra J, Gastaminza G, Goikoetxea MJ, et al. Comparable actions of omalizumab on mast cells and basophils. *Clin Exp Allergy* 2016;46:92-102.

Reproduced with permission of copyright owner.
Further reproduction prohibited without
permission.