
Case Report

Characterization of an anaphylactoid reaction to omalizumab

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Background: The novel humanized murine monoclonal antibody omalizumab prevents binding of human IgE to its high-affinity receptor. A contraindication to therapy with omalizumab is allergy to the medication or previous immediate-type hypersensitivity or anaphylaxis to omalizumab or similar medications.

Objective: To determine whether a 32-year-old woman with asthma, allergic rhinitis, and idiopathic chronic urticaria and angioedema with anaphylactoid reactions to omalizumab could tolerate the medication in a desensitization protocol.

Methods: Omalizumab was administered after pretreatment with nonsteroidal anti-inflammatory drugs (ibuprofen, 600 mg) while the patient was closely monitored in an intensive care unit.

Results: Omalizumab was well tolerated using this protocol, but a serum sickness–like reaction developed that required discontinuation of the medication after the seventh dose.

Conclusions: Our experience suggests that some patients with anaphylactoid reactions to omalizumab can tolerate the medication when pretreated with nonsteroidal anti-inflammatory drugs but that a serum sickness–like illness may develop, requiring discontinued use of the medication.

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INTRODUCTION

The novel humanized murine monoclonal antibody omalizumab prevents binding of human IgE to its high-affinity receptor. A contraindication to therapy with omalizumab is allergy to the medication or previous immediate-type hypersensitivity or anaphylaxis to omalizumab or similar medications. Herein, we report the case of a 32-year-old woman with asthma, allergic rhinitis, and idiopathic chronic urticaria and angioedema with anaphylactoid reactions to omalizumab to determine whether she could tolerate the medication in a desensitization protocol.

CASE REPORT

A 32-year-old woman was referred for the evaluation of poorly controlled asthma complicated by mixed allergic and idiopathic chronic urticaria and angioedema (ICUA). She had been in good health with mild asthma and allergic rhinitis before the birth of her third child 2 years previously. During that pregnancy she developed preterm labor and was treated with bed rest and high-dose oral corticosteroids to promote maturation of the fetus. After delivery of a healthy preterm infant by cesarean section, she had evidence of intraoperative anaphylaxis, suspected of being caused by latex or anesthesia.

Subsequently, her mild intermittent asthma became severe and oral corticosteroid dependent. She began to have episodes of hives, facial swelling, and wheezing without specific triggers

while taking 40 to 60 mg of prednisone daily and potent non-sedating antihistamines (10 mg of cetirizine and 180 mg of fexofenadine). She began to use an epinephrine autoinjector (EpiPen; Dey LP, Napa, CA) or to visit the emergency department for epinephrine injections several times a month for relief of hives and wheezing because wheezing did not respond to inhaled albuterol therapy. Another allergist diagnosed dust mite allergy by means of skin prick testing but advised against immunotherapy owing to her high-risk asthma.

On initial evaluation the patient was a cushingoid woman weighing 212 lb with otherwise normal examination findings. Pulmonary function testing showed normal values predicted for height (65 in), forced expiratory volume in 1 second (3.43 L [106% of predicted]), and forced vital capacity (4.01 L [105% of predicted]) while taking 40 to 60 mg of prednisone daily and her usual nonsedating antihistamines. Radioallergosorbent test results confirmed dust mite allergy (5.17 and 6.21 kU/L to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, respectively) but were negative to other common aeroallergens, including animal danders, grass, trees, weeds, molds, hymenoptera, and latex. The total serum IgE concentration was 33 kU/L, and the serum tryptase level was 4 ng/mL (reference range, 2–10 ng/mL). Findings from chest radiography and abdominal ultrasound were normal. Serum protein electrophoresis findings were normal. Results of an evaluation for carcinoid syndrome, autoimmune thyroid disease, hereditary or acquired complement abnormality, and other systemic illnesses were negative.

Therapy with montelukast sodium (Singulair; Merck, West Point, PA), 10 mg/d, and budesonide (Pulmicort Turbuhaler;

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AstraZeneca, Wilmington, DE), 400 μ g twice daily, was added to attempt to taper oral corticosteroid use. She continued to have wheezing, hives, and variable pulmonary testing, with forced expiratory volume in 1 second ranging from reference values to lower values of approximately 75% to 80% of predicted, and daily hives with efforts to reduce prednisone use. No response to treatment with low-dose cyclosporine (2 mg/kg daily) was noted in an attempt to taper prednisone use, and cyclosporine therapy also caused oral ulcerations.

