

Dupilumab for Treatment of Food-Dependent, Exercise-Induced Anaphylaxis: Report of One Case

Li-Ping Zhu[#], Rui Tang[#], Qing Wang, Hong Li^{*}

Allergy Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China.

ABSTRACT

Food-dependent, exercise-induced anaphylaxis (FDEIA) is a potentially life-threatening disorder that often occurs with exercise, and patients typically have eaten a specific food within hours before disease onset. This disease is exceedingly rare, with a prevalence of 0.02%. No well-recognized prevention or treatment strategy has been available for FDEIA except avoiding triggers strictly. Here we report an 11-year-old boy with a history of recurrent anaphylaxis of unknown etiology more than 10 times within two years. As the anaphylactic symptoms had not been controlled after traditional treatments, the patient was given subcutaneous injection of dupilumab seven times within 33 weeks. During dupilumab treatments, the patient was exposed to culprit mushrooms plus exercises at least twice a month but without notable anaphylaxis. Thus, dupilumab may improve the allergic reactions in FDEIA patients.

Key words: food-dependent, exercise-induced anaphylaxis; anaphylaxis treatment; food allergy; mushroom allergy; dupilumab

INTRODUCTION

Food-dependent, exercise-induced anaphylaxis (FDEIA) is a potentially life-threatening disorder that often occurs during exercise, and patients typically have a history of eating culprit foods within hours before disease onset; however, eating or exercise alone does not induce allergic symptoms^[1]. FDEIA is exceedingly rare, with an approximately 0.02% prevalence^[2].

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4R α subunit of the IL-4 and IL-13 receptor complex. Its roles in treating atopic dermatitis, uncontrolled asthma, severe chronic sinusitis with nasal pol-

yps, and eosinophilic esophagitis have been explored^[3]. In a 23-year-old female patient with severe asthma and unexplained severe allergic reactions unrelated to exercise, no serious anaphylaxis requiring epinephrine occurred after treatment with dupilumab for asthma in two doses within the next 2 years^[4]. However, no published report has clarified the clinical implication of dupilumab treatment for anaphylaxis, especially for FDEIA.

CASE DESCRIPTION

General information

The patient we reported was an 11-year-old boy with a history of recurrent anaphylaxis, asthma, allergic rhinitis, and allergic conjunctivitis due to cat, mites, and fungus sensitization. In June 2019, the patient developed anaphylaxis characterized by systemic wheals itching, facial edema, eyelid redness and swelling, nasal congestion, cough, chest tightness, dyspnea, lip cyanosis, and wheezing while exercising after eating a common food for approximately 2 hours. The child

Received January 28, 2023; accepted April 24, 2023; published online May 18, 2023.

[#]These authors contributed equally to this work.

^{*}Corresponding author: Hong Li, E-mail: lihong@pumch.cn.

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had experienced more than 10 episodes of anaphylaxis in 2 years and had been hospitalized twice for emergency treatment. On previous visits, his family members felt that the episodes were not related to specific foods. The patient's asthma [Asthma Control Test (ACT) score: 20], allergic rhinitis [combined symptom-medication score (CSMS): 2.33], and allergic conjunctivitis were controlled after treatment with Ventolin and budesonide formoterol powder for inhalation, cetirizine, and fluticasone propionate nasal spray. For more than half a year, he had been receiving sublingual dust mite drops for allergen immunotherapy (AIT). However, the anaphylaxis did not improve after traditional treatments including the above-mentioned medications, AIT, and allergen avoidance. Specific IgE (ImmunoCAP) showed *Alternaria alternata* was 25.7 kUA/L, cat dander was 14.9 kUA/L, and *Dermatophagoides farinae* was 15.4 kUA/L. The total IgE was 621.0 kU/L. The acetylcholine bronchial challenge test was positive: forced expiratory volume in one second (FEV_1) decreased by 37%, peak expiratory flow (PEF) decreased by 27%, and the provocative cumulative dose of methacholine that causes a 20% fall in FEV_1 ($PD_{20}FEV_1$) was 0.0961 mg. Pulmonary function: FEV_1 (L), 1.77; FEV_1 predicted (%), 78.4%; FEV_1/FVC , 82.07%; and FEV_1/FVC predicted (%), 97.1%.

