Hyper-IgE syndrome (HIES) comprises a group of rare primary immunodeficiencies, characterized by severe eczema, elevated serum IgE levels, and eosinophilia [1]. Frequently associated with recurrent severe skin infections and pneumonia, HIES can lead to formation of cold abscesses and pneumatocele. Despite these common findings, the syndrome presents with a wide variety of clinical manifestations [1] and includes diseases of autosomal dominant and recessive transmission. Job syndrome, which is associated with dominant negative mutations in the STAT3 gene [2], is characterized by severe recurrent cutaneous and pulmonary infections and with modest systemic signs of inflammation and connective tissue and skeletal abnormalities [3]. Dedicator of cytokinesis 8 (DOCK8) deficiency is the most frequent cause of recessive HIES and is associated with severe cutaneous viral infections, asthma, allergies, and risk of malignancy [1,4].

Therapeutic options for HIES differ depending on the type of mutation identified and the clinical manifestations. Therefore, prophylactic antimicrobial agents combined with IgG replacement is essential in the treatment of patients with STAT3 deficiencies, and hematopoietic stem cell transplantation, together with control of allergic disease, seems justified in DOCK8-deficient HIES [5].

As control and curative approaches are still lacking, the need for new therapeutic solutions highlights the role of experimental studies. Omalizumab is a humanized recombinant monoclonal antibody that inhibits binding of free IgE to the high-affinity IgE receptors on the surface of mast cells and basophils, thus preventing their degranulation. Omalizumab is currently approved for asthma and chronic spontaneous urticaria [6]. In addition, its off-label use has been reported in several conditions in which IgE has an important pathogenic role, although its use in HIES has received little attention [7-9].

We present 2 clinical and genetically distinct cases of HIES, with different responses to omalizumab.

The first involved a 33-year-old man with characteristic facial features, severe recalcitrant eczema, folliculitis, onychomycosis, multiple recurrent respiratory infections, and esophageal candidiasis since childhood requiring repeated courses of antibiotics and antifungals. He was diagnosed with HIES with a STAT3 mutation (Job syndrome) and had a National Institutes of Health score for HIES of 49 points. At the time of observation, his skin disease was poorly controlled (SCORAD, 50.05), despite a daily dose of 80 mg of prednisolone and 20 mg of bilastine. Serum IgE was 11,802 kU/L (normal <114 kU/L). In order to control his cutaneous symptoms and reduce the dosage of corticosteroids, he was started on omalizumab 375 mg every 2 weeks. In spite of an initial predictable increase in serum IgE levels, previous levels fell significantly (currently 8660 kU/L), and his skin lesions and pruritus improved progressively over 12 months of follow-up (SCORAD, 20.65), thus enabling prednisolone to be withdrawn (Table, Supplementary material [Figure 1A and 1B]). He is currently undergoing monthly treatment with 375 mg of omalizumab, which has had no negative effect on his improvement.

The second case concerned a 39-year-old man with recalcitrant eczematous dermatitis and intense pruritus, frequent skin abscess formation, and intellectual disability with psychomotor impairment since birth. He also had a 14-year history of Hodgkin lymphoma that was managed with curative treatment, without requiring hematopoietic stem cell transplant. The patient was diagnosed with HIES, and a heterozygous variant of the DOCK8 gene was found; the patient was negative for STAT3 and TYK2 mutations. At the time of observation, he continued to experience shortness of breath and wheezing that were refractory to treatment, severe recalcitrant eczema, and frequent cutaneous infections (SCORAD, 71.3) requiring a daily dose of bilastine 40 mg, hydroxyzine 25 mg, deflazacort 30 mg, and multiple courses of topical betamethasone and fusidic acid. He started omalizumab 300 mg every 2 weeks. Serum IgE was initially 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, Supplementary material [Figure 1C and 1D]). Given that symptoms did not improve and the dose of prednisolone could not be reduced quickly, the dose of omalizumab was increased to 450 mg twice per month. The skin symptoms remained stable, with only a slight reduction in pruritus (SCORAD, 50.01), although it was possible to reduce oral corticosteroid therapy to 80 mg of intravenous methylprednisolone per month. There was no
significant improvement in or aggravation of the respiratory symptoms, probably because of the corticosteroids.

Both patients received omalizumab owing to their high serum IgE level, recalcitrant eczema, and prolonged use of systemic corticosteroids. This approach improved their skin lesions and decreased intercurrent infections (only 1 upper tract respiratory infection with no need for antibiotic therapy during the 12 months of follow-up in the first case and no intercurrent infections in the second). Overall, we observed a significant clinical improvement in the first case and only a small improvement in the second one. However, the cognitive limitations of the second patient should be taken into consideration: these make evaluation of progression challenging, as the complaints were mostly subjective. Both cases involved different genetic abnormalities, although the characteristics of eczema and the dose of omalizumab were similar.

Omalizumab is known to be effective in a variety of recalcitrant immune-mediated and autoimmune skin disorders, although its role in HIES is still being defined. Despite its high cost, omalizumab proved beneficial in both cases of HIES, for which therapeutic options are limited. The different responses to omalizumab in the patients we report on suggest that the use of this drug should be assessed on a case-by-case basis.

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

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


Table. IgE level During Follow-up

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<th>IgE Level, kU/L (Normal &lt; 114)</th>
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