

Letter to the Editor

Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis

To the Editor:

We have preliminary data demonstrating omalizumab may have efficacy in the prevention of spontaneous episodes of systemic hypotension (anaphylaxis) in patients with systemic mastocytosis, a disease characterized by a pathologic increase of resident mast cells in tissues such as skin, the gastrointestinal tract, bone marrow, liver, and spleen. The majority of adult patients with systemic disease have a point mutation in the *c-kit* gene at the 816 position (D816V) that is believed to contribute to the abnormal proliferation of mast cells and enhanced mast cell survival.¹

Omalizumab is a humanized murine mAb that inhibits the binding of IgE to the surface of mast cells and basophils by forming complexes with free IgE in the serum.² The result is a downregulation of FcεRI expression on mast cells and basophils, and a reduction in mast cell or basophil activation.³ We hypothesized that these effects would also decrease episodes of unprovoked anaphylaxis in patients with mastocytosis.

PATIENT 1

A 17-year-old white male developed hyperpigmented macules at age 3 months with confirmation of urticaria pigmentosa (UP) by skin biopsy at age 5 months. The UP lesions stabilized and began to regress at about age 4 years when vomiting and diarrhea began. By age 5 years, the patient began to experience syncopal episodes followed by a prolonged confusional state. These episodes increased in severity over time to include loss of consciousness requiring hydration and potassium replacement in the emergency department. These episodes occurred every 2 weeks to 18 months, with a total of 24 episodes recorded in a 7.5-year period until age 12 years. After age 12 years, the frequency stabilized to approximately 4 to 6 episodes per year and continued at that rate until the initiation of therapy. The episodes were associated with hypotension, flushing, and diarrhea; however, they were not associated with angioedema, food, exercise, or stress. The working diagnosis was a seizure disorder or hypokalemic periodic paralysis until a bone marrow biopsy in 2001 led to the diagnosis of systemic mastocytosis based on the World Health Organization consensus guidelines, which included the presence of the D816V mutation in *c-kit*. At the time of diagnosis, the cutaneous lesions were almost completely resolved, whereas the serum tryptase was elevated at 35.5 ng/mL. The patient's medical history includes allergic rhinitis with seasonal symptoms to specific allergens, which was verified by skin tests; exercise-induced asthma; and headaches. A therapeutic trial of corticosteroids had not been undertaken before omalizumab.

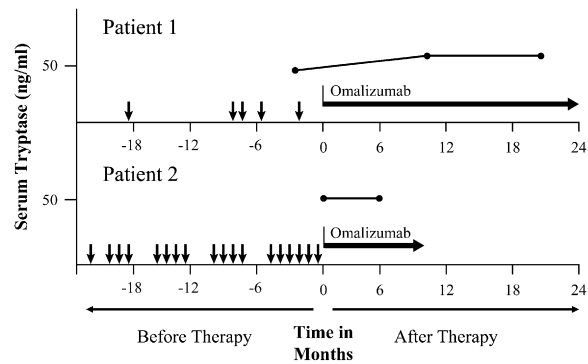


FIG 1. Chronologic course of anaphylaxis before and after therapy. Upper panel, patient 1; lower panel, patient 2. Anaphylactic events are represented by closed arrows. Omalizumab therapy initiated at time 0. The serum tryptase on the y-axis is represented as solid circles above each graph.

Omalizumab therapy was started at age 15 years, and the serum IgE and serum tryptase were 315 IU and 45.9 ng/mL, respectively. At the commencement of therapy, medications included ranitidine, doxepin, montelukast, cetirizine, albuterol metered dose inhalant, diphenhydramine, fluticasone/salmeterol dry powder inhaler, and methylphenidate.

Omalizumab therapy was initiated at 300 mg every 4 weeks and has now continued for 24 months (Fig 1). He has had no episodes of anaphylaxis, and the omalizumab has been well tolerated with only local swelling at the site of injection. Since starting omalizumab, he is no longer taking doxepin and has reduced his dose of Advair 250/50µg to 100/50µg (GlaxoSmithKline, Research Triangle Park, NC).

