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Case Report

A Case of Successful Dupilumab Treatment in Allergic Rhinitis and Atopic Dermatitis in Patient with Multiple Food Allergies, Pollen and Perennial Sensitization

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Abstract

Dupilumab is an interleukin 4 (IL-4) receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4αR subunit. Blockade of IL-4/13 is effective in reducing Th2-oriented response including the release of proinflammatory cytokines, chemokines, and IgE. These mechanisms are mediators in the pathogenesis of atopic dermatitis (AD), food allergy, allergic rhinitis (AR) with and without polyposis, and asthma. We report the clinical case of a patient in whom the Th2-mediated inflammatory substrate is evident in comorbid allergic manifestations and shows a good response after treatment with dupilumab for moderate AD.

Keywords: allergic rhinitis, atopic dermatitis, food allergies, dupilumab, asthma

Abbreviations: AD: atopic dermatitis, AR: allergic rhinitis, CRSwNP: chronic rhinosinusitis with nasal polyps, ILC2: innate lymphoid cell type 2, EASI: Eczema Area and Severity Index, BSA: body surface area, VAS: visual analogue scale, SNOT-22: Sino-Nasal Outcome Test-22, OAS: oral allergy syndrome, nsLTPs: non-specific lipid transfer proteins, ECLIA: electrochemiluminescence immunoassay, NSAIDs: non-steroidal anti-inflammatory drugs, FEV1: forced expiratory volume in 1 second, RQLQ(S): Standardized Rhinoconjunctivitis Quality of Life Questionnaire

1. Introduction

Dupilumab is an interleukin 4 (IL-4) receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4αR subunit. Blockade of IL-4/13 is effective in reducing Th2-oriented response including the release of proinflammatory cytokines, chemokines, and IgE [1, 2].

Thus, Th2 inflammation is found in around 60% of patients with severe asthma. Furthermore, most patients with allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) present Th2 inflammation. Moreover, in atopic dermatitis (AD), there is an intense inflammatory reaction with marked participation of Th2 cytokines.

The Th2 signaling pathway is also recognized to be involved in food allergy. In particular, innate lymphoid cell type 2 (ILC2) has been linked to food allergy pathogenesis in mice through the production of Th2-associated cytokines [3, 4].

These Th2-induced cytokines reprogrammed Tregs have diminished suppressive capacity and contribute to food allergy pathogenesis by producing IL-4 [5].

Moreover, in humans, mutations in the skin structural protein filaggrin, such as in AD, have been noted to confer risk for allergic diseases, including food allergy [6, 7].

In European countries, dupilumab has been approved to treat moderate-to-severe AD and severe asthma in patients aged 12 years or over where the disease is not adequately controlled by a combination of high-dose inhaled corticosteroids. Besides, dupilumab is also the first biologic to receive a license in the US and Europe to treat CRSwNP [8, 9].

We report the clinical case of a patient in whom the Th2-mediated inflammatory substrate is evident in comorbid allergic manifestations and shows a good response after treatment with dupilumab.

2. Case Report

Male patient 22 years, with a history of AD, applied to our clinic with complaints of severe generalized intractable pruritus. On physical examination, erythematous macules with lichenification due to AD were found on the volar surfaces of arms and legs, on the back, and the hands, worsening in the last two years when started working as a plumber. This clinical picture was already present in childhood and treated with topical corticosteroids.

His Eczema Area and Severity Index (EASI) score was 43. The affected body surface area (BSA) was 40%. Visual analogue scale (VAS) of pruritus was 60/100 mm.

Of his other allergic conditions, the patient mentioned rhinitis with seasonal exacerbations in March-June and contact dermatitis associated with costume jewelry and belt buckle contact area. The Sino-Nasal Outcome Test-22 (SNOT-22) questionnaire was 41 (0-110).

No asthma-related symptoms were reported. No family history of allergic diseases was detected.

Even considering the absence of symptoms suggestive of nasal polyposis, this manifestation was excluded by otorhinolaryngological evaluation. Also, the presence of allergic asthma was excluded by spirometry with broncho-reversibility test which showed respiratory parameters within the limits.

In addition, the patient showed oral allergy syndrome (OAS) with bananas and episodes of anaphylaxis like wheezing, diarrhea, and vomiting while eating fresh kiwi fruit. No adverse events with other foods including Rosaceae and tree nuts. During early childhood, for severe AD, he performed prick tests with positivity for casein, egg yolk, banana, and *Dermatophagoides spp*. Despite these results, no restricted diet was performed. No systemic adverse events were reported by the patient eating cow milk, bovine meat, and eggs.

Given the complex picture of polysensitization and the inability to perform prick tests because of AD manifestations on the harm surfaces, it was requested to perform total IgE assay by electrochemiluminescence immunoassay (ECLIA) and Allergy Explorer–ALEX2® (MacroArray Diagnostics, Vienna, Austria).

In the ALEX test, 300 allergens, including molecules and extracts, are spotted onto a nitrocellulose membrane in a cartridge chip, then incubated with 0.5 mL of a 1:5 serum dilution, containing a CCD inhibitor under agitation. We considered positive a concentration of ≥0.3 kUA/L.

