

CASE REPORT

Promising option in the prevention of idiopathic anaphylaxis: Omalizumab

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ABSTRACT

Anaphylaxis is a serious and probably lethal systemic reaction which occurs instantaneously after exposure to an allergen. It can occur after exposure to various triggers including allergic and non-allergic factors. When a trigger cannot be determined, idiopathic anaphylaxis is considered. In idiopathic anaphylaxis presenting with frequent attacks, long-term prophylaxis with H₁ antihistamine and steroid treatment are recommended. Omalizumab, a humanized monoclonal antibody drug which decreases free immunoglobulin E molecules in the circulation, is approved for the treatment of chronic severe persistent allergic asthma. We report a 46-year-old female patient with severe uncontrolled allergic asthma and idiopathic anaphylaxis presenting with attacks of abdominal pain, generalized urticaria, feeling of strangulation in her throat and unconsciousness. Omalizumab at a dose of 375 mg once every 2 weeks was administered and at the end of 3 months anaphylactic attacks had ceased. At the end of the sixth month of omalizumab therapy, her injection intervals were extended to 4 weeks. After she began experiencing moderate attacks of urticaria and hoarsening, however, initial treatment plan was reestablished. Currently, she has completed her first year of treatment without further attacks.

Key words: anti-immunoglobulin E, asthma, idiopathic anaphylaxis, omalizumab, prophylaxis.

INTRODUCTION

Anaphylaxis is a serious and probably lethal systemic reaction which occurs instantaneously after exposure to an allergen.¹ It may present with acute urticaria, angioedema, laryngeal edema, swelling of the tongue, abdominal pain, diarrhea, severe broncho-obstruction or shock. It can occur after exposure to various triggers including allergic and non-allergic factors. When a trigger cannot be determined, idiopathic anaphylaxis is considered. In cases with known etiology, preventive measures such as avoidance of triggers and education about acute attack management including carrying adrenaline auto-injectors are appropriate. In idiopathic anaphylaxis presenting with frequent attacks, long-term prophylaxis with H₁ antihistamines and steroid treatment are recommended.²

Omalizumab (Xolair; Genentech, South San Francisco, CA, USA), a humanized monoclonal anti-immunoglobulin (Ig) E antibody, decreases levels of circulating IgE by binding to the constant region (ce3) of the IgE molecule, which prevents free IgE from interacting with IgE receptors (FcεR and FcεRII) on the allergenic effector cell surface.³ It is administered s.c. once every 2 or 4 weeks depending on the patient's weight and total IgE levels. Omalizumab is approved for the treatment of chronic severe persistent allergic asthma. It is also an efficient therapy for seasonal and perennial allergic rhinitis and chronic urticaria.³ Herein, we present a case

diagnosed as allergic asthma and idiopathic anaphylaxis whose anaphylaxis attacks disappeared after the initiation of omalizumab therapy.

CASE REPORT

A 46-year-old female patient with uncontrolled asthma presented with attacks of abdominal pain, generalized urticaria (Fig. 1), feeling of strangulation in her throat and unconsciousness which had recurred four to five times in the last 2 months. No pathology was detected in her routine tests which were performed to determine an allergic etiology. When her history was detailed, she described rare urticarial episodes due to egg consumption. She was prescribed 16 mg/day prednisolone and 10 mg/day cetirizine and was called for a control visit after 1 month. At this time she declared that she had used her medications regularly but had had to attend the emergency department four times with the same complaints since the previous visit. Consequently, she was hospitalized after her informed consent was provided and the first evaluation for the etiology of anaphylaxis revealed that the attacks were not associated with the drugs she used. The skin test results revealed hypersensitivity to *Dermatophagoides pteronyssinus*, egg white and egg yolk. *In vitro* secretory IgE levels for egg white and egg yolk were found to be 66.5 kU/L (class 6) and 5.78 kU/L (class 3), respectively. Despite the high dosage antihistamines (fexofenadine 180 mg 3 × 1

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Received 17 November 2011; accepted 16 January 2012.