PATIENT 2

This 51-year-old white male has had skin lesions consistent with UP since adolescence. He began to have systemic symptoms with 3 episodes of mild-moderate anaphylaxis and subsequent hospitalization at age 37 years. A subsequent skin biopsy and bone marrow confirmed the diagnosis of systemic mastocytosis, including the presence of the D816V mutation in *c-kit*, during this hospitalization.

At age 38 years, a trial of aspirin and prednisone decreased the severity of the anaphylactic episodes. However, the development of an aspirin allergy associated with anaphylaxis as well as the typical adverse effects associated with chronic use of corticosteroids required discontinuation of that regimen. From age 39 to 41 years, he reported episodes of anaphylaxis at approximately 90-day intervals, although not all required epinephrine therapy. At age 48 years, he had another severe episode of anaphylaxis requiring an intensive care unit admission. Since age 48 years, he has had 15 to 16 episodes of anaphylaxis per year and during these episodes has associated wheezing, vomiting, and hives, but no angioedema. For each episode he

self-administered epinephrine and activated the emergency medical system.

He has a history of mild intermittent asthma, allergic rhinitis with seasonal symptoms diagnosed by CAP-RAST to aeroallergens, penicillin allergy implicated by history, and aspirin sensitivity with associated symptoms of anaphylaxis.

His medications at the time of initiation of omalizumab therapy included ranitidine, fluticasone-nasal, cromolyn sodium, montelukast, diphenhydramine, albuterol metered dose inhalant, hydroxyzine, esomeprazole, and bupropion. Before omalizumab therapy, his serum IgE level was 104 IU; his serum tryptase was 54.9 ng/mL.

Omalizumab therapy was initiated at 300 mg every 4 weeks. The patient has not experienced any episodes of anaphylaxis requiring epinephrine in 5 months since starting therapy (Fig 1). The patient has had 1 episode of diarrhea lasting 2 hours that did not necessitate a visit to the emergency department or activation of the emergency medical system. The drug has been well tolerated with the exception of local swelling and erythema at the injection site. He has discontinued cromolyn sodium and montelukast since starting omalizumab.

This is the first observation of the potential efficacy of omalizumab in the treatment of patients with mastocytosis and unprovoked anaphylaxis. These episodes of anaphylaxis were not associated with food, drugs, exercise, insect stings, or any other identifiable allergen. Both patients had symptoms consistent with anaphylaxis in the emergency department manifested by hypotension, flushing, and diarrhea that required epinephrine, hemodynamic support, occasional hospitalization, and documented elevated serum tryptase levels above baseline with values of >200 ng/mL and 186 ng/mL in patients 1 and 2, respectively. Angioedema was not observed in either patient.

The ability of omalizumab to decrease the frequency of episodes of hypotension in these 2 patients within a short time did not appear to rely on the ability of omalizumab to decrease mast cell numbers, because the serum tryptase levels in these patients did not change during the period of response. Further, because mast cells live for months within tissues, an effect of omalizumab on the turnover rate of mast cells is unlikely. However, serum free IgE as a result of omalizumab therapy has been shown to significantly decrease after 1 dose,² and downregulation of

FcεRI on the surface of basophils has been documented at day 7.⁴ Moreover, in the latter study, there was no change in mast cell numbers from skin biopsy specimens with a documented decrease in FcεRI on the surface of mast cells from the same biopsy specimen between day 7 and day 70. We thus hypothesize, but have not proven, that this downregulation of receptors is accompanied by an increase in the threshold above which degranulation is triggered. The mechanism by which omalizumab decreases episodes of mast cell-dependent hypotension in these patients with mastocytosis thus remains unknown but may relate more to a decrease in the activation state of mast cells concurrent with a decrease in surface IgE and associated decreases in receptor (FcεRI) number.

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