

Effectiveness of omalizumab in a patient with a life-threatening episode of bronchospasm and larynx angioedema after exposure to house dust

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Abstract

Omalizumab is a monoclonal antibody against IgE, nowadays approved for the treatment of persistent severe (EU) or moderate-to severe (USA) IgE-mediated asthma but there is also some evidence (case reports and four published clinical trials) on the effectiveness of this medication in urticaria and angioedema. The case of a 42-year-old woman suffering from severe allergic asthma and severe chronic urticaria with concomitant angioedema is presented in the article. She had a life-threatening episode of bronchospasm and larynx edema after exposure to house dust recorded in her medical history. The patient did not respond to standard therapy. The improvement in asthma control and remission of chronic urticaria and angioedema was achieved after introducing the therapy with omalizumab.

Key words: severe asthma, chronic urticaria, life-threatening angioedema, omalizumab.

Omalizumab is a monoclonal antibody against IgE, approved for the treatment of persistent severe (EU) or moderate-to severe (USA) IgE-mediated asthma. It is very effective in reducing asthma exacerbations as well as patients' hospitalizations and emergency visits due to exacerbations. Moreover, it decreases severity and frequency of asthma symptoms and improves the quality of life.

Omalizumab is administered subcutaneously and thus it shows a more extensive systemic antiallergic effect than the antiasthmatic action. Some clinical trials and case reports which have been published so far show its effectiveness *inter alia* in allergic rhinitis, nasal polyps, severe atopic dermatitis, urticaria, angioedema, food allergy, anaphylaxis, and mastocytosis [1].

This article presents a case report of a patient with the history of a life-threatening episode of bronchospasm and larynx edema after exposure to house dust.

At present, the patient is a 42-year-old woman suffering from severe allergic asthma and severe chronic urticaria with concomitant angioedema. She is allergic to tree, grass and weed pollens, house dust mites and cat dander. Apart from asthma and urticaria she has developed allergic rhinitis, nasal polyps, oral allergy syndrome (apples, carrots, pears, cherries, strawberries, celeriac, walnuts), drug allergy or intolerance (antibiotics, local anesthetics, proton pump inhibitor (PPI), non-steroid

anti-inflammatory drugs (NSAID), some corticosteroids (CS)), and chronic gastritis. She works as a teacher in a primary school but due to the allergy she has been temporary unable to work since asthma and urticaria became severe.

The patient has been suffering from allergy since her childhood. Asthma and allergic rhinitis started at the age of 7. At the beginning, allergy symptoms were seasonal, however when she was 26 years old they became perennial with seasonal exacerbations. At the same time nasal polyps were diagnosed and the patient underwent polypectomy. Two years earlier, oral allergy syndrome had appeared.

In 2002, the woman started allergen immunotherapy with subcutaneous vaccine containing pollen allergens but had to interrupt it due to the suspicion of myocarditis in the course of viral respiratory tract infection.

In 2004, when the patient was 33 years old, asthma became severe and uncontrolled with everyday asthma symptoms despite the maximal antiasthmatic therapy with continuous oral steroids treatment (step 5 acc. to GINA recommendations). She experienced frequent asthma exacerbations due to recurrent viral infections and exposure to allergens, and was hospitalized. Since 2004, recurrent episodes of urticaria and angioedema have occurred, although the first episode of urticaria was at

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Figure 1 A–D. Allergic reaction after exposure to house dust

the age of 7. An attempt to apply cyclosporine therapy appeared to be ineffective as well as long-acting intramuscular steroids.

In 2006, the patient’s health dramatically deteriorated: she was administered up to 60 mg of prednisolone per day besides 1000 µg fluticasone per day, formoterol and montelukast. Additionally, she needed intravenous

steroids. Severe attacks of asthma and edema of larynx occurred due to the exposure to house dust. In consequence, she had to be treated with epinephrine and hospitalized (Figures 1 A–D).

