Received: 2 February 2024 | Revised: 24 July 2024 | Accepted: 26 July 2024

DOI: 10.1111/pai.14215

CLINICAL LETTER

WILEY

Use of dupilumab for atopic dermatitis in pediatric and young adult patients with inborn errors of immunity

To the Editor,

Inborn errors of immunity (IEIs) are inherited disorders characterized by defects in both innate and adaptive immunity. More than 450 distinct defects are described in the 2022 classification of the International Union of Immunological Societies (IUIS).[1]

IEIs present with a variety of symptoms. The hallmark is recurrent and severe infections often treated with intravenous and/or prolonged antibiotic therapy. Patients with IEIs also commonly experience immune dysregulation manifestations such as autoimmune and inflammatory diseases, and increased susceptibility to cancer and atopy.[2] Among atopic manifestations dermatitis, asthma, and food allergies are the most frequently observed.

Atopic dermatitis (AD) in IEIs typically manifests with early onset, a recurrent or relapsing course, and a poor response to conventional medical therapy. Dermatitis is characterized by intense itching, dry skin, erythematous lesions, erosions, and exudation. In the chronic phase, lichenification may occur.

Preserving the integrity of the skin barrier is a key goal in AD therapy. The first-line treatment involves topical therapy such as emollients and corticosteroid anti-inflammatory drugs. Immunosuppressive medications are currently used for moderate to severe AD,[3] but they can increase the risk of iatrogenic immunodeficiency. Therefore, prolonged use of steroids is often contraindicated due to adverse events, alterations in the immune system, and an elevated risk of skin infections. Biologics, with their targeted action on specific components or pathways of the immune system, offer a significant advantage and are increasingly recognized as effective and safe treatments for various skin diseases.[4] Dupilumab is a chimeric monoclonal antibody that binds to IL-4Rα and decreases IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE. Dupilumab was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in children aged 6 years and older with moderate to severe AD who have inadequate control with topical therapies and since January 2023, the approval has been expanded to include children 6 months and older with severe AD.[5,6] To be eligible, they must present Eczema Area and Severity Index (EASI) ≥ 24 or one of the following: (1) location in visible and/or sensitive areas such as face/neck and/or hands and/or genitals; (2) evaluation of itching on the numeric rating scale itch intensity (NRS) ≥ 7 scale; (3) quality of life assessment with children's dermatology life quality index (cDLQI) index ≥10. The experience in immunocompromised patients with concomitant atopic manifestations is limited to single case reports.[4] Beneficial effects of dupilumab have been described in controlling severe and extensive AD in patients with STAT3 deficiency, ZNF341 AR deficiency, DOCK8 mutation, and CARD11-associated atopy with dominant interference of NF-kB signaling (CADINS) disease.

Here, we present six pediatric and young adult patients with IEIs and early onset, moderate to severe and unresponsive AD treated with dupilumab. The clinical and immunological features are summarized in Table 1.

All patients presented moderate to severe AD with a mean EASI score at baseline of 24.8 and failed topical therapy. Subcutaneous injections of dupilumab (Dupixent; Regeneron-Sanofi) were administered in the standard AD dosing regimen.

EASI, NRS, and cDLQI for *patients* aged 4–*16 years* or DLQI >16 years were recorded for each patient at baseline and at follow-up visits.

Peripheral blood samples to evaluate eosinophils and total IgE, serology, and PCR for Herpes virus 1/2, parasitological stool examination, and ophthalmological evaluation were performed before starting therapy and at follow-up visits. Hydrating eye drops were recommended to everyone. We reported a long follow-up visit at Week 24 in five out of six patients and at Week 52 in four out of six.

All patients presented moderate to severe AD with elevated Th2 biomarkers (blood eosinophils and/or IgE levels) except for patient 4. In patient 4, we observed high levels of IL-4 and IL-13 at proteomics assay (Olink technology, data not shown), performed in selected cases in order to integrate the cytokine profile with clinical data and strengthen the decision to treat with dupilumab.

