Effect of dupilumab in a patient with severe asthma complicated with recurrent anaphylaxis: a case report

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Anaphylaxis is a life-threatening allergic reaction characterized by the involvement of multiple organs, including the skin and the respiratory, cardiovascular, and gastrointestinal systems. The incidence of anaphylaxis is higher in patients with severe asthma than in those without severe asthma [1]; moreover, anaphylaxis is a risk factor for asthma-related mortality [2]. Strict avoidance of the allergen is recommended in patients with anaphylaxis; however, approximately 6.5%–35% of cases may be classified as idiopathic or unexplained anaphylaxis, for which there is no standard long-term prophylaxis [3, 4].

Dupilumab inhibits the activity of interleukin (IL)-4 and IL-13 and is used to treat severe asthma [2]. IL-4 and IL-13 might play pivotal roles in anaphylactic reactions [5-8]; however, the therapeutic effects of dupilumab on anaphylaxis are unknown. Here, we present the first case of the effects of dupilumab in a patient with severe asthma complicated with recurrent anaphylaxis.

In 2013, a 17-year-old girl was referred to our hospital for severe uncontrolled

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asthma despite maximal medical therapy including inhaled steroids, long-acting bronchodilators, leukotriene receptor antagonist, prednisone 15 mg/day, and omalizumab. Diagnosis of asthma was confirmed by a positive result in bronchodilator test (440ml, 23.4%). She was diagnosed with asthma at the age of 14 years and was treated with inhaled corticosteroids. However, she had frequent asthma exacerbations and hospitalizations, and was treated with omalizumab for 6 months before the referral to our hospital.

Oral prednisone was gradually tapered to 4 mg/day within 8 months after the referral to our hospital; however, she had frequent episodes of asthma exacerbations and hospitalizations, and a maintenance prednisone dose of 10–40 mg/day was required (Figure 1). In addition to asthma exacerbations, the patient experienced frequent episodes of either unexplained anaphylaxis or anaphylaxis due to the intake of multiple foods, food additives, and various classes of medicine. Most of her anaphylactic episodes occurred at rest and were unrelated to exercise or strenuous activity. She seemed to react to triggers including nonsteroidal anti-inflammatory drugs, acetaminophen (> 500 mg/day), pentazocine, lidocaine, crustaceans, fish, bananas, melons, pineapples, wheat, soybean, alcohol, and latex. Unfortunately, the
frequency of her recurrent unexplained anaphylaxis increased despite avoiding possible triggers. She had frequent emergency department visits for urgent epinephrine intramuscular injections and adjunctive treatments, and subsequent hospitalization (≥ 4 times/year) owing to severe anaphylactic events (Figure 1). Her typical anaphylaxis symptoms started with abdominal pain, pruritus, and redness of the face and anterior chest, followed by wheezing, hypoxia, and hypotension (systolic blood pressure < 90 mmHg).

Differential diagnosis, such as angioedema, mast cell activation disorders, or pheochromocytoma, was ruled out by clinical course considering normal laboratory test findings of baseline serum tryptase (1.0 ng/mL), CH50, C3, C4, C1-INH protein, urinary metanephrine-to-creatinine ratio, and plasma catecholamines (norepinephrine, epinephrine, and dopamine). Serum tryptase during anaphylactic reactions could not be measured. Moreover, C-reactive protein, anti-nuclear antibody, and antineutrophil cytoplasmic autoantibody were negative. The patient’s fractional exhaled nitric oxide level was 12 ppb. In 2019, during her treatment with 10 mg prednisone and omalizumab; total IgE level was 86.6 IU/mL and eosinophil count of 60 cells/μL. In 2012, before her long-term treatment with systemic steroid, total IgE was high (2100
IU/mL), eosinophil count was 168 cells/μL, and specific IgE for food (crab and shrimp) and aeroallergen (house dust mites, cat and dog dander, Japanese cedar, rag weeds, cockroach, and moth (*Bombyx mori*, frequent sensitizer in Japan)) were positive. Specific IgE for anisakis, ω-5-gliadin and α-GAL were negative. Due to her unstable symptoms and her intense anxiety, we were unable to perform the skin prick tests.

In 2019, when she was 23 years old, her treatment was switched from omalizumab to dupilumab because of worsening asthma. The first (600 mg) and second (300 mg) subcutaneous injections of dupilumab were safely initiated during hospital admission. Since then, the number of asthma exacerbations and anaphylaxis decreased markedly; Asthma Control Test value improved from 10 to 20, FEV₁ increased from 1.74 L to 2.42 L, and prednisone dose was safely tapered to 5 mg/day. There were no further asthma exacerbations requiring hospitalization nor anaphylactic episodes requiring epinephrine administration for 2 years (Figure 1).

Dupilumab was thus effective in preventing recurrent anaphylaxis and in treating severe asthma. Although there is a reported case of acquired tolerance to specific food antigens after treatment with dupilumab [9], there are no reports on improvement in
severe recurrent anaphylaxis. The pathogenesis of anaphylaxis varies and includes immunologic (IgE-dependent or -independent) and nonimmunologic mechanisms [3]. In the present case, before long-term treatment with systemic steroids, the patient’s total IgE level was high and specific IgE for multiple aeroallergens and food was positive. Although total IgE level was low prior the start of dupilumab treatment, we suggest that an underlying IgE-mediated mechanism could be involved in her anaphylaxis episodes. Omalizumab may suppress anaphylaxis by reducing the total free IgE levels and number of FceRI receptors in addition to mast cell stabilization [10]. Dupilumab inhibits the IL-4 and IL-13 pathways, which may play pivotal roles in the pathogenesis of anaphylaxis. Previous studies have indicated that IgE production is induced by IL-4 and IL-13 and is suppressed by anti-IL-4Ra antibodies [5, 6]. Furthermore, IL-4 promotes mast cell proliferation and survival and high-affinity IgE receptor expression [7]; and increases vascular permeability by acting simultaneously with histamine through IL-4Ra expressed in the vascular endothelium [8]. Therefore, we hypothesize that dupilumab can potentially inhibit the mechanisms of anaphylaxis in various ways.

The findings presented in this case report indicate that dupilumab could be a treatment option for patients with severe asthma complicated with recurrent anaphylaxis and suggest the need for further studies.
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Conflicts of Interest

The authors report no conflicts of interest.
References


**Figure.** Clinical time course.

ICS, inhaled glucocorticoid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist. Each bar represents an incidence of hospitalization, while the width of the bar denotes the duration of hospitalization.