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Dupilumab to induce tolerance to SLIT-Melocotón®

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Key words

Dupilumab; LTP-syndrome; food allergy; Pru p3; SLIT-melocotón®.

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Impact statement

Monoclonal antibodies switch is used as a tool to induce tolerance in SLIT. In case of multiple food allergy syndrome, off-label indication must be considered.

Summary

Food allergy is an increasing problem for population, and treatments inducing tolerance using sublingual immunotherapy is currently under study. Our aim as allergists is to achieve tolerance to sublingual allergen specific immunotherapy with sublingual immunotherapy (SLIT-peach). We present a case report consisting of a 40-year-old woman with anaphylactic reactions after eating fruit and other plant-foods due to sensitization to nonspecific lipid transfer proteins (nsLTP). Her diagnose was LTP-syndrome. This protein is the main pannallergen in our area and causes crossed reaction to multiple plant foods. The principal allergen in this syndrome is rPru p3, present in peach and most vegetables, fruits, nuts and grains. Serum specific IgE levels were performed using microarrays and positive for seven nsLTPs: rAra h9, rCor a8, nJug r3, rPru p3, rTri a 14, nArt v3 and rPla a3. Immediate reaction to SLIT in the fourth month of maintenance-dose led us to interrupt pru p3 immunotherapy. Immediate reaction to omalizumab in the fourth dose in hospital consisting in anaphylaxis prompted us to switch to dupilumab. After four months with this monoclonal antibody, we reintroduced sublingual immunotherapy with pru p3 SLIT-peach® achieving maintenance dose of four drops a day with no clinical reactions. SLIT-peach® in our patient is crucial for her due to her restricted diet, the severity of reactions and lack of quality of life measured by Europevall questionary. There are no cases reported for dupilumab in this use.

Introduction

Food allergy is an abnormal immune response as a result of genetic and epigenetic factors. Over the last years, prevalence has significantly increased (1). There are multiple causes of this rise of food allergy. The use of genetically-modified foods including hybrids resulting from the crossing of species, the strong rise of global trade, the cooking method (for example roasted in peanuts increase allergens (2) to the gastrointestinal mucosal immune system) and expansion of international cuisine in our modern society has led to a more complex diagnosis of food allergic reactions. Indeed, there are large geographical differences in the prevalence of food allergy and food sensitization in Europe (3).

Prevention and defining risk factors are the cornerstone of clinical trials. According to clinical presentations, there is a wide range of forms for food allergy. In our area – southern Europe – the peach nsLTP allergen Pru p 3 is a dominant sensitizing allergen and peaches are a common food trigger, although multiple foods can be involved (4). Symptoms can range from mild to severe, from oral pruritus (oral allergy syndrome) to anaphylactic shock, which is a severe and potentially life-threatening al-

lergic response. Current management of food allergy consists of removing the allergen from the diet. This still remains the gold standard approved in treatment by the US Food and drug administration (FDA), but an exclusion diet can become a nightmare. Food allergy patients must always carry rescue medication including epinephrine and use it in case of accidental exposure (5). This condition can cause a significant impact on quality of life for patients and their families, which may lead to social changes and nutritional deficiencies caused by the extensive dietary restrictions (6).

As allergists, immunotherapy is our *modus vivendi* to improve quality of life (7). There are currently no treatments approved by the FDA for food allergy. New advances in food immunotherapy have been developed, including allergen-specific treatments which can be administered in specialized centers (8) through various routes (oral, sublingual and subcutaneous). The lack of protocols and the time spent in active treatment, including human resources are well known in the allergy office. The new biologic therapies have been recently proposed either as monotherapy or as adjuvant therapy in food allergy-immunotherapy (9).