Four out of six patients have an IEI genetically defined (Table 1). Patient 1 was diagnosed with ARPC1B deficiency, patients 2 and 6 with STAT3 deficiency, and patient 3 with a novel monogenic cause of early onset atopic disease due to STAT6 gain-of-function (GoF) mutation. Patients 4 and 5 have a common variable immunodeficiency (CVID) phenotype and a hyper IgE syndrome (HIES) respectively, with a next-generation sequencing (NGS) panel not informative. In particular, patient 5 presented severe refractory AD associated with food allergies, recurrent respiratory infections, severe asthma, and IgA nephropathy. His immunological phenotype is summarized in

TABLE 1 Clinical and immunological findings, genetic mutation, and therapeutic regimen.

		Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
Clinical phenotype	Sex	F	F	F	F	M	F
	Age (years)	10	11	23	21	17	13
	Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
	AD comorbidity	Food and inhalant allergies	Food and inhalant allergies	Food, inhalant, drug allergies	Food allergies	Food and inhalant allergies	Recurrent pneumonia
					Allergic Rhinitis		Severe fungal infections
			Recurrent otitis	Asthma	Asthma	Asthma	Cold abscesses
		RRIs	RRIs	RRIs	RRIs	RRIs	
		Hartnup disease				IgA Nefropathy (Berger Disease)	
		IBD like				Hashimoto's Thyroiditis	
		HPV epidermodysplasia verruciformis					
	AD onset (months)	1	1	2	2	2	2
Therapy	Conventional treatment	Topic therapy	Topic therapy	Topic therapy	Topic therapy	Topic therapy	Topic therapy
		Oral Steroid	Oral Steroid	Oral Steroid	Oral Steroid	Oral Steroid	Oral Antistaminics
		Oral Antistaminics	Oral Antistaminics	Oral Antistaminics	Oral Antistaminics	Oral Antistaminics	
		Cyclosporine				Cyclosporine	
	Other therapy	IVIG	IVIG	-	IVIG	Omalizumab	IVIG
		Anakinra			SCIg	IgE Immunoapheresis	SCIg
		Rituximab					
		Dupilumab					
		Everolimus					
		HSCT at 12 yo					
	AD current therapy	-	Dupilumab	Dupilumab	Dupilumab	Dupilumab	Dupilumab
Genetic mutation	NGS panel for IEI	ARPC1B	LoF	GoF	NGS panel for IEIs not informative	NGS panel for IEIs not informative	LoF
			STAT3	STAT6			STAT3
Immunological phenotype	IgE highest value (kU/L)						
		56.200 at 7 yo	38.227 at 9 yo	12.000 at 8 yo	<2 at 20 yo	32.170 at 11 yo	12.006 at 11 yo
	IgG (g/L)	8.43 at 7 yo	10.74 at 6,5 yo	7.93 at 21 yo	3.19 at 14 yo	6.39 at 14 yo	10.59 at 3 yo
		[6.33-10.16]	[6.33-10.16]	[6.04-19.09]	[6.04-19.09]	[6.04-19.09]	[4.62-17.10]
	IgM (g/L)	27 at 7 yo	1.16 at 6,5 yo	1.7 at 21 yo	4.5 at 14 yo	0.25 at 14 yo	1.67 at 3 yo
		[0.56-2.61]	[0.56-2.61]	[0.59-2.97]	[0.59-2.97]	[0.59-2.97]	[0.62-2.57]
	IgA (g/L)	14.26 at 7 yo	1.27 at 6.5 yo	0.76 at 21 yo	<5 at 14 yo	3.82 at 14 yo	1.98 at 3 yo
		[0.41-3.15]	[0.41-3.15]	[0.61-3.01]	[0.61-3.01]	[0.61-3.01]	[0.27-1.73]
	WBC (10^3/μL)	6.51	4.49	6.45	5.53	6.75	5.08
	Lymphocytes (10^3/μL)	0.89	1.63	1.99	1.08	1.73	1.76
		[1.71-3.06]	[1.71-3.06]	[1.37-3.47]	[1.37-3.47]	[1.37-3.47]	[1.71-3.06]
	Eosinophils (10^3/μL)	0.42	0.28	1.02	0.38	0.4	0.3

TABLE 1 (Continued)