Diagnosis and treatment

The patient received 7 subcutaneous injections of dupilumab over 33 weeks for an unknown etiology. In the first 14 weeks, 300 mg of dupilumab was administered subcutaneously every 4 weeks and then changed to every 6 - 7 weeks for the next 19 weeks as symptoms improved. During the follow-up period of dupilumab treatment, skin prick tests (SPT) were performed on the suspected foods of *Ostrea gigas* Thun-

berg, scallops, soybeans, corn, whole grains, and raw/cooked peanuts based on the patient's parent-reported medical history and relative food diary, and all results were negative. Of these, *Ostrea gigas* Thunberg and scallops were previously thought to be most associated with disease onsets. After recommendation of avoidance of these two foods, the symptoms continued to occur, so the possibility of these food triggers was tentatively ruled out. At the patient's 7th follow-up visit on dupilumab treatment, SPT results were positive for *Morchella esculenta* (wheal diameter: 12 mm × 4 mm), *Russula vinosa* Lindblad (wheal diameter: 6 mm × 3 mm), and *Pleurotus eryngii* (wheal diameter: 4 mm × 3 mm), which were associated with the patient's attack. Notably, if the patient had just consumed these mushrooms without exercise before having several attacks, he never felt discomfort. The patient was advised to avoid these mushrooms and to discontinue the dupilumab treatment at the same time, and he has had no episodes of anaphylaxis. Based on the positive SPT results, the patient's history, and the good efficacy of avoiding mushrooms, the patient was diagnosed with FDEIA based on the positive SPT results, the patient's onset history, and the good efficacy of avoiding mushrooms^[5] and the mushroom was considered as the causative food.

Efficacy

During dupilumab treatments, the patient experienced 2 times of mild allergic reactions, including itchy skin, eyelid edema, or itching throat; meanwhile, he was exposed to the trigger of mushroom plus exercise at least twice a month, but no anaphylaxis recurred within this time and after stopping dupilumab and avoiding mushrooms (**Fig. 1**). With improved quality of life and no side effects, the patient returned to normal exercise (e.g., running 1 - 2 km and playing soccer).

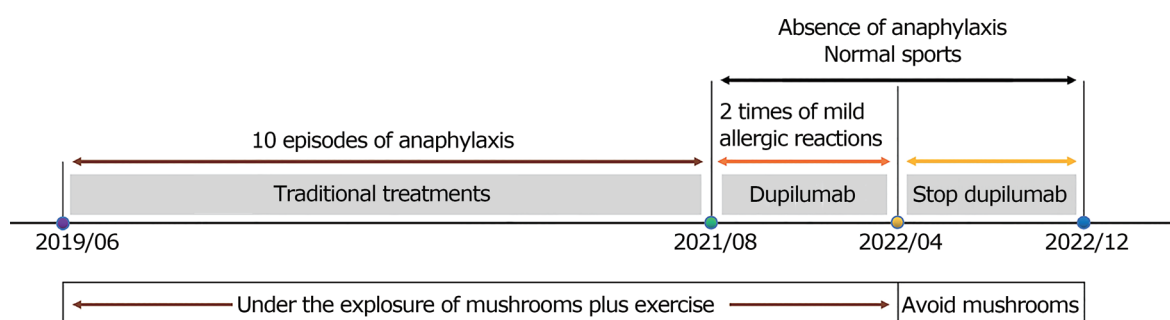


Figure 1. Changes in anaphylaxis following different treatments.

Total IgE and specific IgEs significantly decreased after dupilumab treatment (**Fig. 2**): total IgE, 197.0 kU/L; *Alternaria alternata*, 16.4 kUA/L; cat dander, 2.36 kUA/L; and *Dermatophagoides farinae*, 3.78 kUA/L. Asthma (ACT score: 23), allergic rhinitis (CSMS: 2.17), and conjunctivitis were well controlled.

