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SHORT PAPER

Omalizumab for treatment of refractory severe atopic dermatitis. A pediatric perspective

Mauro Iannelli[1] | Lucia Caminiti[1] | Mario Vaccaro[2] | Ilenia Marafioti[2] | Antonietta Spinuzza[1] | Ilenia Panasiti[1] | Andrea Barbalace[1] | Giuseppe Crisafulli[1] | Giovanni B. Pajno[1]

[1]Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", Allergy Unit, University of Messina, Messina, Italy

[2]Department of Clinical and Experimental Medicine—Dermatology, University of Messina, Messina, Italy

Correspondence
Mario Vaccaro, MD, PhD, Department of Clinical and Experimental Medicine—Dermatology, University of Messina, Via C. Valeria, Gazzi, Messina 98125, Italy.
Email: mario.vaccaro@unime.it

Abstract

Omalizumab is a monoclonal antibody, targeting Fc receptor of IgE, approved for the treatment of allergic asthma and chronic spontaneous urticaria. Its utility in atopic dermatitis appears controversial from data in literature since the molecule is well tolerated but it seems less effective than other medications used in adult patients (eg, Dupilumab). At present, the use of Dupilumab is not approved in pediatric patients therefore there are no second level treatments available in this age group. Here we report two clinical cases of patients (15 and 16 years old) suffering from both atopic dermatitis and asthma, treated with Omalizumab. Our experience suggests that atopic eczema of young patients with allergic comorbidities can benefit from asthma treatment with Omalizumab observing improvement on both conditions.

KEYWORDS

atopic dermatitis, eczema, pruritus, therapy-systemic

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease that is caused by genetic and environmental factors.[1] In pediatric worldwide population it occurs in the percentage of 5% to 20% of children[2] and in the 2% of adults. If we consider children with concurrent asthma, this percentage grows up on 30% to 50%. Anyway, atopic dermatitis is associated progressively to other atopic conditions like allergic rhinitis, asthma and food allergies. AD may often start in infants aged 2 to 6 months and in most cases the onset of this disease occurs in the first 5 years of age. A history of intense pruritus and dry skin is presented by the majority of children and most of the young patients have a lowered itch threshold in response to cutaneous stimuli. At the basis of this condition are an impaired skin barrier function and defects in skin innate immunity. This condition causes a vicious itch-scratch-itch cycle that determines a worsening of skin inflammation, affecting daily activities and sleep. It is responsible of a worse quality of life and psychiatric comorbilities like anxiety, depression, and attention deficit disorder.[3]

Common characteristics in the history of this ill are personal or family history of atopy, chronic relapsing dermatitis, xerosis and pruritus, typical distribution of lesions (extensor and facial involvement), cheilitis, perifollicular accentuation, and bacterial sovra-infections.

The most important and basic step in AD treatment is skin hydration end the restoring of stratum corneum using topical emollients. First line of medical therapy is the use of topical corticosteroids[4] and topical calcineurin inhibitors (eg, Pimecrolimus, tacrolimus) that are especially useful for treating face, groin, axillary areas where use of steroids is not recommended. Both of them have benefits, but calcineurin inhibitors are more expensive and may reduce skin burning and pruritus.[4]

Second and third line therapies are based on systemic steroids and immunosuppressors like cyclosporine, azathioprine, methotrexate, and mycophenolate. In order to relieve pruritus intensity, topical, or systemic antihistamines may be additionally considered. Ultraviolet light may improve skin lesion and reduce need of medical therapy.[5]