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
Lymphocyte subpopulations						
CD3+ (10^3/μL)	0.509	1.31	1.71	0.88	1.3	1.34
	[1.07-2.27]	[1.07-2.27]	[1.09-2.6]	[1.09-2.6]	[1.09-2.6]	[1.07-2.27]
CD4+ (10^3/μL)	0.336	0.692	1.01	0.44	0.82	0.86
	[0.64-1.29]	[0.64-1.29]	[0.56-1.45]	[0.56-1.45]	[0.56-1.45]	[0.64-1.29]
CD8+ (10^3/μL)	0.139	0.252	0.52	0.38	0.34	0.38
	[0.38-0.88]	[0.38-0.88]	[0.32-0.96]	[0.32-0.96]	[0.32-0.96]	[0.38-0.88]
CD19+ (10^3/μL)	0.308	0.22	0.12	0.16	0.38	0.32
	[0.17-0.63]	[0.17-0.63]	[0.14-0.56]	[0.14-0.56]	[0.14-0.56]	[0.17-0.63]
CD16+CD56+(10^3/μL)	0.056	0.081	0.13	0.03	0.03	0.07
	[0.17-0.53]	[0.17-0.53]	[0.15-0.7]	[0.15-0.7]	[0.15-0.7]	[0.17-0.53]
T helper 17[a]	1.8	0.55	1.1		1.42	0.10
CD3+CD4+CD17+ (%)	0.5–1	0.5–1	0.5–1		0.5–1	0.5–1
CD4+CD45RA+ (%)	2.6	28.1	20.4	19	31.8	30
	[25–63]	[25–63]	[31–57]	[31–57]	[31–57]	[25–63]
CD4+CD45RO+ (%)	35.2	14.4	30.7	22.3	15.8	19.3
	[11–25]	[11–25]	[10–27]	[10–27]	[10–27]	[11–25]
CD8+CD45RA+ (%)	5.2	14.1	19.1	25.8	16.8	14
	[22–58]	[22–58]	[18–61]	[18–61]	[18–61]	[22–58]
CD8+CD45RO+ (%)	10.5	1.4	7.2	10	2.8	7.6
	[2–15]	[2–15]	[3–12]	[3–12]	[3–12]	[2–15]
B phenotype						
Transitional	34.50	10.60	2.50	15.40	17.00	5.20
CD19+ CD38++ IgM++ (%)	[8–21]	[8–21]	[5–15]	[5–15]	[5–15]	[8–21]
Mature	36.60	79.30	62.90	57.30	75.80	86.80
CD27-IgM+IgD+ (%)	[64–84]	[64–84]	[65–88]	[65–88]	[65–88]	[64–84]
Memory	1.80	8.80	26.3 (67% IgM)	27.8 (96% IgM)	4.8 (71% IgM)	5.5 (22% IgM)
CD19+ CD27+ (%)	[6–16]	[6–16]	[4–16]	[4–16]	[4–16]	[6–16]
Plasmablasts	13.40	1.60	8.80	0.10	2.50	2.50
CD27+IgM-CD24-CD38+ (%)	[2–11]	[2–11]	[4–15]	[4–15]	[4–15]	[2–11]
T cell proliferation (PHA and OKT3)	Normal	Normal	Normal	Normal	Altered	Normal

Note: Normal range values reference: Garcia-Prat M, et al.[10]

Abbreviations: AD, atopic dermatitis; GoF, gain of function; IBD, inflammatory bowel disease; IEIs, inborn errors of immunity; IgG*, value of IgG after the start of IVIG; IVIG, intravenous immunoglobulin, LoF, loss of function; RRIa, recurrent respiratory infections; WBC, white blood cell; YO, years old.

[a]Frequency of T helper type 17 (Th17) lymphocytes in peripheral blood mononuclear cells. PBMCs from patients were stimulated for 18 h with phorbol myristate acetate (PMA) and calcium ionomycin and the frequency of interleukin (IL)-17 and interferon (IFN)-g-producing CD4 memory T cells were determined by flow cytometry. Normal range values reference: Horvath R, et al.[11]

Table 1. Furthermore, reduced DOCK8 expression was observed on flow cytometry and western blot analysis in CD19+ cells, but not in CD3+ lymphocytes. DOCK8 variants were not detected by NGS panel and a whole-genome sequencing (WGS) analysis is currently ongoing.

