



Successful treatment of exercise-induced anaphylaxis with omalizumab

Omalizumab, a monoclonal antibody against immunoglobulin E (IgE), is approved for the treatment of moderate to severe allergic asthma. Furthermore, case reports have documented its successful use in the treatment of anaphylaxis of various causes: idiopathic,^{1,2} systemic mastocytosis,³ and venom induced.^{4,5} To date, omalizumab has not been reported in the treatment of exercise-induced anaphylaxis (EIA).

Exercise-induced anaphylaxis is a potentially life-threatening clinical syndrome, manifesting with a variety of symptoms occurring during or shortly after exercise. EIA can occur independently or in association with specific food ingestion, known as food-dependent exercise-induced anaphylaxis (FDEIA). The pathophysiology of both EIA and FDEIA is not fully understood, but it is likely mediated by mast cell degranulation with histamine release.⁶ Current preventative treatments include exercise avoidance, food avoidance in FDEIA, and pretreatment with medications such as antihistamines, cromolyn, or montelukast before exercise.⁷ At the time of this manuscript's writing, this is the first successful off-label use of omalizumab in the prevention of EIA.

A 14-year-old male competitive athlete, with a history of EIA and allergic rhinitis, presented to the University Allergy Clinic after 2 episodes of anaphylaxis after running. Two hours before the initial episode, he had eaten a full meal, which consisted of milk, hamburger, celery with peanut butter, orange, and banana. His symptoms included diffuse redness with itching, facial angioedema, lightheadedness, and hypotension (blood pressure = 70/50 mmHg), which began 5 minutes after completing a 1-hour run. In the emergency room, he received intramuscular epinephrine, intravenous methylprednisolone, diphenhydramine, and famotidine. On discharge, he was started on daily cetirizine and given an injectable epinephrine kit. He has never had a history of food-allergy. Nevertheless, he underwent evaluation for a food-induced trigger. The skin testing was positive to celery and peanut. Serologic testing was significant for elevated specific IgE to peanut, apple, barley, oat, rice, soy, wheat, orange, banana, beef, and celery (all values were class I or class II positive). Total IgE level was 235 IU/mL. He was instructed not to eat these foods before running. He continued to exercise without difficulty, until 5 weeks later, when he had a second episode of anaphylaxis 5 minutes after completing a 3-mile race. Thirty minutes before exercise, he had eaten a chocolate-flavored nutritional bar. He received 2 epinephrine doses in the field and was taken to the emergency room, where he received additional treatment with intravenous steroids and antihistamines. He was subsequently referred to our center, where he was started on montelukast 10 mg, fexofenadine 180 mg, cromolyn 200 mg, and ranitidine 150 mg 2 hours before exercise. Additionally, he was instructed to avoid all foods 6 hours before exercise. Baseline tryptase was normal (4 ng/mL).

Despite these measures, he continued to have breakthrough anaphylactic reactions with even minimal exercise (playing frisbee) and once, after ingestion of 200 mg ibuprofen. The patient was subsequently instructed to avoid all nonsteroidal anti-inflammatory medications and to stop exercise completely. Dietary and activity restriction were very diffi-

cult for this young high school athlete. He opted to participate in weight lifting over the next 2 months, which caused recurrent facial swelling. Given his refractory symptoms, a decision was made to add omalizumab therapy (300 mg monthly) to his maintenance therapies. Four months after the onset of treatment, the patient resumed exercise activity. He did not change his premedication regimen, but he resumed eating before exercise without any restrictions. His daily exercise consisted of 2 hours of combined anaerobic and aerobic activity in the gym: warm-up sessions, weight lifting, and intermittent cardio-exercises; however, he has not resumed competitive running. He was able to tolerate all these activities without difficulty with no epinephrine use or emergency room visits. He continues to receive monthly treatments.

This is the first case report of the successful use of omalizumab in the treatment of EIA. The pathophysiology of EIA remains unknown. In addition to IgE-mediated mast cell degranulation, other proposed mechanisms include exercise-induced changes in plasma osmolality, alterations in blood pH, alteration in tissue transglutaminase, redistribution of blood flow and antigen presentation, and changes in gut permeability.^{6,7}

Omalizumab has been previously shown to treat anaphylaxis in case reports.^{1–3} In these cases, the proposed mechanism of omalizumab action was to decrease serum concentration of IgE as well as stabilize mast cells by downregulating the expression of the high-affinity IgE receptor. Although omalizumab does not target all proposed pathways in EIA, its mast cell stabilizing effect likely contributed to the clinical response in this patient.

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