Refractariety to this wide range of medications is a main problem in case of severe AD. Progress in understanding immunopathology of atopic dermatitis have allowed identification of therapeutic molecular targets in

the field of biological therapy.[6] For this reason, nowadays new therapeutic strategies include Omalizumab, an IgG-type recombinant humanized monoclonal antibody which selectively binds to IgE and inhibits binding to IgE receptors on surface of mast cells and basophils, limiting their degranulation. Remarkable progress has been made with the recent approval of dupilumab, an antibody to the IL-4 receptor which blocks the receptor binding of IL-4 and IL-13. Contrasting results suggested the efficay of ustekimumab, an antibody that targets the common p40-subunit shared by IL-12 and -23 essential for development of autoimmune diseases, including psoriasis and vitiligo .[6,7] Other immunomodulatory agents, such as anti IL-4/IL-13 agents (Lebrikizumab, Tralokinumab), IL-31 directed therapy (Nemolizumab), IL-22 blockade (Fezakinumab), phosphodiesterase inhibitors (Apremilast, Crisaborole), and JAK inhibitors (Tofacitinib) show promising results, but further study are needed to confirm their efficacy and safety in severe atopic dermatitis.[7]

2 | CASE REPORT

Case 1: A 15-years-old adolescent with history of AD and asthma since early months of life, presented a worsening of skin lesions after 5 years of age with recurrent episodes of skin infections, bacterial conjunctivitis and vulvovaginitis. She is affected by miastenia gravis (MG) diagnosed at the age of 13. Asthma had a low control with inhaled corticosteroids plus long-acting-beta-agonists and get worse after the start of Pyridostigmine treatment for MG, therefore later suspended.

Since the onset, AD was severe and refractory to first and second line therapies, for this reason she underwent a cycle of oral cyclosporine for 3 months with mild benefit (maximum dosage of 300 mg/day). Because of uncontrolled asthma, she was treated with 600 mg of Omalizumab every 15 days according to weight and IgE serum levels (384 UI/mL at the beginning of treatment). At the beginning of the treatment, the patient presented eczematous lesions classically distributed on skin folds (eyelids, neck, armpits, upper and lower limbs) with moderate oozing, several scratch-induced erosions and widespread xerosis. Eczema Area and Severity Index (EASI) score was 31, 10 points were attributed to the Numerical Rating Scale (NRS) for the assessment of pruritus and Dermatoloy Life Quality Index (DLQI) was 14. After 3 months the results were the remission of respiratory symptoms with poor effect on skin lesions, persistent itching and increased use of topic and systemic corticosteroids (EASI score 24, NRS for pruritus 6, DLQI 8). The treatment is still ongoing (Figure 1).