We observed a significant clinical improvement in all our patients, already at week 4 follow-up, with a mean change of 10.4 points for EASI, 7 for DLQI, and 5.1 for NRS. We recorded a 50% EASI (EASI-50) improvement at week 16 in 6/6 patients and 75% (EASI-75) at week 24 in 4/5 patients. The NRS score showed a 50% reduction in four out of six patients at Week 4, and cDLQI/DLQI scores decreased by 50% in three out of six patients at Week 4 and in all patients at Week 16 (Figure 1). The drug impacted AD symptom severity with a persistent improvement at subsequent follow-up visits. Patient 4 showed a marked cutaneous improvement until Week 16 and after an upper respiratory tract infection experienced a skin worsening. At Week 16, the levels of IgE exhibited a 50% reduction in 3 out of 6 patients, whereas we did not report significant variations in absolute eosinophil count except in patient 3 that experienced a transient increase (Figure 1). Compared to data from randomized clinical trials in children and adolescents with AD and without immunodeficiency, the impact of the drug on itch reduction seems to be similar while the improvement in severity appears faster in immunocompetent patients with the achievement of EASI-75 at Week 16.[7,8] This may be due to a marked Th2 imbalance in our cases and to other involved immunological pathways not restored by the drug.

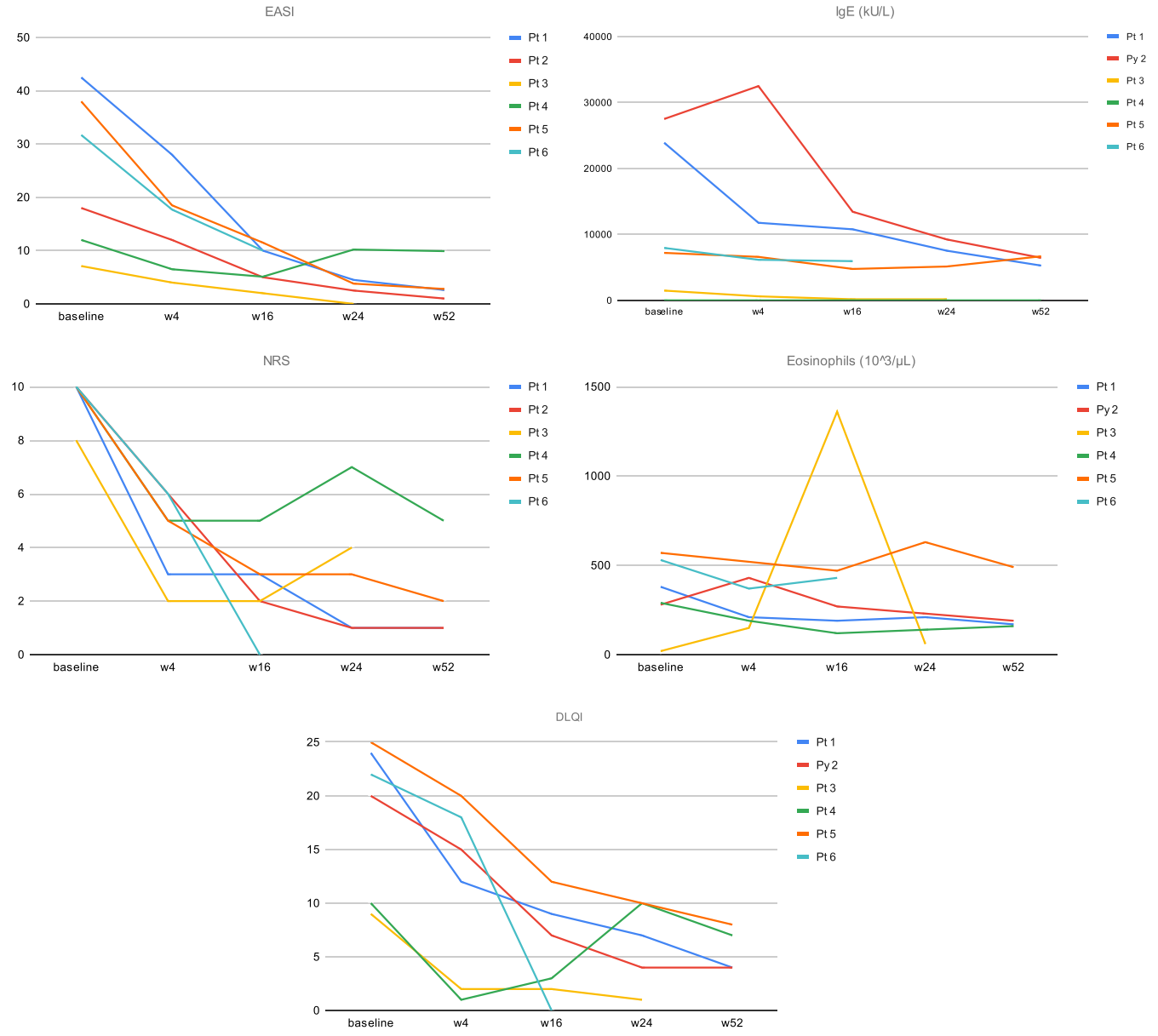

FIGURE 1 Clinical parameters assessing AD severity Eczema Area and Severity Index (EASI) score, Numerical Rating Scale (NRS), and Dermatology Life Quality Index (DLQI) before and after treatment with dupilumab. Th2 biomarkers include Immunoglobulin E (IgE) and absolute eosinophil count (AEC).

No serious adverse effects (AEs) have been reported in clinical trials. The most reported side effect in clinical trials, which has also been confirmed in real-life data, is blepharoconjunctivitis.[8]

In our cohort, dupilumab has been generally well tolerated, except for some mild adverse events. Patient 3, with a history of multiple drug allergies, developed a mild immediate adverse event after the first and second injections of dupilumab. The AE was characterized by moderate respiratory distress and conjunctivitis, which were successfully treated with antihistamines and steroids, resulting in rapid resolution. For this reason, the treatment was initially discontinued, despite an improvement of dermatitis and a reduction of asthma flares. Since the encouraging clinical response, she restarted the treatment after steroid and antihistamine premedication without any new AEs. Patient 5 presented mild conjunctivitis 3 months after starting dupilumab with a temporary drug discontinuation, resolved in 4 weeks.

