

OMALIZUMAB IN IDIOPATHIC ANAPHYLAXIS

Anaphylaxis is a life-threatening systemic allergic reaction that is usually IgE mediated but that can occur through other immunologic (non-IgE-mediated) or nonimmunologic mechanisms. Idiopathic anaphylaxis is a diagnosis of exclusion after known causes of anaphylaxis have been ruled out.¹ The prevalence of idiopathic anaphylaxis in the United States is estimated to be 20,000 to 47,000 cases.² It is potentially fatal, and although deaths from idiopathic anaphylaxis are rare,³ morbidity from the disease is significant. Allergen specific IgE plays a central role in IgE-mediated anaphylaxis. Cross-linking of receptor-bound IgE on mast cells and basophils by allergen leads to the release of inflammatory mediators that cause symptoms. In idiopathic anaphylaxis, FcεRI receptors may be aggregated by autoimmune mechanisms.⁴ The current approach to treatment is based on disease frequency; short-term treatment is usually sufficient for infrequent attacks, but prophylactic therapy with glucocorticoids is sometimes used for patients with frequent attacks.⁵ Although there are no validated quality-of-life measures for idiopathic anaphylaxis, patients with idiopathic anaphylaxis have to be prepared at all times for an attack.

Omalizumab is a 95% humanized monoclonal antibody that recognizes and binds to the Fc portion of the IgE molecule at the same site that it uses to attach to FcεRI. Thus, omalizumab prevents IgE expression on allergic effector cells and subsequent allergen-induced cross-linking of IgE.⁶ Omalizumab is an established treatment for chronic, moderate to severe persistent allergic asthma. Omalizumab has been shown to have positive therapeutic effects in other

IgE-mediated allergic disorders, including seasonal and perennial allergic rhinitis and chronic urticaria.⁶ Because anaphylaxis is an IgE-mediated reaction, we hypothesized that omalizumab could be effective in treating anaphylactic events from known and undetermined causes. Treatment of idiopathic anaphylaxis with anti-IgE has been suggested in the past⁷; however, to our knowledge, this is the first report of its efficacy for this diagnosis.

A 12-year-old boy had a history of uncontrolled allergic asthma, allergic rhinitis, multiple food allergies, and recurrent episodes of anaphylaxis. He had frequent asthma exacerbations requiring multiple courses of oral corticosteroids. His Asthma Control Test score was 9 initially. He also had multiple anaphylactic episodes, some triggered by foods that he was allergic to and some due to undetermined causes. He had 4 to 5 anaphylactic episodes per month that manifested with urticaria, shortness of breath, and wheezing. He missed 45 school days in the previous year due to asthma exacerbations or anaphylactic events. The results physical examination showed "allergic shiners" and a nasal crease but were otherwise unremarkable. He had no evidence of urticaria, urticaria pigmentosa, or other cutaneous findings. He was skin test positive to grasses, trees, dog, cat, and mold. Spirometry showed a prebronchodilator forced expiratory volume in 1 second (FEV₁) of 2.10 (87%) and a postbronchodilator FEV₁ of 2.4 (99%). He had a normal complete blood cell count with a differential count, and his total IgE level was 1,848 IU/mL. Results of IgE radioallergosorbent testing for foods were class 3 (3.51–17.5 kU/L) for milk, soybean, chicken, and pork; class 2 (0.71–3.50 kU/L) for peanut, lentil, tuna, tomato, sesame seed, paprika, mustard, codfish, beef, and turkey; and class 1 (0.35–0.70 kU/L) for kidney bean, corn, carrot, and casein.

