Remission of eczema and recovery of T h1 polarization following treatment with Dupilumab in STAT3 hyper IgE syndrome

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To the Editor,

the clinical features of Hyper IgE syndrome (HIES) have been clearly highlighted. The syndrome is a complex immunodeficiency characterized by recurrent staphylococcal skin and lung infections, chronic mucocutaneous candidiasis and atopic dermatitis-like eczema, associated with hyper IgE and often high eosinophil levels.

Other features are scoliosis, osteoporosis, primary teeth retention and joint hyperextensibility. The autosomal dominant form is caused by STAT3 dominant-negative mutations, while the autosomal recessive forms are caused by ZNF341, DOCK8, PGM3 or CARD11 biallelic mutations.

Several studies have shown that the STAT3 protein is involved in signal transduction of a broad number of cytokines such as IL-6, IL-10 and IL-21. Impairment of IL-6 signalling causes a reduction in Th17 polarization and is responsible for the chronic mucocutaneous candidiasis (1), while defective IL-10 and IL-21 signalling leads to an imbalance towards IL-4 production and Th2 polarization possibly linked to the susceptibility to pathogens controlled by Th1 lymphocytes.

Dupilumab is a fully human monoclonal antibody targeting the alpha-subunit of IL-4 receptor, inhibiting the IL-4 and IL-13 signalling, that are key cytokines in the development of atopic dermatitis. In 2020, FDA approved the use of dupilumab for the treatment of atopic dermatitis in patients over 6 years of age.

Herein, we report the successful treatment of a 17-year-old patient affected by STAT3 HIES with a severe atopic-like dermatitis with a recovery of Th1 polarization.

Since the very first months of life, the patient presented with recurrent bronchospasms and severe atopic dermatitis with frequent Staphylococcal superinfections, later followed by allergy to several oral and inhalant allergens. From 5 years of life, he developed recurrent cutaneous cold abscesses and frequent upper airway infections. His laboratory work-up was characterised by a hyper IgE (>5000), hypereosinophilia (>20%) and a multiple sensitisation to oral allergens (assessed by serum specific IgE). He was treated with topical and oral corticosteroids, anti histaminergics and oral Ciclosporine A (5 mg/kg), with a partial benefit on the cutaneous manifestations.

The patient presented for the first time to our attention when he was 16 years old because of severe pruritic eczematous lesions with signs of superinfection (SCORAD 45/103, DLQI 8/30), scoliosis, joint hyperextensibility, arched palate and a retained tooth. The IgE levels were > 5000 and eosinophils 20%, while lymphocytic proliferation test and neutrophil oxidative index were normal. An increase of Th2 lymphocytes (CD4+IL4+IFNg-), and a decrease of Th1 (CD4+IL4-IFNg+) lymphocytes was detected (Fig.1, Fig2). An autosomal dominant HIES was suspected and an NGS panel for primary immune deficiencies revealed a de novo heterozygous STAT3 mutation (c.1150T>C; p.F348L).

The inefficacy of previous treatments prompted the choice of an anti IL-4/IL-13 therapy with Dupilumab. The first injection of 600 mg, followed by 300 mg every other week, induced a progressive clearing of skin lesions with a complete remission after the 3rdinjection. At follow up after 12 months, the SCORAD (28/103), and DLQI (2/30) showed a significant clinical improvement with an initial increase in the eosinophil count, as observed in previous report in atopic dermatitis treated with dupilumab and a subsequent normalisation, while IgE remained elevated (Fig1). After 10 months a decrease of Th2 lymphocytes was evident, together with an increase in Th1 lymphocytes. These changes were associated with a reduction of IL-4 and an increase in CXCL10 (Fig.1-2).

In the literature, an excellent clinical response to dupilumab has been described in 6 cases of STAT3-HIES (2-5), and 10 cases of AR HIES (6-7), with evidences of amelioration of cutaneous lesions and IgE levels (2-3,6) along with a reduction of Th1 and Th2 cytokines (6). In one case, also eosinophilic esophagitis resolved (3).

Our case confirms the clinical efficacy of dupilumab and suggests for the first time a potential effect on Th1 and Th2 lymphocyte polarization with a decrease of the latter following treatment. This evidence corroborates the role of an altered lymphocyte polarization in the genesis of the main clinical features that characterise this syndrome. In fact, not only the eczema resolved, but also the diffuse skin infections were promptly cleared by the treatment with a stable efficacy in time. IL-4 has been shown to inhibit Th1 and 17 differentiation (8) and to influence keratinocytes, diminishing the expression of fibronectin and impairing wound healing (9). Our observation suggests that IL-4/IL-13 block could partially reverse the Th1 defect present in these patients, with a possibly positive role in preventing skin infections.

Several areas remain to be understood in this syndrome. In fact, in all the described cases, IgE remained extremely high despite the brilliant clinical result (2-3,6). This observation suggests a limited role of IgE in HIES eczema with consequent implication in drug choice. Furthermore, Th17 cells do not appear to be stably affected by IL4/IL13 pathway blockade despite the known role of IL-4 signalling in inhibiting Th17 polarization (10). Obviously, both observations will require independent confirmations to draw reliable conclusions.

In conclusion, the treatment with dupilumab in STAT3-HIES may achieve a satisfactory clinical remission and immunological restore of physiological T cell polarization thus allowing the patient to recover a better quality of life.

Keywords : Hyper IgE syndrome, Dupilumab, STAT3, Job syndrome, Th2, Th1

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Figure Legends

Figure 1 : Cutaneous lesions before (upper pictures) and after (lower pictures) treatment with Dupilumab. Behaviour of: SCORAD, DLQI, IgE, eosinophils, IL-4, CXCL1, Th1, Th2 and Th17 lymphocytes before and after 5 and 12 months of dupilumab.

Figure 2: Behaviour of IL-13, IL-10, CXCL9, TNFα, IL-6 and IL-1β before and after 1, 5, 12 and 13 months of Dupilumab.

Cytokine/chemokine profiling: The BD CBA assays for Human Soluble Protein (BD Bioscience 558264) was used to assess plasma cytokine/chemokines according to the manufacture's protocols. Data were analyzed with FCAP Array software.

Flow cytometry evaluation of lymphocytes was performed on 50 µl of whole blood. Cells were stained with membrane markers CD3, CD4, CD8, fixed and permeabilized (Cytofix/Cytoperm (BD)); T lymphocyte polarization was defined in CD3+CD4+CD8- cells by intracellular expression of IFN-g for Th-1, IL-4 for TH-2, IL-17 for Th17