As extensively reported, dupilumab reduces the incidence of skin infections.[9] This reduction is attributed to the improvement of skin integrity by decreasing scratching, as well as changes in the cutaneous microbiome and increasing production of antimicrobial peptides triggered by IL-4 blockade, which is a key component of the innate immune system. In our cohort, patient 1 presented two skin abscesses at Week 48 which were successfully treated with systemic antibiotics, and developed new cutaneous warts at Week 52. This patient had a history of recurrent and persistent HPV warts. However, no further lesions appeared in subsequent follow-up visits despite the ongoing therapy. These skin infections were attributed to the concomitant immunosuppressive drug administered for immune dysregulation manifestations.

Overall, in our cohort dupilumab has been proven to be effective and safe to treat AD in IEI patients although it does not constitute a definitive therapy for the immunodeficiency. As reported, patient 1 started treatment with dupilumab due to severe refractory AD complicated by recurrent skin infections at 10 years of age. Dupilumab significantly improved both skin rash and itchiness but did not impact on the patient's comorbidities as expected. Considering the combined immunodeficiency, recurrent infections, thrombocytopenia, and multiple manifestations of immune dysregulation, including colitis, vasculitis, and severe dermatitis, associated with eosinophilia, hyper-IgA, and hyper-IgE patient 1 performed hematopoietic stem cell transplantation (HSCT) at 12 years. HSCT led to the successful resolution of immunodeficiency, immunodisysregulation, and autoimmunity and the interruption of immunomodulatory drugs including dupilumab. Thus, dupilumab represents a valid bridge treatment in patients waiting for HSCT, in order to control skin infectious and inflammatory complications. Our patients didn't experience severe AEs but, considering comorbidities and the immunocompromised status, a close and careful clinical monitoring is needed.

To date, a comprehensive molecular and immunological characterization of AD under long-term IL-4Rα inhibition has not been conducted. This information could be useful for therapeutic decisions and to guide potential tapering strategies in patients receiving dupilumab.

Further and larger multicenter studies are needed to evaluate long-term safety and efficacy in this special population.