The traditional treatments include Ventolin and budesonide formoterol powder for inhalation, cetirizine, fluticasone propionate nasal spray, and dust mite sublingual drops for allergen immunotherapy.

DISCUSSION

There are no uniform diagnostic criteria for FDEIA. A positive food-exercise challenge may confirm the diagnosis of FDEIA; however, a negative test does not exclude the diagnosis^[6] and the test may also trigger anaphylaxis^[7], which limits its application in clinical practice. In our current case, the fact that we did not conduct a food-exercise challenge was indeed a limitation. In fact, the patient refused to undergo this time-consuming test due to private time factors, so we were unable to obtain informed consent for this challenge test from the child and his parents. Fortunately, pre-allergic diet and exercise may provide diagnostic clues, and a positive SPT or/and serum sIgE for a specific food allergen that is highly correlated with medical history may aid in the diagnosis^[1,8]. The patient was eligible for a diagnosis of FDEIA based on

his positive SPT results, history of onset, and good efficacy of mushroom avoidance.

Wheat-dependent, exercise-induced anaphylaxis (WDEIA) is a special form of FDEIA. For 1,501 times of anaphylaxis caused by food, wheat was the most common cause, accounting for 37%^[9]. However, in our current case, the patient could tolerate both wheat plus exercise and wheat alone. Therefore, we did not test for ω -5 gliadin-specific IgE, an important indicator for the diagnosis of WDEIA.

In recent years, biological agents (e.g., omalizumab) have been widely used. As a specific IgE antibody, omalizumab has been used to treat allergic asthma and urticaria. However, the safety of treatment must be carefully considered in children with recurrent anaphylaxis. Studies have shown that dupilumab is associated with a lower risk of anaphylaxis when compared to omalizumab and allergen immunotherapy (AIT)^[10,11], and therefore dupilumab may be a more appropriate choice for this patient than omalizumab. In fact, in this case, there were no adverse reactions during dupilumab treatment, although the therapeutic safety needs to be validated in more cases.

The pathogenesis of FDEIA is not completely understood. One study^[12] summarized that exercise and other exacerbating factors could lower the tolerance threshold to allergens, increase the severity of allergic reactions, and reverse the acquired clinical tolerance, which might lead to anaphylaxis. We speculate that