She underwent a thorough allergological testing and medical examination. Skin-prick tests revealed positive reactions to trees, grass and weed pollens, dust mites,

Table 1. Diagnostic procedures

Total IgE level – 630 IU/ml	Compliment C3 and C4 levels reduced (in acute phase)
Specific IgE – above class 2 for mites and animal dander	↑ Total IgG (subclasses within normal limits), IgM and IgA normal
Skin prick tests positive to house dust mites, cat, trees, grass, weeds	ANA and ANCA negative
Spirometry – severe obturation	Thyroid hormones TSH and FT4 – normal range
Morphology normal except eosinophilia > 1500 cells/mm ³	Test for parasites – negative
X-ray of thorax – normal	Marrow biopsy – without evidence of neoplastic growth, eosinophilia
CT of lung – normal	Bronchoscopy – chronic bronchitis
Cardiac USG – normal	Gastroscopy – non active chronic gastritis, specific IgG and urease test – <i>Helicobacter pylori</i> (+); incomplete eradication due to angioedema to PPI

cat dander, nuts (hazel and walnut), kiwi allergens, the total IgE level was 631 IU/ml and specific IgE levels were greater than class 2.0 for mites mix and animal dander mix. The patient was comprehensively diagnosed (Table 1) due to high blood eosinophilia (over 1500 eosinophils/mm³) but no signs of neoplastic proliferation of bone marrow and eosinophilic syndromes were detected.

In 2007, she started omalizumab therapy. The calculated dose of omalizumab based on the IgE level and weight initially was 375 mg every 2 weeks and was later modified due to weight change. Urticaria and angioedema disappeared within 1 month of therapy, and after 2 months, asthma control started to improve (Figure 2 A). The need for systemic corticosteroids decreased and asthma exacerbations rate significantly decreased (Figure 2 B). The blood eosinophil count normalized and lung functions improved. The patient's quality of life improved (Figure 2 A) and she returned to work.

The therapy has been continued up to the present day with the sustained improvement (Figures 2 A and 2 B), but an interruption (up to 3 months due to administrative problems with reimbursement of therapy) in the treatment resulted in the loss of asthma control, recurrence of asthma exacerbations (within 8 weeks) as well as urticaria and angioedema episodes (within 4 weeks), and an increase in the need for corticosteroids.

Nowadays, the patient takes 450 mg of omalizumab every 2 weeks, feels well and works. As she takes medicine regularly, no urticaria and angioedema appear, asthma exacerbations due to viral infection or allergen

exposure do not exceed 2 episodes per year (usually 1 per year) and can be treated at home, the daily dose of oral corticosteroids has maintained between 2.5 mg to 5 mg of prednisolone. The patient needs to be treated continuously and any interruption in the treatment is a life-threatening condition due to the risk of severe bronchospasms and larynx edema.

The effectiveness of omalizumab in severe asthma has been proved in many clinical trials [2, 3], pooled [4] and meta-analysis [5, 6] as well as real-life reports [7–9]. The therapy improves asthma control, decreases the number of severe exacerbations and hospitalizations due to asthma exacerbations, enables to decrease the daily dose of systemic corticosteroids as well as improves asthma-related quality of life. This medication was approved for asthma treatment initially in Australia in 2002, then in the USA and Europe, in 2004 and 2005, respectively.

The evidence regarding the effectiveness of this drug in urticaria and angioedema is based on a few case reports and four clinical trials.

The first report on the effectiveness of omalizumab in urticaria comes from 2006 and was written by Boyce [10] who described the case of a girl suffering from moderate asthma and idiopathic cold urticaria with severe reactions despite therapy with H₁ antagonists and cysteinyl leukotrienes receptor antagonist. Therapy with omalizumab (375 mg every 2 weeks) resulted in asthma control improvement and complete resolution of her urticaria and its associated manifestations.

