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 aeroallergens, 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 of 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 (FEV_1), which was 4030 mL (94% of predicted value [PV]), increased to 4310 mL (101% of PV) at week 16 and to 4680 mL (110% of PV) at week 48. At this point, we attempted to halve the dose of the inhaled corticosteroid (to fluticasone-vilanterol 92/22), although at 72 weeks we decided to double the dose again owing to the decrease in FEV_1 (to 4470, 106% of PV) and the relatively high reversibility of FEV_1. The baseline Asthma Control Test (ACT) score, which was 13, improved markedly to 24 at 48 weeks.

Serum total IgE levels were still elevated at the 20-month evaluation, while AEC, after increasing to 2880/µL 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 (T_H2)–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

Table. Baseline and Follow-up Assessment

	Baseline	4 Weeks	16 Weeks	32 Weeks	48 Weeks	64 Weeks	72 Weeks	80 Weeks
Atopic dermatitis								
Comment			A 3-wk course of prednisone was prescribed		A 3-wk course of triamcinolone/ chlorpheniramine was prescribed			
EASI	62.4	24.9	29.5	9	19	9	–	9
NRS pruritus	6	5	5	3	2	2	–	1
NRS sleep disturbance	4	2	2	0	0	0	–	0
DLQI	18	9	11	7	5	1	–	1
Asthma								
Comment					The dose of inhaled corticosteroid was halved		The dose of inhaled corticosteroid was doubled	
FEV_1, mL	4030 mL	–	4310	–	4680 mL	–	4470 mL	–
Percent of PV	94%	–	101%	–	110%	–	106%	–
FEV_1 reversibility in milliliters, %	410 mL, 10%	–		–		–	330 mL, 7%	–
ACT	13	–		–	24	–	25	–
Laboratory								
AEC, cells/μL	1230	2350	2880	1000	1220	1320	–	560
Total IgE, kU/L	>20 000	65 502	–	27 277	18 580	11 413	–	14 880

Abbreviations: ACT, asthma control test; AEC, absolute eosinophil count; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FEV_1, forced expiratory volume in the first second; NRS, Numeric Rating Scale.

score was paralleled by significant amelioration in patient-reported outcomes and quality of life.

In asthma, IL-4 plays a major role in regulating T_H2-cell proliferation, T_H2-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 FEV_1 (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 FEV_1 was not statistically significant, the ACT and Asthma Control Questionnaire scores improved significantly [6]. In the case we report, FEV_1 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

The authors declare that they have no conflicts of interest.

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