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, although approximately 6.5% to 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 by recurrent anaphylaxis.

In 2013, a 17-year-old girl was referred to our hospital for severe uncontrolled asthma despite optimal medical therapy including inhaled corticosteroids, long-acting bronchodilators, a leukotriene receptor antagonist, prednisone 15 mg/d, and omalizumab. Diagnosis of asthma was confirmed by a positive bronchodilator test result (440 mL, 23.4%). While she had been diagnosed with asthma at the age of 14 years and was treated with inhaled corticosteroids, she had frequent asthma exacerbations and hospitalizations, and was treated with omalizumab for 6 months before referral to our hospital.

Oral prednisone was gradually tapered to 4 mg/d within 8 months after referral to our hospital. Nevertheless, she continued to experience frequent episodes of asthma exacerbations requiring hospitalization, and a maintenance prednisone dose of 10-40 mg/d was required (Figure). 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

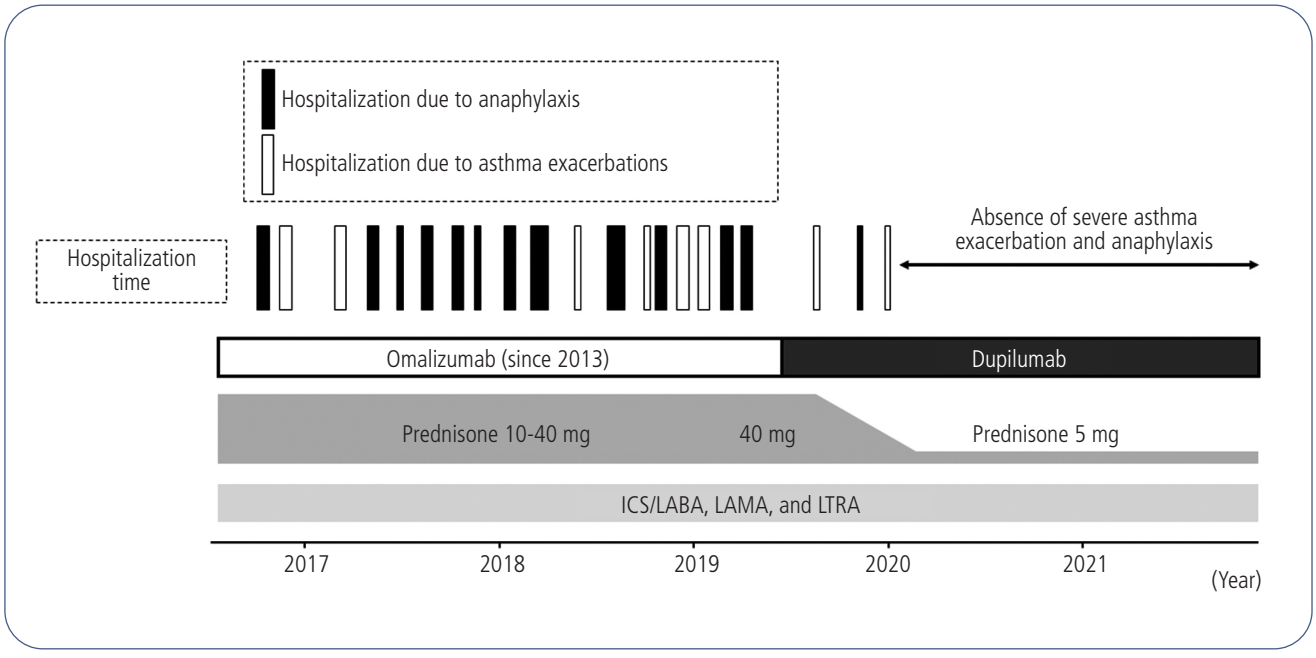

Figure. Timeline of the clinical course. Each bar represents an incidence of hospitalization, while the width of the bar denotes the duration of hospitalization. ICS indicates inhaled corticosteroid; LABA, long-acting ß-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

(>500 mg/d), pentazocine, lidocaine, crustaceans, fish, bananas, melons, pineapples, wheat, soybean, alcohol, and latex. Unfortunately, the frequency of her recurrent unexplained anaphylaxis increased despite avoidance of possible triggers. She visited the emergency department frequently for urgent intramuscular epinephrine injections and adjunctive treatments and had to be hospitalized (≥4 times/y) owing to severe anaphylactic events (Figure). Anaphylaxis typically started with abdominal pain, pruritus, and redness of the face and anterior chest, followed by wheezing, hypoxia, and hypotension (systolic blood pressure, <90 mmHg).

A differential diagnosis with conditions such as angioedema, mast cell activation disorders, and pheochromocytoma was ruled out owing to the clinical course, which was characterized by normal laboratory test findings for 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 could not be measured during the anaphylactic reactions. Moreover, the results for C-reactive protein, antinuclear antibody, and antineutrophil cytoplasmic autoantibody were negative. The patient's fractional exhaled nitric oxide level was 12 ppb. In 2019, during treatment with 10 mg prednisone and omalizumab, the total IgE level was 86.6 IU/mL and the eosinophil count was 60/μL. In 2012, before long-term treatment with systemic corticosteroids, total IgE was high (2100 IU/mL), the eosinophil count was 168/μL, and findings were positive for specific IgE for food (crab and shrimp) and aeroallergens (house dust mites, cat and dog dander, Japanese cedar, ragweed, cockroach, and moth [*Bombyx mori*, a frequent sensitizer in Japan]). Specific IgE for anisakis, ω-5-gliadin, and α-GAL were negative. Given the patient's 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 and second subcutaneous injections of dupilumab (600 mg and 300 mg, respectively) were safely administered during hospital admission. Since then, the number of asthma exacerbations and anaphylaxis episodes has decreased markedly. In addition, the Asthma Control Test value improved from 10 to 20, FEV_1 increased from 1.74 L to 2.42 L, and the prednisone dose was safely tapered to 5 mg/d. There were no further asthma exacerbations requiring hospitalization or anaphylactic episodes requiring administration of epinephrine for 2 years (Figure).

Dupilumab was, therefore, 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 mechanisms (IgE-dependent or -independent) and nonimmunologic mechanisms [3]. In the present case, before long-term treatment with systemic corticosteroids, the patient's total IgE level was high, and specific IgE for multiple aeroallergens and food was positive. Although the total IgE level was low before initiation of dupilumab, we suggest that an underlying IgE-mediated mechanism could be involved in the anaphylaxis episodes. Omalizumab may suppress anaphylaxis by reducing the total free IgE levels and number of FcεRI receptors and stabilizing mast cells [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-4Rα 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-4Rα expressed in the vascular endothelium [8]. Therefore, we hypothesize that dupilumab can 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 by recurrent anaphylaxis and suggest the need for further studies.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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