Therapy with omalizumab (Xolair; Genentech Inc, South San Francisco, CA) was attempted; however, she developed marked generalized itching and erythema within 5 minutes of the first administration of a subcutaneous 300-mg dose. Epinephrine was given along with additional nonsedating antihistamines. Pulmonary function and other vital signs were stable, and itching subsided during a 4-hour observation period. During the next 4 weeks she felt subjective improvement in her wheezing and decreased her daily prednisone use to 20 mg from 40 to 60 mg without flares of urticaria or wheezing. Risks of continuing omalizumab therapy were discussed relative to the possibility that her corticosteroid dose could be reduced, and her clinical status improved with continued omalizumab therapy. After discussion of risks and benefits, she elected to continue omalizumab treatment but in a divided dose, and informed consent was obtained. At her next scheduled injection 4 weeks later, the final target dose of omalizumab was reduced to 150 mg total in view of her weight of 100 kg (the cutoff weight for an increased dose from 150 to 300 mg for this medication is 90 kg). When omalizumab was given subcutaneously at 30-minute intervals in divided doses beginning with 0.06 cm³ (7.5 mg) and increasing to 0.12 cm³ (15 mg), then 0.24 cm³ (30 mg), then 0.48 cm³ (60 mg), and then remaining at 0.3 cm³ (0.45 mg), she still had marked generalized erythema and pruritus beginning with the last 3 injections and persisting for several hours. Pulmonary function monitored after each injection was stable.

Additional monthly doses were given under close supervision in the Intensive Care Step-down Unit at St Mary's Hospital, Waterbury, CT. This monitoring revealed spikes of elevated temperature to 103°F and blood pressure to 160/110 mm Hg beginning after the second or third subcutaneous omalizumab divided doses, with stable pulmonary function. These systemic changes in temperature and blood pressure confirmed that her reactions to the medication had a systemic component and were not limited to flares of erythema and urticaria. The serum tryptase concentration obtained while these symptoms were evident was 4 ng/mL, unchanged from the level obtained before starting omalizumab therapy; thus, the systemic and cutaneous symptoms could be classified as anaphylactoid rather than as classic mast cell-mediated anaphylaxis. Her complete blood cell count, liver and kidney function, and urinalysis results were normal before and after the injections. Normal cardiology evaluation and stress test findings were obtained during omalizumab therapy despite an

episode of chest pain after self-administration of epinephrine not associated with omalizumab administration.

Remarkably, all clinical abnormalities were absent when the patient was pretreated with 600 mg of ibuprofen 1 hour before receiving her fourth dose of omalizumab. She tolerated 2 additional injections of 150 mg of omalizumab without any further hypersensitivity noted when she was pretreated with 600 mg of ibuprofen. She tapered her prednisone to a stable dose of 20 mg 4 times daily, her lowest maintenance dose for at least the previous 2 years. Her use of epinephrine was reduced from 1 to 2 times weekly before omalizumab use to a single use during the months while taking omalizumab. Subjectively, her greatest improvement was that she could participate in exercise class without experiencing exercise-induced flushing, hives, and facial swelling, suggesting that omalizumab had some beneficial effects on her underlying ICUA and asthma. She had lost weight because of increased exercise and decreased prednisone use.

Her seventh dose of omalizumab, again after pretreatment with 600 mg of ibuprofen, was well tolerated initially. Beginning 1 to 2 days after the injection she developed generalized pruritic petechia that slowly worsened and then resolved during the next 2 weeks. This seemed to be a serum sickness-like reaction, although mild, because total complement levels, urinalysis results, and liver and kidney function remained normal. Further therapy was discontinued. During the next 6 months, her asthma and flares of urticaria and oral corticosteroid dose returned to their original state, and there was no other change in her overall health.

After this experience, we were concerned that subsequent patients with ICUA would have similar anaphylactoid reactions to omalizumab. We have since given omalizumab for more than 6 months to 2 additional patients with coexisting corticosteroid-dependent asthma and ICUA without any worsening of urticaria or anaphylactoid symptoms. In fact, urticaria is improved in these patients, suggesting that many patients with ICUA can tolerate and even benefit from using omalizumab.

