

Clinical Communications

Rheumatoid arthritis-like polyarthralgia after the initiation of omalizumab treatment: A case series

Yasuo To, MD, PhD, Yuta Kono, MD, PhD,
Ryuta Tsuzuki, MD, Hiroshi Kaneko, MD, PhD, and
Masako To, MD, PhD

Clinical Implications

- The potential development of rheumatoid arthritis (RA)-like polyarthralgia in patients treated with omalizumab needs to be taken into consideration in clinical practice. Serological markers of RA might be helpful in identifying patients who are vulnerable to these adverse events.

Omalizumab is a monoclonal antibody that binds to free human IgE in the blood and interstitial fluid. The accepted indication of this medication for asthma is moderate-to-severe persistent asthma patients having a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.¹ After omalizumab was approved for commercial use, acute exacerbation of asthma and systemic steroid administration are known to be reduced in asthmatic patients.²⁻⁴ Importantly, only rare serious adverse effects from long-term omalizumab treatment has been recognized so far. Even though omalizumab is an antibody, no autoimmune arthritis-like symptoms likely attributable to an immune complex were observed during the clinical trial to develop this medicine. However, previously unrecognized adverse effects sometimes become apparent after a medicine is approved for commercial use and prescribed to many patients. We present a case series of 3 patients with rheumatoid arthritis (RA)-like polyarthralgia with elevated serological markers of RA during omalizumab therapy for severe asthma.

Case 1 is a 73-year-old woman with severe asthma (Table I). She had no medical history except a 48-year history of severe asthma and RA. Her arthritis had been stable and had caused no symptoms for years without medication for RA. Her asthma was not stable even under a combination treatment of high-dose inhaled corticosteroids (ICS), long-acting β_2 -agonist (LABA), theophylline, and daily use of oral corticosteroids (OCS); therefore, omalizumab was introduced at a dose of 300 mg per month. Daily use of OCS was continued after the initiation of omalizumab. Seven months after the initiation of omalizumab therapy, the patient experienced pain and swelling of the bilateral metacarpophalangeal (MP) joints and wrists with elevated serum matrix metalloproteinase-3 (MMP-3), a marker of RA. Omalizumab was discontinued and her symptoms disappeared with decreasing serum MMP-3 (Table II). After stopping the omalizumab therapy, she had been treated with ICS, LABA, theophylline, and daily OCS for several years. Currently, she has been receiving dupilumab therapy without adverse events.

Case 2 is a 45-year-old woman with severe asthma (Table I). She had no medical history except for a 4-year history of severe

TABLE I. Patients' asthma characteristics

Case	1	2	3
Age (y)	73	45	44
Sex	F	F	F
Smoking history	NS	Ex-S	NS
Pack-year	0	5	0
Domestic exposure, Pet	+	—	—
Comorbidities			
Allergic rhinitis	—	+	+
Atopic dermatitis	—	—	—
Food allergy	—	—	—
Drug allergy	—	—	+
Aspirin sensitivity	—	—	—
Laboratory data			
Peripheral blood			
Eosinophils (μ L)	132	56	46
IgE (IU/mL)	674	45	812
RAST	HD, mites	HD, mites	HD, mites
Asthma therapy			
ICS	+	+	+
LABA	+	+	+
LTRA	—	+	+
Theophylline	+	—	+
Daily use of OCS	+	—	—

Ex-S, Ex-smoker; F, female; HD, house dust (actual house dust containing cotton dust, soil, sand, hair, scurf, pet hair, fungus, mites, and so on); ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists; mites, *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*; NS, never smoked; OCS, oral corticosteroids; RAST, radioallergosorbent test.

asthma. She had a family history of RA. Because her asthma was not stable under a combination treatment of high-dose ICS, LABA, and leukotriene receptor antagonists (LTRA), omalizumab was introduced at a dose of 150 mg per month. Twenty months after the initiation of omalizumab therapy, her asthma control was getting better, but she experienced morning stiffness in the bilateral proximal interphalangeal and MP joints with elevated rheumatoid factor (RF). Omalizumab was discontinued and her symptoms disappeared as her RF level decreased (Table II). Her asthma remained stable after stopping omalizumab therapy.

Case 3 was a 44-year-old woman with severe asthma (Table I). She had no medical history except for severe asthma. She had a family history of collagen vascular diseases. She often had acute exacerbation of asthma despite a combination treatment with high-dose ICS, LABA, LTRA, and theophylline. We therefore introduced omalizumab at a dose of 600 mg per month. Two weeks after the initiation of omalizumab therapy, the patient experienced pain in the bilateral knee joints with elevated MMP-3. Omalizumab was discontinued and her symptoms disappeared as her MMP-3 levels decreased (Table II). After stopping omalizumab therapy, she had been treated with high-dose ICS, LABA, LTRA, and theophylline with oral corticosteroids on demand.