Dupilumab is a human monoclonal IgG4 antibody that specifically targets the alpha subunit of interleukin 4 receptor (IL-4R), thereby inhibits IL-4 and IL-13 signaling (cytokines produced by intestinal mast cells) and reduces type 2 inflammation involved in this type of IgE mediated reactions. It was firstly approved by the FDA (U.S. Food and Drug Administration) and later by the EMA (European Medicines Agency) for moderate to severe atopic dermatitis, severe asthma with type-2 inflammation and more recently for chronic rhinosinusitis with nasal polyposis (10). It is currently being investigated in clinical trials for food allergy and eosinophilic esophagitis (Phase 2 and 3, respectively) (11).

Case presentation

We report a case of a 40-year-old woman that first consulted for recurrent episodes of food-induced anaphylaxis (consisting in generalized urticaria, angioedema, dyspnea and hypotension). At least she experienced sympthoms of anaphylaxis seven times in one year. The first episode reported in our allergy office was in 2007. She recognized the ingestion of vegetable food as the cause (fruit: peaches, pineapple, kiwi, hazelnuts; veggies: tomato, lettuce; and legumes: lentils). She is also asked about cofactors due to a careful anamnesis taking; physical exercise, NSAIDs and emotional stress was present in most cases.

We performed an extensive allergy study in our patient in March 2019. We first carried out a Skin Prick Test (SPT) for common aeroallergens in our area and tropho-allergens. Our method to read skin prick test is to characterize the wheal size by its average diameter. The mean wheal diameter is considered positive for a measure of > 3 mm. The results obtained were positive for *Chenopodium, Salsola,* olive and mugwort pollen with no clinical expression at the current time; she referred neither asthma nor rhinitis. Food allergy tests were also performed. The commercial skin prick test used is from Roxall® Industry 0.1 mg/ml. The results were positive for hazelnut, peanut, walnut, sunflower seed, pistachio, tomato, corn, pepper, pear, strawberry, kiwi, banana, celery, cayenne, grains (wheat, rice, rye) and peach LTP. Also, Prick-by-prick tests were positive for soybean, lentils, carrot, sesame and grapes.

Allergen-specific IgE were determined using *in vitro* quantitative assay (microarray analysis-ISAC-112). Crossed reactivity markers showed the results for seven nonspecific lipid transfer protein (nsLTP). Results are measured in standard ISAC units (ISU): rAra h9 (peanut): 0.9 ISU, rCor a8 (hazelnut): 0.7 ISU, nJug r3 (walnut): 1.6 ISU, rPru p3 (peach): 1.9 ISU, rTri a 14 (wheat): 0.3 ISU, nArt v3 (*Artemisa*): 2.6 ISU and rPla a3 (*Platanus*): 1.8 ISU. There is no specie-specific sensitization for food allergens. Neither primary sensitization for aeroallergens is found.

Based on these findings, our patient was diagnosed with "LTP Syndrome" that manifested as recurrent anaphylactic reactions and recurrent urticarial due to multiple food ingestion (oFASS-5: Grade 5 severe reaction) according to the oFASS-5 Score (Food Allergy Severity Score). NSAIDs and exercise were tolerated without eating plant foods. She turned out to avoid those foods that she recognized as a trigger. She avoided nuts, kiwi, pear, peach, corn, soybean, wheat and corn. After the years, she started to avoid other foods that she recognized as triggers (her diet was restricted to egg, meat, chicken, eggplant and zucchini, she avoided all fruits because of recurrent generalized urticaria and also avoided grains such as wheat, corn, rice and soya).

Sublingual immunotherapy can prevent severe allergic reactions to LTP-containing foods. In October 2019, we prescribed sublingual immunotherapy with a Pru p 3-enriched peach extract (SLIT-peach 100% ALK) due to the patient's impaired quality of life (FAQLQ-AF of 161 points from a total of 174), the restricted diet and the severity of the anaphylactic reactions. Previous laboratory tests were carried out, obtaining the following results: total IgE 18.40 kUA/l, specific IgE for Pru p 3: 8.87 kUA/l, specific IgG4 for Pru p 3: 0.04 kUA/l, baseline serum tryptase 3 µg/l.