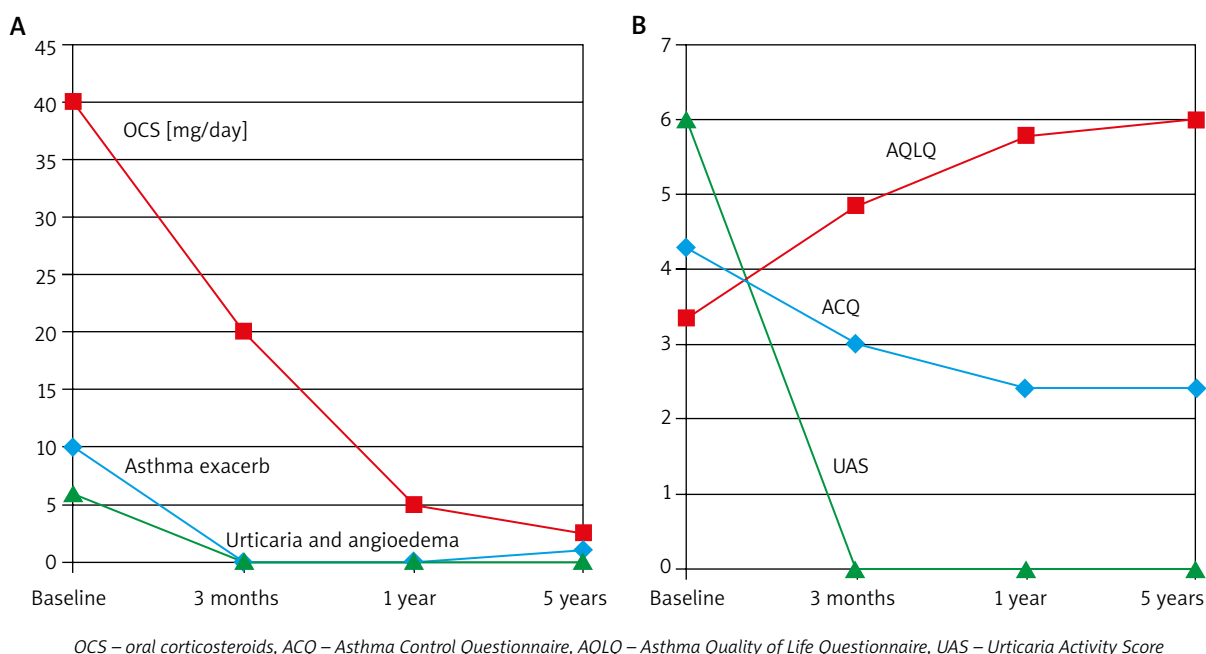


Figure 2. Clinical effect of omalizumab on asthma exacerbation, urticaria/angioedema episodes, need for oral corticosteroids (A), asthma control, asthma-related quality of life and severity of urticaria (B)

The first publication about effectiveness of this medication in angioedema appeared in 2007 and was prepared by Sands *et al.* [11]. They reported three cases of refractory idiopathic angioedema. All patients were men aged 50 to 65 years and experienced severe life-threatening larynx edema without urticaria eruption. Two of them had concomitant asthma, the remaining one – chronic obstructive pulmonary disease (COPD). They were all successfully treated with omalizumab (300 mg every 4 or 3 weeks or 375mg every 2 weeks, respectively) with immediate effect.

Maspero *et al.* [12] described a 12-year-old female who suffered from severe chronic autoimmune urticaria/angioedema. She had a poor response to the highest doses of combined therapy with 3 antihistamines, corticosteroids and antileukotrienes. After introducing omalizumab therapy (150 mg every 4 weeks acc. to the manufacturer's dosing table for asthma treatment), the patient became asymptomatic and had a negative autologous serum skin test result.

Korkmaz *et al.* [13] published a case of a 29-year-old man suffering from severe chronic urticaria and angioedema with unknown provoking factors, resistant to therapy with high-dose systemic corticosteroids and antihistamines, leukotriene antagonist, cyclosporine and antibiotics. Introducing therapy with omalizumab resulted in the complete remission of the chronic urticaria after 2 weeks.

Sánchez-Machín *et al.* [14] reported the case of a 35-year-old woman with severe chronic urticaria and angioedema as well as concomitant allergic rhinoconjunctivitis and episodic allergic asthma. She was sensitized to mites. Her urticaria was poorly controlled with conventional treatments (antihistamines and oral corticosteroids). Cyclosporine at doses of 200 mg per day initially showed good response, but after the dose reduction to 100 mg, symptoms relapsed. Omalizumab therapy (300 mg every 2 weeks acc. to the manufacturer's dosing table for asthma treatment) led to the relief of dramatic symptoms within 72 h. The patient decided to discontinue the therapy and no exacerbation of her state occurred.

Up to now the reports on successful treatment with omalizumab in cholinergic [15], solar [16], delayed pressure [17], heat [18], dermographic [19] and chronic idiopathic [20] or autoimmune [21, 22] forms of urticaria were published.

