Successful treatment with omalizumab in challenge confirmed exercise-induced anaphylaxis

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Clinical Implications

- First case of challenge confirmed successful treatment with omalizumab in a severe case of exercise-induced anaphylaxis.

TO THE EDITOR:

Exercise-induced anaphylaxis (EIA) is a rare and potential life-threatening disorder that can manifest independently or in combination with food ingestion defined as food-dependent EIA. The specific mechanism and pathogenesis is not fully understood, but mast cell activation and release of vasoactive mediators is believed to be responsible for the associated clinical manifestations as in other forms of anaphylaxis.

The efficacy of omalizumab (Xolair), a monoclonal antibody against immunoglobulin E (IgE), is well documented in allergic asthma[1] and recently in chronic spontaneous urticaria[2] case reports, and small clinical trials have shown promise in treatment of atopic dermatitis, food allergy, mast cell disorders, idiopathic anaphylaxis, and other allergic disorders,[3] but a challenge-documented effect with EIA has never been shown.

Here, we report a case of a 17-year-old competitive male racing cyclist with no prior history of allergy. He was presented to our clinic after one severe episode of anaphylaxis and over the last 5 months' recurrent episodes of diffuse flushing, pruritus, urticaria (not pin-point size wheals as seen in cholinergic urticaria), and angioedema related to exercise, mainly cycling. The severe episode occurred after a 1-hour cycling race; 1 hour before the initiation of the race he had eaten a chicken sandwich with dried tomatoes. Symptoms included itching, redness, generalized urticaria, facial angioedema, asthma (wheezing and persistent cough), and hypotension (62/34 mm Hg). Prehospital he was successfully treated with intramuscular epinephrine (0.3 mg) with instant effect and thereafter with intravenous methylprednisolone (80 mg) and antihistamine (clemastin 2 mg) together with inhalation of a short-acting anticholinergic and β2-sympathomimetic agonist and observed overnight at the hospital.

Related to the episodes, the only partial consistent potential food trigger had been whey protein isolate supplement drink with chocolate flavor, High5 Protein Recovery (H5 Ltd, Leicestershire, UK), but episodes had also occurred without intake, including the anaphylactic reaction.

He had no prior history of food allergy or atopy; nevertheless he underwent evaluation for possible food triggers induced by exercise. Skin prick testing (ALK-Abello, Copenhagen, Denmark) and prick-to-prick followed by serologic testing with specific IgE and basophil histamine release test (BHR-test) were all negative to food (wheat, gluten, omega-5 gliadin, rye, oat, barley, buckwheat egg, milk, soya, peanut, hazelnut, brazil nut, sesame, poppy seeds, alpha gal, chicken, shrimp, codfish, and celery) and standard inhalant panel (birch, grass, mugwort, cat, horse, dog, house dust mites, and mold) including normal baseline tryptase (3.15 μg/L), negative KIT D816V mutation in blood, and a negative TempTest (Freyer & Siegel Elektronik GmbH & Co, Hennigsdorf, Germany). The prick-to-prick test and BHR-test to the whey supplement drink were also negative. Testing was done several months after the severe reaction, and 2 months after the last episode.

A fasting challenge on a treadmill with 20 minutes of moderate running (pace: 10.5-13.0 km/h, heart rate: 108-186 BPM) was performed. During the challenge he presented initial pruritus and diffuse redness followed by urticaria (hives of 5-20 mm in diameter) primarily on the thighs (Figure 1); no significant change in tryptase (3.16 μg/L) was measured. He was instructed to avoid exercise and always carry an epinephrine autoinjector.

Given his competitiveness and desire to resume competitive cycling, we decided after a month, without recurred reactions, to add omalizumab 300 mg every 2 weeks with approval from the parents. This dose regimen was chosen based on other patients, treated prophylactically for anaphylaxis off label in our clinic (off-label treatment is possible in Denmark at the doctor's discretion and responsibility). A new fasting challenge was performed after 1 week of treatment where after 30 minutes of moderate running (pace: 9.5-13.5 km/h, heart rate: 98-186 BPM) he presented milder symptoms of diffuse redness and urticaria compared with initial challenge without omalizumab. After 16 weeks of omalizumab treatment, a negative treadmill challenge was performed (pace: 9-13 km/h, heart rate: 100-185 BPM) followed by a multistage exercise test, where both pace and inclination were increased every minute to physical fatigue (pace: 11-16 km/h, inclination: 1%-6%, heart rate: 133-200 BPM). As most reactions had occurred during or after cycling lasting normally 2-3 hours, a challenge mimicking a regular training pass was performed on the patient's own racing bike in the allergy center (average cadence: 91 per minute, watt: 150-307) (Figure 2). To ascertain full covering during the