DISCUSSION

Preliminary experience with omalizumab has reflected a consensus that repeated urticarial reactions to omalizumab are a contraindication to the use of this medication.¹⁻³ The number of cases in which therapy has been discontinued owing to urticaria is not known, reflecting the appearance of urticarial reactions in 1% or fewer injections, and whether all immediate hypersensitivity-type reactions are a relative or absolute contraindication is not established. A desensitization protocol with omalizumab was devised for the patient described herein with recurrent anaphylactoid reactions to the medication. Although the patient tolerated omalizumab when pretreated with ibuprofen, she developed an unanticipated serum sickness-like reaction after receiving her seventh dose of omalizumab, and therapy was discontinued despite clinical improvement in asthma and urticaria.

Regarding the mechanism of this patient's anaphylactoid reactions, most of her symptoms seemed to be resistant to oral

corticosteroids, because they occurred while she was taking 60 mg of prednisone daily, and to the leukotriene antagonist montelukast and high doses of nonsedating antihistamines. By analogy to reactions to infusions of intravenous immunoglobulin, it seems most likely that her symptoms were due to a combination of complement activation and release of related inflammatory mediators, such as prostaglandins. In many cases, intravenous immunoglobulin reactions are due to activation of the complement pathway possibly related to IgG aggregates or rapid infusion rates.^{4–11} No improvement was noted by giving the medication in divided doses rather than in a single dose, but marked improvement was noted with nonsteroidal anti-inflammatory drug (NSAID) pretreatment, suggesting that prostaglandins instead of leukotrienes or histamine played a major role in the patient's hypersensitivity. Prostaglandins are released by mast cells but not by basophil degranulation; however, her serum tryptase level remained normal during a documented hypersensitivity reaction, suggesting that prostaglandins may have arisen from another cell type than either mast cells or basophils. Omalizumab has been shown to decrease leukotriene biosynthesis, thus a corresponding increase in prostaglandin production with repeated doses of omalizumab may have contributed to her final serum sickness-like illness because prostaglandins and leukotrienes are metabolites of arachidonic acid.

Omalizumab therapy could not have led to the generation of a novel autoantibody because the reaction to the medication was noted at the first dose. The patient had not had any previous therapy with intravenous immunoglobulin or humanized monoclonal antibodies. She may also have experienced a hypersensitivity reaction to a component of omalizumab other than the human monoclonal antibody itself. The medication currently is prepared from mammalian cell lines, is supplied in a lyophilized powder form that requires rehydration, and may contain poorly soluble components of either the antibody or components of the purification process (Dennis Wong of Genentech, personal communication, 2004). In the future, an aqueous solution of omalizumab may be available that might be tolerated in this patient if her reactions were due to components of the current lyophilized form of the medication other than the medication itself. It is not likely that the medication was prepared incorrectly from lyophilized powder because similar reactions were observed when multiple highly trained individual nursing staff prepared omalizumab, and reactions were not observed in other patients during the treatment interval.

Experience with hypersensitivity reactions to human polyvalent immunoglobulins and humanized murine monoclonal antibodies has shown that some but not all reactions, such as urticaria or localized inflammation, may, in some cases, be prevented by decreasing the rate of medication administration and by pretreatment with antihistamines, NSAIDs, and oral corticosteroids.^{4–11} Adverse reactions may not recur with different formulations of the same therapy or with different humanized monoclonal antibodies. Other complications, such as vasculitis, coagulation abnormalities, and myocardial in-

farction, have been reported and are an absolute contraindication to further therapy.^{8,9,12,13}

Our experience suggests that some patients can tolerate omalizumab therapy even in the presence of documented hypersensitivity if the medication is given with pretreatment including NSAIDs. Risks and benefits of the therapy must be carefully evaluated and informed consent obtained before giving omalizumab to patients with previous anaphylactoid reactions; in addition, the medication must be administered under close observation. Patients with corticosteroid-dependent asthma and ICUA may benefit from omalizumab therapy owing to its effects on coexisting asthma and IgE-mediated airway reactivity and possible direct effects of omalizumab on ICUA due to down-regulation of IgE receptors. Whether patients with preexisting ICUA may be at increased risk of adverse reactions, as noted in the patient described herein, remains to be determined.

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