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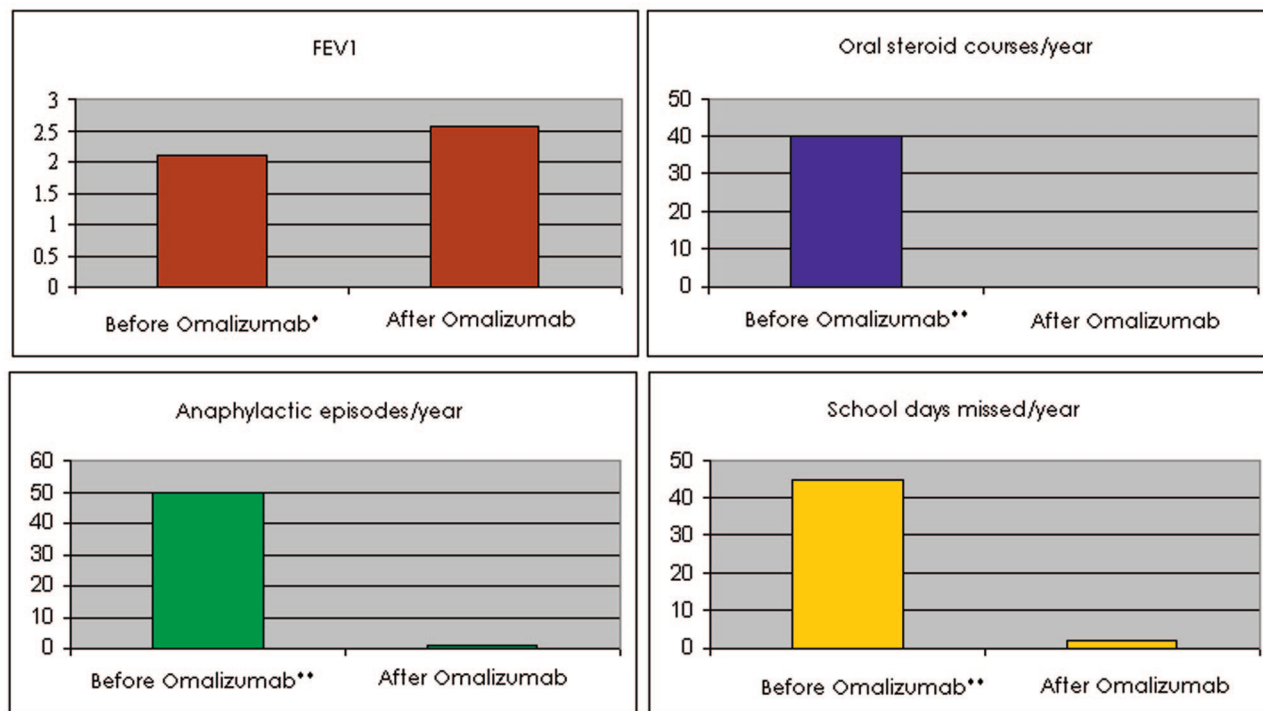


Figure 1. Effects of omalizumab on clinical variables. *Two weeks before omalizumab therapy was started. **An average of the preceding 5 years. FEV₁ indicates forced expiratory volume in 1 second.

The patient was given omalizumab at the maximum dose according to the package insert, 375 µg subcutaneously every 2 weeks, which corresponded to 0.01 mg/kg per IU/mL of IgE per month. Soon thereafter, he had resolution of acute allergic reactions, anaphylaxis, and asthma exacerbations (Fig 1). The FEV₁ improved to 2.58 (104%), and the Asthma Control Test score 1 month after starting omalizumab therapy was 22. His quality of life improved significantly. He continues to avoid known food triggers. He has not missed a single day of school since starting omalizumab therapy 10 months ago, and he is able to participate in sports.

Omalizumab, prescribed for severe allergic asthma, markedly improved this patient's asthma while significantly decreasing the episodes of idiopathic anaphylaxis. Although it may be debated that his idiopathic anaphylaxis naturally waned across time, it is much more likely that omalizumab contributed to his improvement because the frequency of his anaphylactic episodes had not decreased for at least the preceding 5 years.