Recently, the results of four clinical trials have been published. The first two papers were published in 2011, including one by Maurer *et al.* [23]. They showed the results of a multicenter, randomized, double-blind, placebo-controlled study on patients with autoimmune chronic urticaria with or without angioedema refractory to conventional treatment (X-QUISITE study). From 49 randomized patients (omalizumab, $n = 27$; placebo, $n = 22$), 42 completed the study. The active phase lasted

for 24 weeks and the omalizumab dose was consistent with the approved asthma dosing table. At the end of the study, patients who received omalizumab demonstrated a greater reduction in the weekly urticaria activity score ($p = 0.0089$). Complete protection from wheal development was observed in 19 (70.4%) patients in the omalizumab group compared with only 1 (4.5%) patient in the placebo group. A similar effect was observed in the case of angioedema – complete absence of angioedema was observed in 77.8% of patients in the omalizumab group compared with only 36.4% in the placebo group. The therapy was well tolerated.

Just after the Maurer's publication, a paper by Saini [24] *et al.* was published. It was a prospective, double-blind, placebo-controlled, dose-ranging study investigating omalizumab in patients with chronic urticarial symptoms despite antihistamine therapy (MYSTIQUE study). Ninety patients were enrolled and randomized for the study to one of the four groups: 75, 300, or 600 mg of omalizumab or placebo. All of them received one dose of the drug and were observed subsequently for 4 weeks. Both the 300-mg and the 600-mg omalizumab groups showed a greater improvement versus the placebo group in Weekly Urticaria Activity Score (UAS7). The effect of treatment was visible after 1 to 2 weeks. The effect of 75 mg dose was small and statistically insignificant. There was no information about the number of subjects with angioedema and the effect of omalizumab therapy on this symptom. Omalizumab was well tolerated, and the incidence of adverse events was similar across treatment groups.

In 2013, the results of two studies were published. One was performed by Maurer *et al.* [25]. It was a multicenter, randomized, double-blind study evaluating the efficacy and safety of omalizumab in patients with moderate-to-severe chronic idiopathic urticaria, who remained symptomatic despite H_1 -antihistamine therapy (licensed doses). A total of 323 patients were randomly assigned to receive 12-week omalizumab therapy (75 mg, 150 mg, or 300 mg or placebo every 4 weeks) with a subsequent 16-week observation period. Angioedema was present during the week before randomization in 41% of patients. The therapy with omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in a dose-dependent manner. The effect of 75 mg dose did not differ from placebo, the maximal effect was achieved at the dose of 300 mg for all measured parameters except for the difference in the number of angioedema-free days from week 4 to week 12, which reached significance only in the 300 mg group.

The most recent publication has been written by Kaplan *et al.* [26]. It is a study evaluating the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) despite treatment with H_1 -antihistamines at up to 4 times of the approved

dose plus H₂-antihistamines, leukotriene receptor antagonists, or both (Glacial study). A total of 336 patients were randomized 3 : 1 to 300 mg of omalizumab or placebo administered every 4 weeks for 24 weeks and subsequently observed for 16 weeks. The therapy with omalizumab was well tolerated and significantly reduced the signs and symptoms of CIU/CSU compared with placebo in all measured efficacy end points including an improvement in days free from angioedema. These significant improvements were sustained throughout the 24-week treatment period.

Urticaria is a heterogeneous group of diseases with a distinctive skin reaction pattern: urticarial skin lesions and/or angioedema elicited by various provoking factors [27–31]. The pathomechanism is not fully known. Our patient had chronic urticaria with concomitant angioedema and known (mite allergens, NSAID, PPI) and unknown triggers. The omalizumab dose was calculated acc. to the manufacturer's dosing table for asthma treatment since asthma was the first indication for that therapy and its effect on urticaria and angioedema was unknown at that time, however it appeared to be spectacular.

Omalizumab works by blocking free circulating IgE and inhibits their binding to the specific receptors. Omalizumab also down-regulates IgE receptors on the effector cells. Additionally, omalizumab has been shown to exert an anti-inflammatory effect by the impact on peripheral eosinophil and T-lymphocyte function. This way it decreases or even completely blocks allergic reaction and asthma symptoms [1]. But the mechanism by which it works in urticaria and angioedema is still unknown. Both IgE-related and alternative pathways have been postulated.

Irrespective of the mechanisms, omalizumab appeared to be effective in patients with the history of severe, life-threatening angioedema and its use should be considered in cases refractory to standard treatment. The effect of omalizumab in urticaria is dose dependent, the effective dose begins from 150 mg every 4 weeks and is independent of the IgE level. The dose of omalizumab for patients suffering from urticaria with concomitant angioedema probably should be higher (minimum 300 mg every 4 weeks) than for patients with urticaria alone.

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