

CASE REPORT

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Adverse Reaction to Omalizumab in Patients with Chronic Urticaria: Flare Up or Ineffectiveness?

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ABSTRACT

Omalizumab is a recombinant humanized anti-Ig E monoclonal antibody used as the third line treatment of chronic spontaneous urticaria (CSU). We report four patients with severe antihistamine-resistant CSU, who developed angioedema, anaphylaxis and/or flare up of urticaria at different times following omalizumab therapy.

Keywords: Chronic urticaria; Omalizumab; Adverse reaction

INTRODUCTION

The spontaneous occurrence of wheals and angioedema lasting for six or more than six weeks is defined as chronic spontaneous urticaria (CSU).^{1,2} According to epidemiological studies, the prevalence of CSU is estimated to be 1% of the population.³ Omalizumab, a recombinant humanized anti-IgE monoclonal antibody, has been recommended for the third line treatment in CSU patients. The efficacy of the drug begins 3 days after subcutaneous administration and continues for 4 weeks.⁴ However, knowledge on the safety of omalizumab in treatment of CSU patients is lacking.^{1,5,6}

The aim of this report is to introduce four patients who experienced anaphylaxis, angioedema and flare up of urticaria during omalizumab administration.

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Case 1

The first subject was a 68-year-old man with a history of CSU and angioedema lasting for 4 years. Urticarial lesions lasted for less than 24 hours and left no residual purpura. Episodes of angioedema accompanied by swelling of the lips occurred two times in a month. Challenge tests were performed and all physical urticaria types and dermographism were excluded.

Omalizumab therapy 300 mg/month was introduced. There was only a little clinical improvement after the first injection. After the next administrations of omalizumab, a better clinical improvement was observed. Four hours following the fifth administration of omalizumab, he developed mild angioedema on the lips and the neck. This reaction was thought to be a flare up in CSU. He was treated with oral antihistamines and systemic steroids for three days. About five hours after the sixth administration of omalizumab, urticarial lesions flared up and a mild angioedema was seen on his lips. He was treated with

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high dosages of antihistamines and systemic steroids. Omalizumab was discontinued after the sixth administration.

Case 2

The second subject was a 49-year-old woman with a history of CSU and angioedema persisting for 25 years. Urticarial lesions lasted for less than 24 hours and left no residual purpura. Challenge tests were performed and all types of physical urticaria and dermographism were excluded.

Omalizumab 300 mg/month was introduced. There was a marked improvement in asthma symptoms, with fewer and shorter attacks occurring within one month. However, there was partial remission of urticaria during that time. She developed angioedema on her tongue after 30 minutes of the second omalizumab administration. That was the first angioedema attack on her tongue. She has had no angioedema two months before the second administration of omalizumab. She was treated with oral antihistamines and systemic steroids for ten days. Omalizumab treatment was discontinued.

Case 3

A 33-year-old woman presented with a 7-year-history of urticaria and angioedema, requiring systemic steroids weekly for symptomatic control. Urticarial wheals occurred weekly on every site and lasted for less than 24 hours and angioedema accompanied by urticarial wheals on her lips and eyelids occurred weekly. Challenge tests were performed and all types of physical urticaria and dermographism were excluded.

Omalizumab 300 mg/month was introduced. The patient had weakness and developed hypotension within 30 minutes after the first administration. She was treated with bolus administration of 0.9% NaCl 500cc. She recovered hemodynamically within 10 minutes. This reaction was considered as a non-specific adverse reaction. Three hours after the second administration of omalizumab, urticarial lesions flared up and angioedema was seen on her lips and tongue. She was treated with subcutaneous epinephrine, antihistamines and systemic steroids. Omalizumab treatment was discontinued.