Figure 1. Diffuse urticarial plaques on the forearm during an attack.

plus pheniramine maleate 4 × 22.7 mg daily) and a special diet which lacked egg and other potential allergenic foods, her anaphylactic attacks continued to recur one to two times a week during her stay in the hospital. All her attacks were similar, consisting of acute pruritic wheals on her arms and body, generalized flushing, broncho-obstruction and fainting with mild hypotension. The attacks required treatment with epinephrine, antihistamines and corticosteroids. A dental patch test was performed because she had dentures and hypersensitivity to ethylene glycol dimethacrylate and potassium dichromate was detected. Although her dentures were removed after consultation with the department of dentistry, her attacks recurred. Systemic mastocytosis was excluded after normal tryptase levels and normocellular bone marrow were established. Catecholamine metabolites in urine and 5-HIAA levels were tested for other conditions which take place in differential diagnoses, such as carcinoid syndrome and pheochromocytoma; both were within normal limits. Thorax and abdominal screening did not reveal any pathology.

In the light of these findings, idiopathic anaphylaxis was diagnosed and methylprednisolone 16 mg/day was initiated, in addition to her daily antihistamine doses. With this therapy, the severity and frequency of anaphylactic attacks decreased slightly; however, as fasting blood glucose levels raised above 200 mg/dL and blood pressure level increased up to 170/100 mmHg, systemic steroid treatment was stopped. Because uncontrolled asthma despite the inhaled steroids and beta agonists, the IgE level of 402 IU/mL and unpreventable anaphylaxis were taken into consideration, omalizumab 375 mg once every 2 weeks was initiated. At the end of 3 months, the initial forced expiratory volume in 1 s (FEV1) value raised to 3.1 L from 2.2 L, asthma control test score raised to 25 from 12 and meanwhile she did not have any anaphylactic attack. At the end of the sixth month of omalizumab therapy, her injection intervals were extended to 4 weeks. However, because she began experiencing moderate attacks of urticaria and hoarsening, the initial treatment plan was reestablished. Currently, she has completed her

first year of treatment without further attacks. The total IgE level of the patient did not display an important change at the last control (372 IU/mL).

DISCUSSION

Omalizumab, rhuMAb-E25, is a humanized anti-IgE antibody which prevents allergic cascade by blocking binding of free IgE in circulation to the FcεRI receptor.⁴ Omalizumab therapy may decrease T-cell activation by downregulating FcεRI receptor expression on basophils and antigen-presenting dendritic cells.^{4,5} It also causes increase in FEV1, decrease in need for steroids and improvement in quality of life as it decreases disease flares in asthma.^{6,7}

Successful anti-IgE therapy with omalizumab has been demonstrated in some other immunological conditions such as chronic urticaria, latex hypersensitivity, peanut allergy and physical urticaria.⁸

There are several case reports which have demonstrated that omalizumab has been successfully used in the treatment of idiopathic anaphylaxis. First, Jones *et al.*⁹ reported the ceasing of anaphylactic attacks in a 48-year-old man after the initiation of 375 mg omalizumab bimonthly. Later, Warrier and Casale in 2009 presented a 12-year-old boy with a history of uncontrolled allergic asthma, allergic rhinitis, multiple food allergies and recurrent episodes of anaphylaxis who responded very well to 375 mg of omalizumab every 2 weeks.¹⁰ Finally, Pitt *et al.*¹¹ observed the effectiveness of omalizumab in a 15-year-old girl having idiopathic anaphylaxis presumably due to systemic mastocytosis. Similarly, it was demonstrated that omalizumab decreased the frequency of anaphylaxis episodes in two patients with mastocytosis.¹²

Although idiopathic anaphylaxis is described as a diagnosis in which all the causes or triggers of anaphylaxis are excluded, its mechanism is unknown. As Jones *et al.*⁹ proposed, our patient's response to omalizumab and her atopic background may suggest a mechanism involving IgE. It was postulated that omalizumab may not only decrease the concentration of serum IgE but may also serve as a mast cell stabilizer by downregulating the high-affinity IgE receptors on mast cells and basophils.⁹ As a matter of fact, the efficacy of omalizumab on anaphylactic episodes in patients with mastocytosis unprovoked by any allergen, has been postulated to be related to a decrease in the activation state of the mast cell concurrent with a decline in surface IgE and associated receptor (FcεRI) numbers.¹² Furthermore, a reduction of eosinophil numbers and IgE-expressing B lymphocytes may also be attributable to anti-inflammatory effects of omalizumab.

In conclusion, omalizumab seems to be a promising preventive therapy in idiopathic anaphylaxis which does not have a currently known treatment. In our opinion, the dosage and treatment schedule of omalizumab in anaphylaxis should be determined individually. Large, comprehensive clinical trials are needed to elucidate this matter.

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