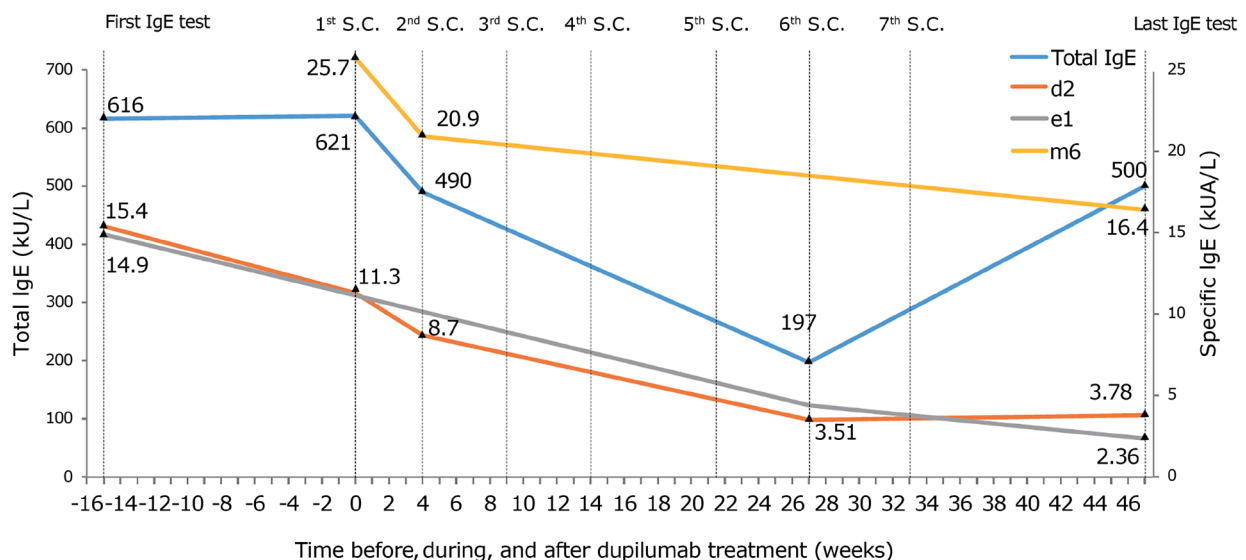


Figure 2. Changes in total IgE and specific IgE following dupilumab treatment.

d2: *Dermatophagoides farinae*; e1: cat dander; m6: *Alternaria alternata*; S.C.: subcutaneous injection.

the mechanism of dupilumab in the treatment of FDEIA may be due to its role in lowering IgE and blocking this allergic inflammatory pathway. A retrospective study showed a significant decrease in IgE between 4 and 32 weeks in atopic dermatitis patients treated with dupilumab^[13]. In addition, food allergens can stimulate the release of inflammatory mediators such as histamine and cytokines (e.g., IL-4 and IL-13) from mast cells and basophils, thus enhancing IL-4Rα chain signaling and leading to mast cell expansion, IgE-dependent mast cell and basophil activation, and ultimately anaphylaxis^[14]. Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complex. Therefore, dupilumab may reduce the symptoms of anaphylaxis by blocking the IL-4Rα signaling pathway.

There are no known therapies that can prevent anaphylaxis. Bruton's tyrosine kinase inhibitors may be an option in the future^[15]. Traditional treatments for anaphylaxis (including FDEIA) consist mainly of avoiding triggers and promptly administering epinephrine at the onset of symptoms^[1, 5]. However, strict avoidance of triggers is difficult, and the availability of adrenaline autoinjectors is limited^[16]. As the clinical role of dupilumab in treating anaphylaxis has not been reported, our current case may provide a novel research perspective on the treatment of food-induced IgE-mediated anaphylaxis with dupilumab. However, more evidence needs to be investigated in the future.

Patient consent

Informed consent was obtained from the patient's caregiver to publish this case report along with all accompanying visual elements.

Competing interests

The authors declare that they have no relevant conflicts of interest.

Authors' contributions

Li H conceived and designed the study. Zhu LP, Wang Q, and Tang R acquired, analyzed, and interpreted the data. Zhu LP, Li H, and Tang R drafted and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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病例报告

度普利尤单抗治疗食物依赖运动诱发严重过敏反应

朱丽萍[#]，汤蕊[#]，王青，李宏^{*}

中国医学科学院 北京协和医学院 北京协和医院变态（过敏）反应科，过敏性疾病精准诊疗
研究北京市重点实验室，国家免疫性疾病临床医学研究中心，北京 100730，中国

摘要

食物依赖运动诱发严重过敏反应（food-dependent, exercise-induced anaphylaxis, FDEIA）是一种潜在可威胁患者生命的过敏性疾病，常在进食可疑致敏食物数小时内运动时发作。该病极罕见，患病率约为 0.02%，目前尚无预防方法。现报告一例度普利尤单抗治疗 11 岁 FDEIA 患儿。该患儿在就诊前 2 年内发生了 10 余次不明原因的严重过敏反应，常规治疗后症状未获控制。后在我科行 7 次度普利尤单抗皮下注射治疗，为期 33 周。在第 7 次治疗时被诊断为菌菇引发的 FDEIA。度普利尤单抗治疗期间，患儿每月至少有 2 次在进食蘑菇数小时内进行运动，但未再发严重过敏反应。目前尚未见报告阐明度普利尤单抗治疗食物诱导的 IgE 型严重过敏反应的临床意义，尤其是对于 FDEIA 这种罕见疾病。因此，本病例或可为儿童严重过敏反应症状的控制和改善提供新的治疗思路。

关键词：食物依赖运动诱发严重过敏反应；食物过敏；蘑菇过敏；度普利尤单抗