Type 2-driven Inflammation - Atopic Dermatitis, Asthma, and Hypereosinophilia - Successfully Treated with Dupilumab.

Benzecry V[1,2], Pravettoni V[3], Segatto G[1,3], Marzano AV[1,2*], Ferrucci S[2*]

[1]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

[2]UOC Dermatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]UO Medicina Generale, Immunologia e Allergologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[*]These authors contributed equally to this manuscript

Corresponding author

Valentina Benzecry

Via Pace 9, 20122 Milan, Italy

E-mail: valenbenzecry@gmail.com

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During the last years, a deeper understanding of the pathogenesis of type 2 inflammatory diseases affecting different tissues has resulted in significant therapeutic progress [1]. Dupilumab is a fully human monoclonal antibody directed against the α-subunit of the interleukin (IL) 4 receptor, thereby inhibiting the 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 herein report a paradigmatic patient with AD, asthma, and hypereosinophilia, that exceptionally illustrates the efficacy of the IL-4/IL-13 blockade induced by dupilumab.

Our patient was a 24-year old man who presented severe and relapsing widespread AD since childhood. 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 was diagnosed with hypereosinophilia and hyper-IgE, being his highest absolute eosinophil count (AEC) 2140 cells/ml and his total IgE persistently above 5000 kU/L. He also had generalized non-specific lymphadenopathy with histologic examination showing reactive lymphoid hyperplasia consistent with dermatopathic lymphadenopathy. Relevant haematologic workup had already been performed including bone marrow biopsy that reported eosinophilic hyperplasia without increased blasts, suggesting that hypereosinophilia was secondary to atopic status. Likewise, relevant genetic analysis ruled out Job Syndrome. Skin biopsy reporting spongiotic dermatitis confirmed the clinical diagnosis of AD.

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

At the moment of the evaluation, the patient was suberythrodermic (online-only supplementary figure) despite being under 3-month cyclosporine treatment (200 mg/day), along with topical corticosteroid and twice-daily emollients. He was taking rupatadine once-daily, with up-dosing to three times daily during seasonal worsening of rhinitis; he was also using inhaled fluticasone-vilanterol 184/22 mcg once-daily for asthma. Given the lack of response to the treatments mentioned above, dupilumab was administered at an initial dose of 600 mg followed by 300 mg every two weeks, tapering and then discontinuing cyclosporine over two weeks.

Clinical and analytical outcomes are reported in Table 1. Eczema Area and Severity Index (EASI) score that was 62.4 at baseline dropped to 24.9 at week 4 and to 9 at week 24 after dupilumab starting. At week 32, patient-reported outcomes markedly improved, as demonstrated by the Numeric Rating Scale (NRS) for pruritus (NRS= 3, baseline=6) and sleep disturbance (NRS=0, baseline 4), as well as, the quality of life (Dermatology Quality of Life Index (DLQI)=7, baseline=18), allowing to withdraw both topical corticosteroids and oral antihistamines. Albeit with few disease flares requiring short systemic corticosteroid cycles, EASI score remained stable at a value of 9 up to a period of 20-month follow-up (online-only supplementary figure).

Under dupilumab treatment, patient's baseline forced expiratory volume in the first second (FEV1), that was 4030 ml (94% of predicted value (PV)), increased to 4310 ml (101% of PV) at

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week 16, and to 4680 ml (110% of PV) at week 48. At this time point, we attempted to halve the dose of the inhaled corticosteroid (to fluticasone-vilanterol 92/22), but at 72 weeks we decided to double the dose again due to the decrease of FEV1 (to 4470, 106% of PV) and the relatively high FEV1 reversibility. Baseline Asthma Control Test (ACT) that was 13, markedly improved to 24 at 48 weeks.

Serum total IgE levels were still elevated at 20-month patient's evaluation, while AEC, after increasing up to 2880 cell/ml at week 16, progressively diminished reaching a value of 560 cell/ml, without 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 two cytokines by dupilumab impacts on the overall AD molecular signature [5], consequently improving signs and symptoms of the disease. Clinical trials on dupilumab for AD have documented roughly 65 to 72% change in the EASI score from baseline to week 16 [3]. Our patient showed a rapid 60% drop of EASI score at week 4, reaching an 86% drop at week 24. Although few flares occurred during dupilumab treatment requiring short systemic corticosteroid cycles, EASI score remained stable until the last observation at week 80 after dupilumab treatment. The EASI improvement was paralleled by significant amelioration in patient-reported outcomes and quality of life.

In asthma, IL-4 plays a major role in regulating Th2 cell proliferation and Th2-related cytokine production, as well as, IgE synthesis, while IL-13 has a relevant part 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

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ml, 9.4%) at week 12 of dupilumab as add-on therapy in patients with moderate to severe uncontrolled asthma [4]. Moreover, in a recent study of dupilumab for patients with AD and comorbid asthma and rhinitis, although FEV1 increase did not yield a significant increase as compared to baseline, Asthma Control Test and Asthma Control Questionnaire scores significantly improved [6]. In our patient, FEV1 considerably improved at week 16 and this trend was maintained up to 18-month follow-up.

Regarding eosinophilia, dupilumab has been associated with transient increases in AEC without 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 showed initial small increases in AEC, however with a trend to rapidly revert to levels close to baseline, as seen in our case. In fact, blockade of IL-4 and IL-13 signaling by dupilumab prevents eosinophils from entering tissue, thus the cells accumulate in the bloodstream [7]. Asthmatic patients are more likely to respond to dupilumab if baseline AEC are above 300 cell/ml [4], while eosinophilia inversely correlates to 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. Our patient can be considered a paradigm of the type-2 inflammatory diseases, and a witness of the efficacy of dupilumab in treating these disorders. Although we administered dupilumab mainly given the severity of AD and this therapy was “life-changing” by improving AD-related quality of life, dupilumab achieved a great impact on the patient’s whole clinical picture that included also asthma, rhinitis, and hypereosinophilia, supporting the close clinical and pathophysiological link among all these conditions.

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Conflict of interest

The authors certify that there is no conflict of interest regarding the material discussed in the manuscript.

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Table 1. 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 week course of prednisone was prescribed		A 3 week 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 steroid was halved		The dose of inhaled steroid was doubled	
FEV1 (ml)	4030 ml	/	4310	/	4680 ml	/	4470 ml	/
Percent of PV	94%	/	101%	/	110%	/	106%	/
FEV1 reversibility in milliliters (%)	410 ml (10%)	/		/		/	330 ml (7%)	/
ACT	13	/		/	24	/	25	/
Laboratory								
AEC (cells/ml)	1230	2350	2880	1000	1220	1320	/	560
Total IgE (kU/L)	>20.000	65.502	/	27.277	18.580	11.413	/	14.880

*EASI: Eczema Area and Severity Index, NRS: Numeric Rating Scale, DLQI: Dermatology Life Quality Index, FEV1: forced expiratory volume in the first second, ACT: asthma control test, , AEC: absolute eosinophil count.