Omalizumab in the treatment of Hyper-IgE Syndrome – 2 case reports

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Hyper-IgE Syndrome (HIES) is a group of rare primary immunodeficiencies, characterized by severe eczema, elevated serum IgE levels and eosinophilia [1]. Frequently associated to recurrent severe skin infections and pneumonia, it can lead to "cold abscesses" and pneumatocele formation. In spite of these common findings, this syndrome presents with a wide variety of clinical manifestations [1], and includes entities of autosomal dominant and recessive transmission. Job Syndrome, related with dominant negative mutations in the STAT-3 gene [2], is associated with severe recurrent cutaneous and pulmonary infections with modest systemic signs of inflammation, connective tissue and skeletal abnormalities [3]. On the other hand, DOCK 8 deficiency is the most frequent cause of recessive HIES and is associated to severe cutaneous viral infections, asthma, allergies and risk of malignancy [1,4].

Therapeutic options for HIES are also different considering the type of mutation identified and clinical manifestations. Therefore, prophylactic antimicrobial treatment combined with IgG replacement are essential in the treatment of patients with STAT-3 deficiencies; hematopoietic stem cell transplantation, alongside with allergic disease control, seems justified in DOCK8-deficient HIES [5].

As control and curative approaches are still lacking, the need for new therapeutic solutions accommodates the will for experimental studies. Omalizumab is a humanized

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recombinant monoclonal antibody that inhibits the binding of free IgE to the high-affinity IgE receptors on the surface of mast cells and basophils, preventing their degranulation. Omalizumab is currently approved for asthma and chronic spontaneous urticaria [6]. In addition, its off-label use has been described in several conditions in which IgE has an important pathogenic role and its use has rarely been described in HIES [7-9].

Herein, we present two clinical and genetically distinct cases of HIES, with different responses to Omalizumab therapy.

The first case concerns a 33-year-old man with a characteristic face, severe recalcitrant eczema, folliculitis and onychomycosis, multiple recurrent respiratory infections and esophageal candidiasis since childhood, requiring repeated courses of antibiotics and antifungals. He was diagnosed with HIES with STAT-3 mutation (Job Syndrome), with a NIH score for HIES of 49 points. At the time of observation, he held a poor control of his skin disease (SCORAD 50.05), despite a daily dose of 80 mg of prednisolone and 20 mg of bilastine. Serum IgE was 11802 kU/L (normal < 114 kU/L). In order to control his cutaneous symptoms and reduce his steroid dosage, he was started on Omalizumab 375 mg every two weeks. In spite of an initial predictable increase of his serum IgE levels, there was a significant reduction of the previous (currently 8660 kU/L), associated with a progressive improvement of his skin lesions and pruritus during a 12 months' follow-up period (SCORAD 20.65), allowing a withdrawal of prednisolone (Table 1, Figure 1A and 1B – Supplementary material). Currently he is undergoing monthly treatment with 375 mg of Omalizumab, without repercussion on his improvement.

The second case concerns a 39-year-old man with recalcitrant eczematous dermatitis with intense pruritus, frequent skin abscess formation and intellectual deficit with psychomotor impairment since birth. He also had a history of Hodgkin's lymphoma 14 years

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earlier, undergoing curative treatment, without the need for hematopoietic stem cell transplant. A HIES was diagnosed and a heterozygous variant of DOCK8 gene was found; he was STAT3 and TYK2 mutations negative. At the time of observation, he retained shortness of breath and wheezing refractory to treatment, severe recalcitrant eczema and frequent cutaneous infections (SCORAD 71.3), requiring a daily dose of 40 mg of bilastine, 25 mg of hydroxyzine, 30 mg of deflazacort and multiple courses of topical betamethasone and fusidic acid. He started Omalizumab 300 mg every two weeks. Serum IgE initially was 1117 kU/L and, as in the previous case, we observed an increase to 2428 kU/L after 3 months of treatment. However, this was followed by a decrease to 1679 kU/L (Table 1, Figure 1C and 1D – Supplementary material). Because a meaningful reduction in symptoms or prednisolone dose was not quickly achieved, Omalizumab dose was increased up to 450 mg twice per month. Currently, the skin symptoms remain stable, with only a slight reduction of pruritus (SCORAD 50.01), although it was possible to reduce oral corticosteroid therapy to 80 mg of endovenous methylprednisolone per month. There was no significant improvement or aggravation of his respiratory symptoms, probably due to corticotherapy.

Due to high serum IgE level, recalcitrant eczema and prolonged use of systemic corticosteroids, Omalizumab was tried in both patients and exhibited benefit for their skin lesions, as well as a decrease of their infectious intercurrences (having the first case only one upper tract respiratory infection with no need for antibiotherapy on the 12 months follow-up period and the second one no infectious intercurrences throughout). Overall, we observed a significant clinical improvement in the first case and only a small improvement in the second one. However, it should be taken into consideration the cognitive limitations of the patient described on the second case, which makes it challenging to evaluate his progression, as

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complaints were mostly subjective. Both cases had different genetic abnormalities although the eczema characteristics and Omalizumab dosage were similar.

It is well known that Omalizumab is effective in a variety of recalcitrant immune-mediated and autoimmune skin disorders, but its role in HIES is still being defined. Albeit being costly, Omalizumab has proven beneficial in both patients with HIES, in which we have very limited therapeutic options. The different responses of two HIES entities to Omalizumab therapy suggest that the use of this drug should be weighted on a case-by-case basis. It is known that in asthma Omalizumab is recommended for IgE levels < 1500 IU/mL. A study published by Hsiao-Han Wang et al. in 2016 concerning the use of this drug on atopic dermatitis documented an association of serum IgE concentrations of less than 700 IU/mL with more favorable clinical responses to this treatment, suggesting a better IgE neutralization in patients with lower concentrations [10]. In our report, the patient with higher IgE levels had better response to Omalizumab. As the IgE role in HIES is still unknown, this unexpected outcome remains unexplained.

Prospective studies and long term follow-up are still required to confirm the effectiveness of Omalizumab in HIES.

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Table 1. Evolution of IgE level during follow-up

Patient/IgE level (kU/L, normal < 114)	Pré-omalizumab	3 months follow-up	6 months follow-up	9 months follow-up	1 year follow-up
Case 1	11802	12340	8820	8980	8660
Case 2	1117	2428	2698	1679	1599

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