The total IgE assay was >2500 U/mL. After evaluation with macroarray proteomics, the following reactivities were shown: food allergy driven by non-specific lipid transfer proteins (nsLTPs) sensitization and Act d 1 (cysteine protease) of kiwi-fruit and reactivity towards multiple pollen allergens such as cypress, olive tree, and grass pollens. Also, an important sensitization to several molecular allergens of *D. pteronyssinus* and *D. farinae* was detected, accounting for rhinitis symptoms. Because of anaphylaxis episodes, self-injectable epinephrine was prescribed. Moreover, the patient was recommended to avoid kiwi-fruit and cofactors such as alcohol, exercise, and non-steroidal anti-inflammatory drugs (NSAIDs) when eating previously tolerated vegetable foods, potentially nsLTPs sources.

The patient started therapy with an antihistamine (ebastine) and nasal corticosteroid spray (mometasone furoate) for rhinitis symptoms and cyclosporine 5 mg/kg/day (300 mg die) for AD. After three months of treatment, the patient had mild improvement of dermatitis but had to discontinue cyclosporine treatment due to the presence of hypertension and nausea. Rhinitis also improved, but the patient worsened during spring, probably due to poor control of seasonal allergies.

Therefore, dupilumab (anti-IL-4/IL-13 monoclonal antibody) was started (600 mg initial dose followed by 300 mg every 14 days). His intractable pruritus decreased within 4 weeks after the initiation of dupilumab treatment.

At the follow-up visit, after 3 months the EASI score decreased (from 43 to 15) and the patient also had an improvement in rhinitis symptoms such as rhinorrhea, sneezing, and coughing requiring less use of intranasal steroid therapy and antihistamines. SNOT-22 was 20. No systemic food-mediated adverse events were reported, requiring epinephrine auto-injector use.

Considering the improvement of skin lesions on the back, we programmed a patch test in order to investigate a possible allergic contact dermatitis mediated by metals or other working-related options, accounting for dermatological manifestations on the hands.

Despite the short follow-up and short duration of therapy, this case wants to underline the good response to dupilumab treatment in severe AD and comorbid type 2 inflammatory diseases like AR.

Its efficacy and approval are already known for asthma and nasal polyposis but new possible indications are increasingly explored in which Th2 inflammation is involved like AR.

3. Discussion

AD is the most common chronic inflammatory skin disease. It is often the first indicator of allergic diseases, and most patients present AR and/or asthma as comorbidity [10]. The blockade by dupilumab of

these key drivers of Th2-mediated inflammation could help in the treatment of AD and related diseases.

AR is a very common disorder that affects people of all ages. Classic symptoms include sneezing, rhinorrhea, and nasal obstruction. Allergic triggers may include airborne pollens, molds, dust mites, and pet epithelia. The management rests on symptomatic treatment with antihistamines, intranasal, or orally administered corticosteroids which are often unable to control symptoms [11].

Nettis et al. [12] evaluated the benefit of dupilumab after 16 weeks of treatment in perennial AR and perennial allergic asthma caused by indoor allergens in patients with severe AD. In adults with comorbid perennial AR, dupilumab was associated with significant improvements in disease control (measured using the Rhinitis Control Scoring System) and perennial AR quality of life.

Moreover, a post hoc analysis of the phase 3 Liberty Asthma Quest study evaluated the effects of dupilumab in patients with comorbid perennial AR. Dupilumab reduced severe asthma exacerbations and improved forced expiratory volume in 1 second (FEV1), treatment also numerically improved the 5-item Asthma Control Questionnaire and Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)).

Besides, dupilumab treatment with 200 mg or 300 mg every 2 weeks had improved RQLQ(S) + 12 sub score in 6 of 7 domains (activities, sleep, practical problems, nasal symptoms, eye symptoms, and emotions) [13].

Food allergies are characterized by Th2-driven inflammatory responses too. Allergen-induced IL-4 expression in peripheral mononuclear cells is associated with clinical allergy to milk and IgE-sensitization to milk and peanuts [14].

Moreover, patients with mutations in IL-4 receptor alpha (IL-4Rα) and IL-13 have an increased risk of food allergy [15].

A 30-year-old patient with a history of severe AD, AR, asthma, allergic reaction to pistachio during a food challenge, and anaphylaxis to corn, after initiating treatment with dupilumab, has come to tolerate these foods, confirmed by oral challenge after three months of therapy [16].

Currently, there are three randomized placebo-controlled phase 2 clinical trials that evaluate dupilumab treatment in peanut allergy [17–19].

4. Conclusion

Several studies have shown an important role of type 2 immunity in the immunopathology of AD and its comorbidities like asthma and nasal polyposis, but less on AR and food allergy.

Moreover, data on these conditions are from case reports or phase 2 studies which are ongoing.

In our case, despite the short follow-up and short duration of therapy, we want to underline the good response to dupilumab treatment in severe AD and comorbid type 2 inflammatory diseases like AR. Its efficacy and approval are already known for asthma and nasal polyposis but new possible indications are increasingly explored in which Th2 inflammation is involved.

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