



Peeling Skin Syndrome Type 1: Dupilumab Reduces IgE, But Not Skin Anomalies

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To the editor,

Peeling skin syndrome type 1 (PSS1) (OMIM #270,300) is a very rare autosomal-recessive genetic disease due to loss-of-function mutations in *CDSN* which encodes corneodesmosin [1], an adhesive protein specific to corneodesmosomes, the adhesive junctions of the stratum corneum. Patients present with continuous superficial peeling and inflammatory skin. Associated findings include severe refractory pruritus, skin infections, growth delay in infancy, and atopic manifestations (food allergy, urticaria, asthma). Quality of life (QOL) is often impaired and there is no effective therapy. Emollients are commonly used but are of limited efficacy.

Patients with PSS1 exhibit stratum corneum barrier defects that allow the entry of allergens and infectious agents and a subsequent inflammatory response with similar features to atopic dermatitis (AD). Total immunoglobulin E (IgE) are increased in patients with PSS1 [1]. Histologically, the epidermis presents with psoriasiform acanthosis and a slight-to-moderate infiltrate of immune cells in the upper dermis. A previous study showed overlaps in the anomalies of keratinization between AD and PSS1 [2]. More specifically, an increased expression of type-2 (Th2) cytokines was shown in the skin of a PSS1 patient [3]. A detailed analysis

of a mouse model of PSS1 identified a Th2/Th17 response (first Th2, then counterbalanced by Th17) [4].

Dupilumab is a therapeutic monoclonal antibody directed against the common chain of IL-4 and IL-13 receptors and, therefore, is a potent inhibitor of type 2 immune responses and of IgE production. Dupilumab has demonstrated great efficacy and a satisfactory safety profile in patients with atopic dermatitis. It is now approved for adults and adolescents with moderate to severe atopic dermatitis requiring systemic therapy. Based on clinical and pathophysiological similarities, dupilumab may be a useful treatment for PSS1. We report the effects of dupilumab in an affected adolescent female.

The proband was a 17-year-old girl (height and weight less than 3rd percentile), suffering from a severe form of PSS1 [1]. She presented with severe erythroderma, continuous peeling (Fig. 1a), pruritus, loss of sleep, absence of schooling, and impaired QOL. She had no allergic manifestations, such as oral syndrome, urticaria, flushing, abdominal pain, vomiting, cough, bronchospasm, or systemic anaphylaxis. She presented with a very high blood concentration of total IgE (17.496 kUI/L). Pre-treatment peripheral blood eosinophil count was $0.5 \times 10^9/L$. Unfortunately, this was not re-assessed over the course of therapy.

Due to eating disorder and growth delay in infancy (height and weight less than 10th and 3rd percentile, respectively), she had received growth hormone for 8 years and she was fed by a gastrostomy since the age of 8 months. In addition to food for gastrostomy tube feeding (Nutrison®), she had cow's milk, fish, eggs, almonds, and soy.

She currently uses emollients. She has received systemic therapies with acitretin or alitretinoin in the past that were ineffective. She was started on subcutaneously administered dupilumab with 400 mg loading dose followed 200 mg by every 2 weeks. This therapy was provided for a period of 5 months. Eye lubricants were used to avoid conjunctivitis reported in AD patients on dupilumab.

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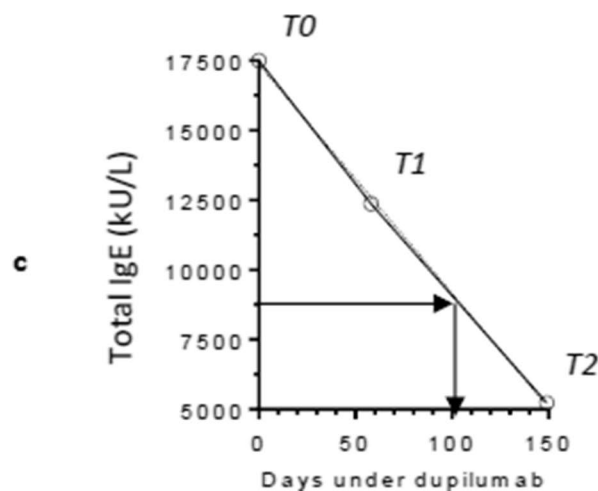
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Fig. 1 a–b Comparative photographs of the patient's skin lesions, taken at the start of dupilumab: **(a)** T0) severe erythroderma and continuous peeling, and at T2 (T0 + 150 days); **(b)** reduced erythroderma. IqoL-32, specific ichthyosis quality of life questionnaire; QOL, quality of life; VAS, visual analogic scale. **c** Effect of dupilumab therapy on total IgE concentrations. Serum samples were drawn at T0 (first dupilumab injection), T1 (58 days after T0), and T2 (150 days after T0). Arrows indicate a decrease by half of total IgE from concentration at T0. IgE levels (ISU-E) were compared between T1 and T2 by using Wilcoxon matched-pairs signed ranks test. *** $p < 0.001$; ** $p < 0.01$