KEYWORDS

atopic dermatitis, biologics, dupilumab, inborn errors of immunity

AUTHOR CONTRIBUTIONS

Paola Zangari: Conceptualization; writing – original draft; writing – review and editing; investigation; data curation; resources. **Carmela Giancotta:** Conceptualization; writing – original draft; writing – review and editing; resources; data curation. **Lucia Pacillo:** Writing – review and editing; data curation; resources. **Nicole Colantoni:** Data curation; writing – review and editing. **Fabrizio Leone:** Data curation; resources. **Donato Amodio:** Data curation; methodology; investigation; resources; writing – review and editing. **Veronica Santilli:** Data curation; resources. **Emma Concetta Manno:** Data curation; writing – review and editing; resources. **Nicola Cotugno:** Data curation; resources. **Beatrice Rivalta:** Data curation; resources. **Gioacchino Andrea Rotulo:** Data curation; resources. **Silvia Di Cesare:** Investigation; methodology. **Andrea Diociaiuti:** Data curation; resources. **May El Hachem:** Data curation; resources. **Caterina Cancrini:** Data curation; writing – review and editing. **Andrea Finocchi:** Data curation; writing – review and editing. **Paolo Palma:** Supervision; writing – review and editing.

ACKNOWLEDGMENTS

This work was supported also by the Italian Ministry of Health with Current Research funds.

FUNDING INFORMATION

Ministero della Salute.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICAL APPROVAL

All patients or caregivers gave their informed consent prior to their inclusion in the study.

Paola Zangari[1]
Carmela Giancotta[1]
Lucia Pacillo[1]
Nicole Colantoni[2]
Fabrizio Leone[2]
Donato Amodio[1,2]
Veronica Santilli[1]
Emma Concetta Manno[1]
Nicola Cotugno[1,2]
Beatrice Rivalta[1]
Gioacchino Andrea Rotulo[1]
Silvia Di Cesare[2]
Andrea Diociaiuti[3]
May El Hachem[3]
Caterina Cancrini[1,2]

Andrea Finocchi[1,2]
Paolo Palma[1,2]

[1]*Clinical and Research Unit of Clinical Immunology and Vaccinology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[2]*Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy*
[3]*Dermatology Unit and Genodermatosis Unit, Genetics and Rare Diseases Research Division, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*

Correspondence
Paola Zangari, Clinical and Research Unit of Clinical Immunology and Vaccinology, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, Rome 400165, Italy.
Email: paola.zangari@opbg.net

Editor: Fabio Candotti

ORCID

Paola Zangari https://orcid.org/0000-0003-0892-6222
Lucia Pacillo https://orcid.org/0000-0002-7950-8848
Donato Amodio https://orcid.org/0000-0003-4550-3018
Paolo Palma https://orcid.org/0000-0002-3066-4719

REFERENCES

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. *J Clin Immunol*. 2022;42:1-35.
2. Vaseghi-Shanjani M, Smith KL, Sara RJ, et al. Inborn errors of immunity manifesting as atopic disorders. *J Allergy Clin Immunol*. 2021;148:1130-1139.
3. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. *Nat Rev Drug Discov*. 2022;21:21-40.
4. Giancotta C, Colantoni N, Pacillo L, et al. Tailored treatments in inborn errors of immunity associated with atopy (IEIs-A) with skin involvement. *Front Pediatr*. 2023;11:1129249.
5. European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR. Last updated: 23/03/2023. Available from: https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf.
6. Food and Drug Administration (FDA). FDA website. 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s042lbl.pdf
7. Paller AS, Simpson EL, Siegfried EC, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2022;400:908-919.
8. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156:44-56.
9. Blauvelt A, Wollenberg A, Eichenfield LF, et al. No increased risk of overall infection in adults with moderate-to-severe atopic dermatitis treated for up to 4 years with dupilumab. *Adv Ther*. 2023;40:367-380.
10. Garcia-Prat M, Álvarez-Sierra D, Aguiló-Cucurull A, et al. Extended immunophenotyping reference values in a healthy pediatric population. *Cytometry Part B: Clinical Cytometry*. 2019;96(3):223-233.
11. Horvath R, Rožková D, Lašťovička J, et al. Expansion of T helper type 17 lymphocytes in patients with chronic granulomatous disease. *Clinical & Experimental Immunology*. 2011;166(1):26-33.