We cannot be certain, however, that he had episodes of idiopathic anaphylaxis. It is possible that all his episodes were related to ingestion of food. If so, then the improvement may have been due to avoidance of relevant foods and the decreased sensitivity to foods caused by omalizumab. However, we believe he had food-induced anaphylaxis and idiopathic anaphylaxis and that omalizumab induced improvement via a mechanism unrelated to decreased sensitivity to foods. Although idiopathic anaphylaxis may have an autoimmune mechanism, in this case, it was probably IgE mediated, as evidenced by the rapid and sustained improvement with anti-IgE therapy. Further studies are warranted to investigate this therapeutic option to prevent a variety of IgE-mediated acute allergic reactions.

PRIYA WARRIER, MD, MPH

THOMAS B. CASALE, MD

Division of Allergy and Immunology
Creighton University School of Medicine
Omaha, Nebraska
tbcasale@creighton.edu

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EOSINOPHILIC FASCIITIS MASQUERADING AS ANGIOEDEMA

We describe an 80-year-old woman who was in her usual state of health until she hit her arm on a door frame. She noticed swelling in the arm thereafter, which did not resolve with time but progressed to the bilateral upper and lower extremities. She experienced occa-

sional associated pain, erythema, and increased warmth. She was treated with nonsteroidal anti-inflammatory medications, diuretics, and antibiotics without symptom resolution. Because of an indolent course, she was admitted for evaluation for acquired angioedema. When she was found to have eosinophilia, the Allergy/Immunology Service was consulted for evaluation of acquired angioedema vs drug reaction. Detailed history revealed her swelling waxed and waned but never completely resolved. It was painful to palpation and occasionally associated with muscle cramping and difficulty in grasping objects. She denied rashes, joint swelling, muscle weakness, or atrophy. Her medical history was significant for collagenous colitis diagnosed 1 year ago and osteoporosis. There was no family history of autoimmune or atopic disorders aside from a sister with angioedema secondary to medication. She denied travel, use of potentially toxic oil, or known exposure to toxins. Medications included lansoprazole and tegaserod. No new medications were prescribed before she developed symptoms. She denied nutritional supplements or L-tryptophan-containing products.

The results of physical examination were unremarkable aside from the swelling in her extremities. She had mild edema and diffuse pitting induration of the skin and subcutaneous tissue with puckering. She had no sclerodactyly or flexion contractions. She had an eosinophil count of 1,009/mm³ (reference range, 40–390/mm³). The results of antinuclear antibody and rheumatoid factor testing were negative. Creatine kinase, tryptase, erythrocyte sedimentation rate, and immunoglobulin levels were normal. Because the edema was restricted to muscle planes while sparing the surrounding connective tissue, a diagnosis of eosinophilic fasciitis (EF) was raised.

Further evaluation included serum immunoelectrophoresis, which revealed 2 faint monoclonal IgG κ bands, and urine immunoelectrophoresis, which revealed monoclonal κ light chains. Magnetic resonance imaging revealed fascial thickening, a hyperintense signal within the fascia on fluid-sensitive sequences, and fascial enhancement after intravenous contrast administration, all findings highly characteristic of EF.¹ A muscle biopsy specimen revealed a lymphoplasmacytic inflammation with rare eosinophils consistent with eosinophilic fasciitis. Serum cytokine levels revealed an increase in the inflammatory cytokines interleukin 1α, interleukin 6, and interleukin 8 and an increase in eotaxin and interleukin 10. T_H2 cytokines were similar to control (Table 1).

Table 1. Serum Cytokine Levels^a

Cytokine	Control	Patient
T _H 2 cytokines, pg/mL		
IL-4	12.14	13.59
IL-5	0.55	0.88
IL-13	3.39	None detected
Inflammatory cytokines, pg/mL		
IL-1α	None detected	219.85
IL-6	0.92	44.71
IL-8	9.56	95.71
IFN-γ	None detected	3.15
Other cytokines, pg/mL		
IL-10	0.17	48.37
Eotaxin	28.2	229.5
IP-10	49.59	None detected

Abbreviations: IFN-γ, interferon γ; IL, interleukin; IP-10, interferon γ-inducible protein 10.

^a Serum samples obtained from the patient and a healthy control were assayed for the indicated substances using a Luminex Bioplex assay.

Disclosures: Authors have nothing to disclose.