Table 1. Characteristics of the patients

	Disease	Age	Sex	Duration of disease	Systemic disease	Concomitant medication use	Concomitant atopy /drug allergy	Concomitant autoimmune thyroiditis	Total IgE (IU/ml)	ASST	Previous therapy
Case 1	CSU+ angioedema	68	M	4 years	HT, OCT	Levocetirizine 20 mg/day, Bethametazon monthly, Amlodipin, Citalopram	Atopy + Allergic rhinitis	None	22.93	(-)	nsAH up to fourfold, S, LTRA, NB UVB, UVA1, autohemotherapy and Cy
Case 2	CSU+ angioedema	49	F	25 years	DM, HT, asthma, psoriasis	Cetirizine 40 mg/day, Inhaler budesonide, ipratropium bromür anhidr, salbutamol, tS	Atopy + Analgesic drug allergy	None	17.5	(-)	nsAH up to fourfold, S, LTRA, NB UVB, autohemotherapy, Mtx, Cy and dapson
Case 3	CSU+ angioedema	33	F	7 years	Goiter	Levotiroksin sodium	Antibiotic and analgesic drug allergy	ATG (+) ATPO (+)	50,60	NA	nsAH up to fourfold, S
Case 4	CSU	38	M	5 years	None	None	Penicillin allergy	None	17.1	NA	nsAH up to fourfold, S, irregular usage of 0,5-1mg/kg Cy

ASST: autologous serum skin test, AH: antihistamines, ATG: antithyroglobulin antibody; ATPO: anti-thyroid peroxidase antibody, CSU: Chronic spontaneous urticaria, Cy: cyclosporine, DM: diabetes mellitus, HT: hypertension, LTRA: leukotriene receptor antagonists, Mtx: methotrexate, NA: not applicable, nsAH: non-sedating H1-antihistamines, OCD: obsessive-compulsive disorder, S: steroids, tS: topical steroids

Table 2. Time of reactions observed during the administration of omalizumab

Time of the reaction	1st, 2nd and 3rd doses	4th, 5th and 6th doses
< 30 minutes	Case 3 (after 1st Dose)	-
30 - 60 minutes	Case 2 (after 2nd Dose)	-
1 - 2 hours	-	-
2 - 12 hours	Case 3 (after 2nd Dose)	Case 1 (after 5th and 6th doses)
> 12 hours	Case 4 (after 1st Dose)	-

Case 4

A 38-year-old man presented with a 5-year history of CSU. Urticarial wheals occurred weekly on every site and lasted for less than 24h. There were no other symptoms accompanying the attacks. Challenge tests were performed and all types of physical urticaria and dermographism were excluded.

He was treated with first and second generations of antihistamines, systemic steroids and irregular usage of 0,5-1mg/kg cyclosporine for years. Cyclosporine therapy was discontinued. Omalizumab therapy was initiated because of frequent exacerbations of the patient's complaints. After 12 hours of therapy, he developed severe urticarial lesions, but he had no angioedema. He was treated with systemic steroids and placed on cyclosporine 400 mg/day. After three days of the treatment, he responded to cyclosporine treatment. Omalizumab therapy was discontinued.

Demographic and clinical characteristics of the patients are shown in Table1.

DISCUSSION

Omalizumab has been known to be a well-tolerated treatment option in severe atopic asthma since 2005.⁷ In 2014, first European Medicines Agency and then Food and Drug Administration granted omalizumab marketing authorization for CSU.⁸ There is little evidence for adverse reactions of omalizumab in patients with CSU. Available data on the adverse events and tolerability have been derived only from the phase III trials in patients with CSU and have shown a well tolerability profile which is similar to that with placebo and without any anaphylactic reactions.⁹⁻¹¹

According to unpublished data we collected in the dermatology clinic in Education and Research Hospital, in 2014, 46 patients diagnosed as CSU were treated with omalizumab. Out of 46 patients, four developed angioedema and/or flare up of urticaria at different

times as described above (Table 2). To our knowledge, there have not been any reports about a similar condition in patients with CSU receiving omalizumab except phase studies.^{3,11}

Limb et al. evaluated anaphylaxis and angioedema profiles in 124 patients with asthma receiving omalizumab. They reported that anaphylaxis, urticaria and angioedema attacks developed hours after administration of the drug. They attributed these delayed reactions to the fact that mean serum concentrations of omalizumab can be obtained 7-8 days after administrations of the drug. They also added that dilution of lyophilized powder form of the drug with fluid less than required might have caused delayed reactions since a viscous solution could be obtained in 15-20 minutes.¹² It has also been proposed that side-effects may appear after the first or cumulative exposure to anti-allotypic or anti-idiotypic antibody.¹³

Polysorbate, part of the drug, is very likely to be responsible for adverse reactions. In a report on two cases of atopic asthma on the long-term omalizumab therapy, the intradermal test showed that anaphylaxis developed due to omalizumab.¹⁴ In the present cases, this test was not performed since it was risky for the patients and that treatment for urticaria and/or angioedema were continuing.

