Type 2 Inflammation: Atopic Dermatitis, Asthma, and Hypereosinophilia Successfully Treated With Dupilumab

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Increased understanding of the pathogenesis of type 2 inflammatory diseases affecting various tissues has resulted in significant therapeutic progress during recent years [1]. Dupilumab is a fully human monoclonal antibody that acts against the α-subunit of the interleukin (IL) 4 receptor, thereby inhibiting IL-4 and IL-13 signaling [2]. It has proven to be effective and safe for atopic dermatitis (AD) [3], asthma [4], and other type 2 immunologic signatures [1,2]. We report the case of a paradigmatic patient with AD, asthma, and hypereosinophilia that clearly illustrates the efficacy of IL-4/IL-13 blockade induced by dupilumab.

The patient was a 24-year-old man with severe and relapsing widespread AD since childhood. His personal history was remarkable for food allergy (fish, shellfish, crustaceans), sensitization to multiple seasonal and perennial allergens, allergic rhinitis, and moderate persistent asthma. Moreover, since 2015 he had been diagnosed with hypereosinophilia. His highest absolute eosinophil count (AEC) was 2140/μL, and his total IgE was persistently above 5000 kU/L. He also had generalized nonspecific lymphadenopathy, and histopathology revealed reactive lymphoid hyperplasia consistent with dermatopathic lymphadenopathy. A full blood-work up had already been performed and included bone marrow biopsy, which revealed eosinophilic hyperplasia without increased blasts, suggesting that hypereosinophilia was secondary to atopic status. Likewise, relevant genetic analysis ruled out Job syndrome. Skin biopsy revealed spongiotic dermatitis, thus confirming the clinical diagnosis of AD.

Previous therapies with courses of topical and systemic corticosteroids, topical calcineurin inhibitors, narrow-band ultraviolet B phototherapy, and methotrexate induced neither significant nor long-lasting improvement of AD. Oral cyclosporine (3 courses of 3-5 mg/kg/d for up to 6 months) achieved only transient remission of AD, with quick relapse upon discontinuation.

At the moment of the evaluation, the patient had generalized inflammatory eczema (online-only supplementary figure) despite receiving a 3-month course of cyclosporine (200 mg/d), along with topical corticosteroids and twice-daily emollients. He was taking rupatadine once daily, with up-dosing to 3 times daily during seasonal worsening of rhinitis; he was also using inhaled fluticasone-vilanterol 184/22 μg once daily for asthma. Given the lack of response to these treatments, dupilumab was administered at an initial dose of 600 mg followed by 300 mg every 2 weeks, and cyclosporine was tapered and then discontinued over 2 weeks.

Clinical and analytical outcomes are reported in the Table. The Eczema Area and Severity Index (EASI) score, which was 62.4 at baseline, dropped to 24.9 at week 4 and to 9 at week 24 after initiation of dupilumab. At week 32, patient-reported outcomes had markedly improved, as demonstrated by the Numeric Rating Scale (NRS) for pruritus (3 vs 6 at baseline) and sleep disturbance (0 vs 4 at baseline). Quality of life also improved (Dermatology Quality of Life Index [DLQI], 7; baseline, 18), enabling us to withdraw both topical corticosteroids and oral antihistamines. The EASI score remained stable at a value of 9 for up to 20 months of follow-up (online-only supplementary figure), except for a few disease flares that required short cycles of systemic corticosteroids.

While the patient was receiving dupilumab, his baseline forced expiratory volume in the first second (FEV1), which was 4030 mL (94% of predicted value [PV]) at week 16, diminished progressively, reaching a value of 560/μL, with no signs or symptoms of eosinophil-related internal organ involvement. Other than eosinophilia, no adverse effects were observed after 24 months.