In spite of the good initial tolerance to the standard immunotherapy regimen, one week after achieving a maintenance dose of 4 drops daily at home, our patient experienced a generalized urticaria with outbreaks of gastroenteritis ten minutes after her daily dose, requiring urgent hospital treatment. No triggers such as food, exercise or non-steroidal anti-inflammatory drugs were involved.

In November 2019, we introduced omalizumab 150 mg every 4 weeks as compassionate treatment (adjusted by weight and

total IgE) to induce SLIT tolerance. We started subcutaneous inoculation of omalizumab each 4 weeks without SLIT in the hospital. One hour after her fourth dose of omalizumab she experienced generalized urticaria, bronchospasm and hypotension, requiring urgent treatment and hospital admission. Serum tryptase was performed one hour after the reaction, with the following result: 18 µg/l. Four weeks after this episode we proceeded in the Allergy office to skin prick test with omalizumab excipients with negative results.

In summary, we were facing a patient with recurrent anaphylaxis to multiple plant-based foods, with LTP-Syndrome and in the beginning cofactors were present. Due to the wide restricted diet, poor quality of life and failed tolerance to SLIT-peach® treatment (including systemic reaction to omalizumab) in December 2020 we started with subcutaneous dupilumab as compassionate use according to the established treatment regimen: an initial subcutaneous dose of 600 mg, following a maintenance dose of 300 mg every two weeks. Three months later (March 2021) and during treatment with dupilumab, we reintroduced oral immunotherapy (IOT) with SLIT-peach® showing good tolerability and achieving a maintenance dosing of four drops a day.

In September 2021, we once again measured total IgE 8.30 kUA/l, specific IgE for Pru p 3: 4.68 kUA/l and specific IgG4 for Pru p 3: 0.90 kUA/l. At that time, we decided to discontinue treatment with dupilumab since the patient did not present any further allergic reactions, and she has maintained a good tolerance to oral immunotherapy up until now. After one year with SLIT she can eat small amounts of tomato and lettuce that she previously didn't tolerate.

Conclusions

We report the case of a young woman patient with severe anaphylaxis due to the ingestion of multiple plant foods with failure treatment to oral immunotherapy (IOT) with SLIT-peach 100%. The use of biologics to induce tolerance to oral immunotherapy has been a tool strategy since anti-IgE is with us (12). There are multiple case reports of patients with food allergy (egg, milk, peanuts) and adjuvant treatment with omalizumab to induce tolerance to IOT. Results of reviews suggest that the use of omalizumab could potentially lead to safer and more efficient IOT protocols (13). Our patient had an immediate reaction with significant serum tryptase elevation compared to baseline-tryptase, after the fourth injection with omalizumab. Anaphylactic reactions to this and other biological treatments are described in several case reports (14). Indeed, within patients that have a history of anaphylactic reactions, women and young patients face a higher risk to have an anaphylactic reaction to omalizumab. These adverse effects are described in the omalizumab data sheet. In a recent review, dupilumab has the lowest rate of anaphylactic reactions (15). Our strategy was to switch to dupilumab, to induce tolerance to IOT.

Our clinical objective was to achieve IOT without adverse reactions. The use of dupilumab as an off-label therapy (16) is in our case a successful achieving IOT tolerance. So far, there are few reported cases in literature supporting evidence for the use of dupilumab as a potential treatment in food allergy (17). Thus, it would be necessary to continue developing lines of research on the use of biologics in food allergy, analyzing its efficacy and safety in this condition.

Fundings

None.

Contributions

MSZP: writing - original draft, writing - review & editing. YPP: data curation, formal analysis. SSRS: investigation, conceptualization. CNG: methodology, project administration. AIEP: resources, software. JCML: validation. ACM: supervision, visualization.

Conflict of interests

The authors declare that they have no conflict of interests.

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