In this case series, patients developed RA-like polyarthralgia and/or swelling of the joints with elevated serum markers of RA

TABLE II. History of collagen vascular disease, clinical symptoms, and laboratory data

Case	1	2	3
History of RA	+	—	—
History of other CVD	—	—	—
Family history of CVD	+	+	+
Omalizumab amount (mg/mo)	300	150	600
Joint symptoms	MP joint Wrist Pain and swelling	PIP, MP joints Morning stiffness	Knee joint pain
Duration between first omalizumab administration and onset of symptoms (mo)	7	20	0.5
Duration between final administration of omalizumab and relief of symptoms (mo)	4	1	1
Laboratory data			
At the onset of symptoms			
RF (IU/mL) (reference range, 0-15)	<6	243	<6
MMP-3 (ng/mL) (reference range, 17.3-59.7)	63.5	43.7	226
CCP Ab (U/mL) (reference range, 0-4.5)	6.7	<0.6	<0.6
At the relief of symptoms			
RF (IU/mL) (reference range, 0-15)	<6	121	ND
MMP-3 (ng/mL) (reference range, 17.3-59.7)	47.3	49.8	75.9
CCP-Ab (U/mL) (reference range, 0-4.5)	<0.6	<0.6	ND

CCP-Ab, Cyclic citrullinated peptide antibody; CVD, collagen vascular disease; MMP-3, matrix metalloproteinase-3; MP, metacarpophalangeal; N/A, not applicable; ND, not done; PIP, proximal interphalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor.

after the omalizumab therapy was initiated, and both the symptoms and the elevated serum markers were eliminated after omalizumab was discontinued. These facts suggest that omalizumab may induce an RA-like reaction, with symptoms in the joints. The amount of time between the initiation of omalizumab and the onset of joint symptoms varied, ranging from 0.5 to 20 months.

Sarcoidosis and polymyalgia rheumatica, which are T-helper 1 (Th1)-related diseases, have been reported in patients treated with omalizumab.⁵ In another case report, sarcoidosis developed in an asthmatic patient treated with omalizumab after concomitant prednisolone was decreased.⁶ Based on these reports and our case series, Th1-dominant immune conditions are speculated to be occasionally induced by omalizumab with the suppression of Th2 immunity. A Th1-Th2 imbalance brought about by omalizumab might trigger unexpected Th1-related adverse events, including RA-like symptoms.

Arthralgia is a rare but reported adverse event of omalizumab. A long-term real-life study reported that 3 of 91 patients treated with omalizumab experienced arthralgia/myalgia.⁷ This is consistent with the incidence in our hospital, where approximately 100 patients have been administered omalizumab, and only the above 3 cases experienced arthralgia/myalgia. We speculate that patients with this adverse event may have a particular pre-existing condition. All of our patients with arthralgia had a past or family history of RA or other collagen vascular disease, strongly suggesting that patients with this particular genetic condition might be vulnerable to Th1-related adverse events. The serological markers of RA (anti-cyclic citrullinated peptide antibody, MMP-3, etc.) might be potential markers for an increased risk of Th1-related adverse events, including RA-like polyarthralgia, under omalizumab treatment.

The limitation of this case series is that precise evaluations of synovitis were not performed, and detailed pathological findings of patients' joints were not available. However, as the joint symptoms

and elevations of serological markers observed after initiation of omalizumab therapy were eliminated after the omalizumab was discontinued, we speculate that the serological markers are important markers for omalizumab-related polyarthralgia.

We have reported the cases of 3 patients who suffered RA-like polyarthralgia with elevated serological markers of RA during omalizumab therapy for severe asthma. The potential development of Th1-related diseases in patients treated with omalizumab needs to be taken into consideration in clinical practice. Serological markers of RA might be helpful in identifying patients who are vulnerable to these adverse events.

Acknowledgments

Y. To and M. To participated in the conception and design of the study. Y. To, Y. Kono, R. Tsuzuki, and M. To participated in the acquisition, analysis, and/or interpretation of data. H. Kaneko provided significant clinical input. Y. To and M. To participated in the writing and critical revision of the manuscript. All authors are accountable for the accuracy and integrity of the work.

Department of Allergy and Respiratory Medicine, The Fraternity Memorial Hospital, Sumida, Tokyo, Japan

No funding was received for this work.

Conflicts of interest: Y. To received lecture fees from GlaxoSmithKline, AstraZeneca, Sanofi, Kyorin-Pharmaceutical, and Novartis Pharma. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 31, 2021; revised April 28, 2021; accepted for publication May 3, 2021.

Available online ■ ■ ■

Corresponding author: Yasuo To, MD, PhD, Department of Allergy and Respiratory Medicine, The Fraternity Memorial Hospital, 2-1-11 Yokoami, Sumida, Tokyo 130-8587, Japan. E-mail: ytou-alg@umin.ac.jp.
2213-2198

© 2021 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2021.05.027>

REFERENCES

1. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6-11.
2. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61.
3. Brodlic M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. *Arch Dis Child* 2012;97:604-9.
4. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J* 2018;51:1702523.
5. Hayashi H, Fukutomi Y, Mitsui C, Watai K, Tomita Y, Kamide Y, et al. Th1-related disease development during omalizumab treatment: two cases with severe asthma. *Allergol Int* 2018;67:405-7.
6. Yung S, Han D, Lee JK. Cutaneous sarcoidosis in a patient with severe asthma treated with omalizumab. *Can Respir J* 2015;22:315-6.
7. Di Bona D, Fiorino I, Taurino M, Frisenda F, Minenna E, Pasculli C, et al. Long-term "real-life" safety of omalizumab in patients with severe uncontrolled asthma: a nine-year study. *Respir Med* 2017;130:55-60.