Allergic diseases are characterized by systemic type 2 helper T cell (Th2)-driven inflammation with overproduction of cytokines such as IL-4 and IL-13, which, in the skin, modulate the epidermal barrier and inhibit antimicrobial peptide production [1]. Blocking these 2 cytokines with dupilumab impacts on the overall molecular signature of AD [5], thus improving the signs and symptoms of the disease. Clinical trials on dupilumab for AD report a change of approximately 65%-72% in the EASI score from baseline to week 16 [3]. In the case we report, the patient experienced a rapid 60% drop in his EASI score at week 4, reaching an 86% drop at week 24. Although the few flares recorded during treatment with dupilumab required short systemic corticosteroid cycles, the EASI score remained stable until the last observation at week 80. The improvement in the EASI...
In asthma, IL-4 plays a major role in regulating TH2-cell proliferation, TH2-related cytokine production, and IgE synthesis, whereas IL-13 plays a relevant role in inducing the clinical features of the disease, such as airway hyperresponsiveness, mucus production, and collagen deposition [2]. A phase 3 clinical trial reported a significant increase in FEV1 (340 mL, 9.4%) at week 12 of dupilumab as add-on therapy in patients with moderate-to-severe uncontrolled asthma [4]. Moreover, a recent study of dupilumab for patients with AD and comorbid asthma and rhinitis showed that while the increase in FEV1 was not statistically significant, the ACT and Asthma Control Questionnaire scores improved significantly [6]. In the case we report, FEV1 improved considerably at week 16, and this trend was maintained for up to 18 months of follow-up.

Regarding eosinophilia, dupilumab has been associated with transient increases in AEC, with no apparent clinical consequences in patients with AD [7] and asthma [4]. In the study of Wollenberg et al [7], patients with AD and baseline AEC >1500/μL experienced initial small increases in AEC, although these tended to revert to almost baseline levels, as seen in the case we report. In fact, blockade of IL-4 and IL-13 signaling by dupilumab prevents eosinophils from entering tissue, leading the cells to accumulate in the bloodstream [7]. Asthmatic patients are more likely to respond to dupilumab if baseline AEC is above 300/μL [4], while eosinophilia inversely correlates with an early response to dupilumab in AD patients [8].

In conclusion, inhibition of the IL-4/IL-13 axis by dupilumab should be regarded as a multisystemic effect. The case reported here can be considered a paradigm of type 2 inflammatory diseases and points to the efficacy of dupilumab in treating these disorders. Although dupilumab was mainly administered because of the severity of AD and proved to be “life-changing” by improving AD-related quality of life, dupilumab considerably impacted the whole clinical picture, which also included asthma, rhinitis, and hypereosinophilia, thus supporting the close clinical and pathophysiological links between these conditions.

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**Conflicts of Interest**

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Unsuccessful Desensitization to Paclitaxel in a Patient With High Basophil Sensitivity

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Immediate hypersensitivity reactions (HSRs) occur during the administration of taxanes in 10%-30% of patients and are severe in up to 10% [1]. Desensitization has proven to be safe and successful in most cases of HSR, enabling patients to be retreated with taxanes [2]. However, even during desensitization, HSRs can occur in 15% of treated patients regardless of the severity of the initial reaction or skin test results. Reactions during desensitization are severe in 13%, regardless of the initial reaction. Since measurement of specific IgE to taxanes is not commercially available [3], the basophil activation test (BAT) could prove useful for detecting IgE-mediated reactions. The BAT result was already shown to be a relevant biomarker of the outcome of rapid desensitization in allergy to platinum compounds [4]. Data on diagnostic testing for taxane allergy are scarce and often limited to case reports [1,3,5]. To the best of our knowledge, the utility of BAT in taxane allergy has not been fully evaluated. In food and insect venom, the allergic sensitivity of basophils can predict the severity and threshold of allergic reactions to allergens [6], although such experiences in drug allergies are limited [4,7]. We report a case of a highly positive BAT result to paclitaxel in a patient with severe HSR at very low concentrations of paclitaxel during initial treatment and an attempt at desensitization.

A 50-year-old woman with estrogen receptor–positive and HER2-positive breast cancer was treated with adjuvant trastuzumab, pertuzumab, and paclitaxel. The first two 3-weekly applications of both anti-HER-2 drugs were uneventful. During the first 5 minutes of the second weekly infusion of paclitaxel, the patient developed a grade 4 reaction with abdominal cramps, dyspnea, generalized erythema, hypotension (blood pressure, 70/40 mmHg), tachycardia (110 bpm), and reduction in peripheral oxygenation to 80%.

References


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