

Dupilumab to induce tolerance to SLIT-Melocotón®

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Summary

Introduction: Food allergy is an increasing problem for population and treatments inducing tolerance using sublingual immunotherapy is currently under study. **Case presentation:** 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, LTP-syndrome. This protein is the main panallergen 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 questionnaire. **Conclusions:** in our case our aim is to achieve SLIT. We report a case of compassionate use with Dupilumab in a patient with multiple food allergy syndrome mediated by nsLTP. There are no cases reported for Dupilumab in this use.

Keywords: LTP-syndrome, panallergen, sublingual immunotherapy, induction, tolerance, r Prup3, dupilumab, omalizumab, food allergy, switch.

Impact statement: Monoclonal antibodies switch is used as a tool to induce tolerance in SLIT. We present a case report of a young woman with several anaphylactic reactions including to biological therapies. Off-label indication in case of multiple food allergy syndromes must be considered.

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 allergic 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 an allergist, 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 REPORT:

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). This happened to her seven times in one year, 2007 we reported the first time she came to the allergy office that year. She recognizes 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 in 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 results: 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) we started in December 2020 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 (16) therapy 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.

CONFLICT OF INTERESTS: All authors declare that they don't have any conflict of interests.

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REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014 Feb;133(2):291-307; quiz 308.
2. Vissers YM, Blanc F, Skov PS, et al. Effect Of heating and glycation on the allergenicity of 2S albumins (Ara h 2/6) from peanut. *PLoS One* 2011;6:e23998
3. Lyons SA, et al. Prevalence of Food Sensitization and Food Allergy in Children Across Europe. *J Allergy Clin Immunol Pract*. 2020 Sep;8(8):2736-2746.e9.
4. Skypala IJ, et al. European Academy of Allergy & Clinical Immunology (EAACI) Task Force: Non-specific Lipid Transfer Protein Allergy across Europe. The diagnosis and management of allergic reactions in patients

- sensitized to non-specific lipid transfer proteins. *Allergy*. 2021 Aug;76(8):2433-2446. doi: 10.1111/all.14797. Epub 2021 Mar 27. PMID: 33655502.
5. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez-Rivas M et al. World allergy organization anaphylaxis guidelines 2020. *WAO Journal* Oct; 13(10): 100472
 6. Sicherer SH, Noone SA, Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol*. 2001 Dec;87(6):461-4. doi: 10.1016/S1081-1206(10)62258-2. PMID: 11770692.
 7. González Pérez A, Carbonell Martínez A, Escudero Pastor AI, Navarro Garrido C, Miralles López JC. Pru p 3 oral immunotherapy efficacy, induced immunological changes and quality of life improvement in patients with LTP syndrome. *Clin Transl Allergy*. 2020 Jun 8;10:20. doi: 10.1186/s13601-020-00325-y. PMID: 32523680; PMCID: PMC7278159.
 8. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, Herbert M. Real-World Experience with Peanut Oral Immunotherapy: Lessons Learned From 270 Patients. *J Allergy Clin Immunol Pract*. 2019 Feb;7 (2):418-426.e4. Epub 2018 May 30.
 9. Fiocchi A, Vickery BP, Wood RA. The use of biologics in food allergy. *Clin Exp Allergy*. 2021 Aug;51(8):1006-1018. doi: 10.1111/cea.13897. Epub 2021 Jun 2. PMID: 33966304.
 10. Bachert C, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019 Nov 2;394(10209):1638-1650.
 11. Hirano I, et al. Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis. *Gastroenterology*. 2020 Jan;158(1):111-122.e10. doi: 10.1053/j.gastro.2019.09.042. Epub 2019 Oct 5. PMID: 31593702.
 12. Albuhairei S, Rachid R. Biologics and Novel Therapies for Food Allergy. *Immunol Allergy Clin North Am*. 2021 May;41 (2):271-283.

13. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management *J Allergy Clin Immunol*. 2018;141:41–58
14. Li L, Wang Z, Cui L, Xu Y, Guan K, Zhao B. Anaphylactic risk related to omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. *Clin Transl Allergy*. 2021 Jun 3;11
15. Sastre J, Dávila I. Dupilumab: A New Paradigm for the Treatment of Allergic Diseases. *J Investig Allergol Clin Immunol*. 2018 Jun; 28 (3):139-150. doi: 10.18176/jiaci.0254.
16. Muñoz-Bellido FJ, Moreno E, Dávila I. Dupilumab: A Review of Present Indications and Off-Label Uses. *J Investig Allergol Clin Immunol*. 2022 Apr 19;32(2):97-115.
17. Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. *J Allergy Clin Immunol Pract*. 2019 Feb;7(2):673-674.