	T0		T2
Erythroderma 0-10 (VAS)	8	Erythroderma 0-10 (VAS)	4
Peeling 0-10 (VAS)	8	Peeling 0-10 (VAS)	8
Pruritus 0-10 (VAS)	10	Pruritus 0-10 (VAS)	9
Pain 0-10 (VAS)	10	Pain 0-10 (VAS)	8
QOL: IqoL-32 0-128	121	QOL: IqoL-32 0-128	124



The patient was evaluated at T0 (dupilumab initiation), T1 (T0 + 58 days), and T2 (T0 + 150 days). At both T1 and T2, erythroderma was reduced but there was no improvement in the other clinical parameters (peeling, pruritus,

pain, and QOL) (assessed with the specific ichthyosis QOL questionnaire IqoL-32) (Fig. 1b). No side effects (including eye anomalies) were reported.

We studied the effect of dupilumab on IgE sensitization (Fig. 1c).

Total IgE concentrations were measured at T0, T1, and T2. At T2, total IgE had decreased by 69% from the initial level at T0, which corresponds to a required time of 100 days for total IgE to decrease by half.

This is the first case of PSS1 treated with dupilumab. In the field of genetic disease with hyperIgE, two patients with autosomal-dominant hyper-IgE syndrome (AD-HIES) due to STAT3 dominant-negative mutations have received dupilumab that was effective and induced a similar reduction of IgE levels [5]. In the literature, 7 cases of Netherton syndrome (NS) have received dupilumab with an improvement of clinical symptoms. There is an ongoing clinical trial (NCT04244006). More recently, two children with a genetic diagnosis of DOCK8 deficiency were treated with dupilumab for their severe dermatitis resulting in a marked improvement of the cutaneous manifestations and pruritus (Ollech A, Mashiah J, Lev A, Simon AJ, Somech R, Adam E, et al. Treatment options for DOCK8 deficiency-related severe dermatitis. *J Dermatol.* sept 2021;48(9):1386-93).

In this PSS1 patient, the decrease in circulating IgE concentration was significant and indicates that the IL-4/13-dependent Th2 pathway was effectively impaired by dupilumab. Despite this impairment, and contrary to other HIES and NS patients, only a modest improvement in skin lesions was observed. Therefore, targeting of the amplified Th2 pathway is not sufficient to reduce symptoms in PSS1 and may suggest counterregulatory mechanisms. Further studies could help to identify other effective targeted therapies.

Availability of Data, Code, and Materials *IgE measurements and data analysis.* Total IgE measurements were performed with ImmunoCAP™ Phadia 250 system (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden), in compliance with ISO 15189 standards.

Multiplex determination of sIgE levels was performed with intact and IgG-depleted serum, using ImmunoCAP™ ISAC i112e IgE (Thermo Fisher). IgG removal from serum samples was obtained by three rounds of absorption cycles using protein G microcolumns (Thermo Fisher). Raw fluorescence data were acquired by a laser scanner (LuxScan 10 K, Capital-Bio, Beijing, China) and were converted into ISU-E (ISAC Standardized Units for IgE) using Microarray Image Analyzer software (Thermo Fisher).

Statistical analysis. IgE values measured at T1 (T0 (dupilumab initiation) + 58 days) and T2 (T0 + 150 days) were compared by using the Wilcoxon matched-pairs signed ranks test (PRISM, GraphPad Software, La Jolla, CA, USA).

Declarations

Ethics Approval Not applicable.

Consent to Participate Informed consent to participate was obtained from the patient, in accordance with current French regulations (standard methodology MR-004) and the 1975 World Medical Association Declaration of Helsinki, duly revised in 2000.

Consent for Publication Informed consent of publication was obtained from the patient, in accordance with current French regulations (standard methodology MR-004) and the 1975 World Medical Association Declaration of Helsinki, duly revised in 2000.

Conflict of Interest The authors declare no competing interests.

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