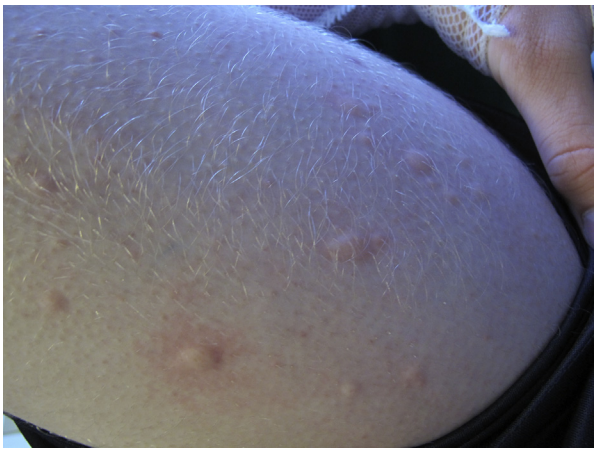

FIGURE 1. Urticaria after fasting treadmill challenge without omalizumab treatment.

FIGURE 2. Cycling challenge with the patient's own equipment in the allergy center.

interval between 2 subsequent doses, a challenge was always performed the day before the next scheduled injection of omalizumab. Challenge outcome was negative (Figure 3), and therefore he could resume previous cycling activity without restrictions, but was still advised to carry an epinephrine autoinjector at all time.

The plan is initially a stable period without symptoms under omalizumab treatment and then gradually to increase the dose interval, followed by, if still asymptomatic, a renewed challenge after a period off omalizumab.

To the authors' knowledge, this is the first clinical challenge that confirmed the successful use of omalizumab in the treatment of EIA. Only 1 previous case report of omalizumab treatment in EIA has been reported,[4] where the patient was sensitized to different foods in both skin prick test and IgE (IgE and skin prick test positive peanut and celery) and the diagnosis as well as the treatment effect never challenge confirmed.

The more selective use of omalizumab has become more widespread, but the current strength of evidence is still low and large controlled trials are needed to evaluate the true potential of omalizumab.

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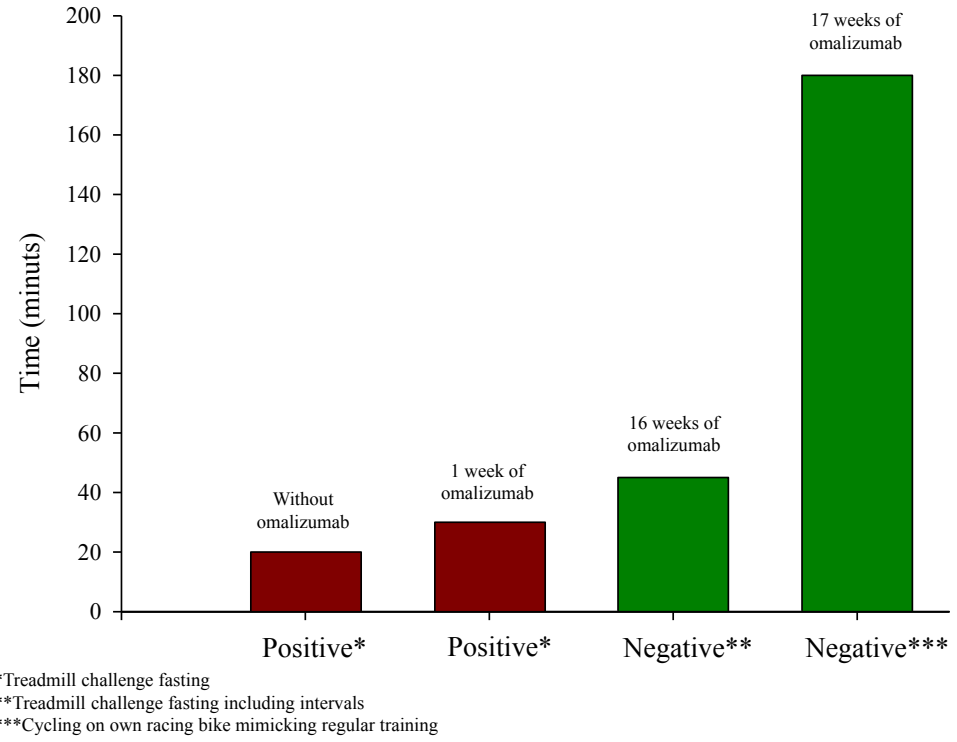

FIGURE 3. Challenge outcome in exercise-induced anaphylaxis before and under omalizumab treatment.

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