In case 2, angioedema developed 30 minutes after the second administration of omalizumab and in case 3, side-effects appeared soon after the first dose of the drug. These findings suggest that both delayed and acute reactions to omalizumab may develop.

So that anaphylaxis due to omalizumab can be diagnosed, there should be at least two of the following symptoms: angioedema in the throat or in the tongue, bronchospasm, hypotension, syncope and/or urticaria.¹⁵

In a study, 0.09% of the asthmatic patients administered omalizumab developed anaphylaxis within two hours of the administration. Based on this finding, it was recommended that patients should be

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monitored in the clinic for two hours after the first three injections of omalizumab and for 30 minutes after the following injections.¹³ Similarly, in our cases, four of the six reactions were observed after the first three doses. The other two reactions were seen after the fourth and later doses in the same patient (case 1). However, assessment of the onset time of the reactions showed that two of the six reactions occurred at the second hour or earlier, three reactions appeared during 2-12 hours and the last reaction lasted more than 12 hours (Table 2). Despite the asthmatic patients,¹³ the knowledge of real time for monitoring the patients with CSU during two injections of omalizumab is lacking. Therefore, we thought that the reactions appearing at the second hour or earlier in the first three doses were adverse reactions. However, the reactions observed later than 2 hours at any number of doses may be adverse reaction, flare up or ineffectiveness.

In the present case series, only case 3 developed delayed anaphylaxis after the second administration of the drug. To our knowledge, this is the first reported case of anaphylaxis due to omalizumab in CSU patients.

In addition, since delayed adverse reactions due to omalizumab can appear, patients may think that these reactions are independent of the drug. They may not tell their doctors about them due to clinical benefits they receive from their treatment.¹⁶ Therefore, it is necessary that patients should be informed about possible adverse reactions before treatment.

Based on the above findings, development of the reactions after the fifth administration of omalizumab in Case 1 showed that the drug was ineffective and that the disease had an exacerbation. However, flare up of urticaria and angioedema appearing one month later in the same case was considered as an adverse reaction. The reaction appearing on the tongue 30 minutes after the administration of omalizumab in case 2 was regarded as an adverse effect. Hypotension 30 minutes after omalizumab administration and lack of any other symptoms in case 3 were proposed to be a non-specific adverse reaction. Delayed angioedema and urticaria occurring after the second administration in the same case were indicative of an adverse reaction. Late-onset urticaria after the first dose in case 4 was thought to be a delayed adverse reaction due to omalizumab or exacerbation of the disease because the medications given were discontinued.

In conclusion, due to exacerbation of urticaria or angioedema normally appearing in the course of the disease, the diagnosis of an adverse reaction can be overlooked. Therefore, possibilities of an adverse reaction, lack of a response to omalizumab and exacerbations due to discontinuation of other medications should be taken into account when a decision about whether the treatment is effective and should be continued has to be made.

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REFERENCES

1. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; 69(7):868-87.
2. Colgecen E, Ozyurt K, Irfan Gul A, Utas S. Evaluation of etiological factors in patients with chronic urticaria. *Acta Dermatovenerol Croat* 2015; 23(1):36-42.
3. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy* 2011; 66(3):317-30.
4. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2007; 99(2):190-3.
5. McCormack PL. Omalizumab: a review of its use in patients with chronic spontaneous urticaria. *Drugs* 2014; 74(14):1693-9.
6. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; 122(3):569-73.
7. McKeage K. Omalizumab: a review of its use in patients with severe persistent allergic asthma. *Drugs* 2013; 73(11):1197-212.
8. Licari A, Marseglia A, Caimmi S, et al. Omalizumab in Children. *Paediatric Drugs* 2014; 16(6):491-502.
9. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic

- on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015; 135(3):925.
10. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Giménez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria 2013; *N Engl J Med* 2013; 368(10):924–35.
 11. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; 132(1):101–9.
 12. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007; 120(6):1378-81.
 13. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; 120(6):1373-7.
 14. Price KS, Hamilton RG. Anaphylactic reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; 28(3):313-9.
 15. Kim HL, Leigh R, Becker A. Omalizumab: Practical considerations regarding the risk of anaphylaxis. *Allergy Asthma Clin Immunol* 2010; 6(1):32.
 16. Barry PJ, O'Mahony A, Finnegan C, O'Connor TM. Delayed allergic reactions to omalizumab: are patients reporting all cases? *J Allergy Clin Immunol* 2008; 121(3):785-6.