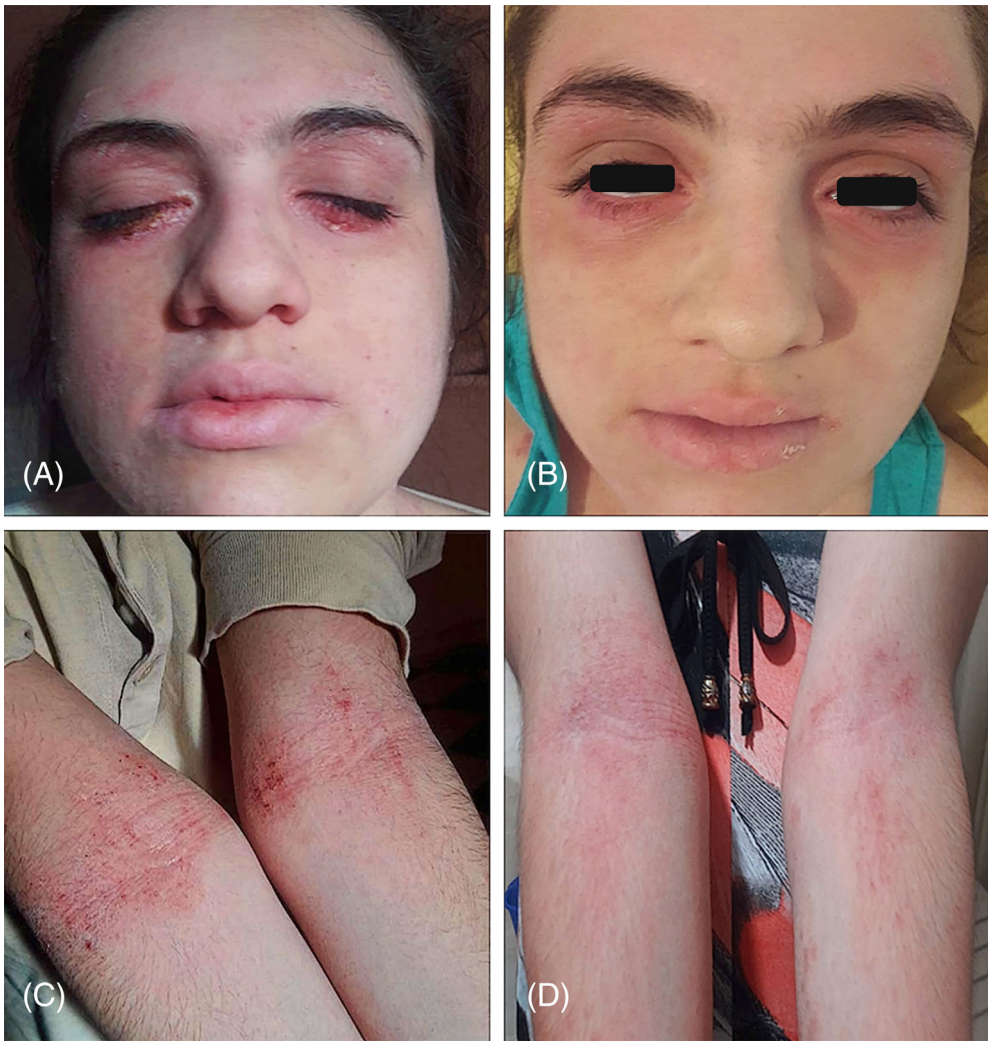

FIGURE 1 A-D, Facial involvement with intense eyelid eczema, A, and eczematous lesions of the cubital fossa, C, before and after 3 months of therapy with Omalizumab, B and D. Whitish lichenification and a lot of scratching lesions are evident

Case 2: A 16-years-old adolescent presents a history of severe AD since the age of 3 years, Cow's milk allergy (with subsequent naturally acquired tolerance) and allergic moderate to severe asthma with positive skin-prick-tests for dust mites, for which he underwent specific Sub-Lingual-Immuno-Therapy for a few months, then suspended because of low tolerance (asthma riacutization). first and second line of medical therapies had no control on AD. The boy presented a significant flare of the eczema with bacterial sovrainfections at the age of 14.

He presented a severe exacerbation of eczema with frequent impetiginizations, not responsive to first and second line therapy. He then was treated with cyclosporin for 3 months (maximum dosage 250 mg), without significant benefit. With the permission of the Ethics Committee, he started treatment with Omalizumab at the dose of 450 mg every 15 days (IgE serum levels at the beginning of treatment 13 908 UI/mL). At the beginning of the treatment he presented wide eczematous areas (involving face, trunk, upper and lower limbs) and severe xerosis (EASI score 27). Itch was intense (NRS 9), quality of life was low (DLQI 10). After 3 months we observed mild benefit on dermatitis (EASI score 18, 6 NRS points for pruritus, DLQI 6), but improvement in asthma. He carried out the therapy for about 6 months. Eight months after the suspension, the patient has maintained a satisfying therapeutic response on both asthma and AD (EASI 8), for which he actually uses only moisturizers (Figures 2-3).

3 | DISCUSSION

Omalizumab is a humanized anti-IgE antibody indicated for the treatment of severe allergic asthma and spontaneous chronic urticaria in patients older than 6 and 12 years, respectively.[8]

Efficacy and safety of Omalizumab in treatment of IgE-mediated conditions like allergic asthma and rhinitis has been demonstrated,[9] some

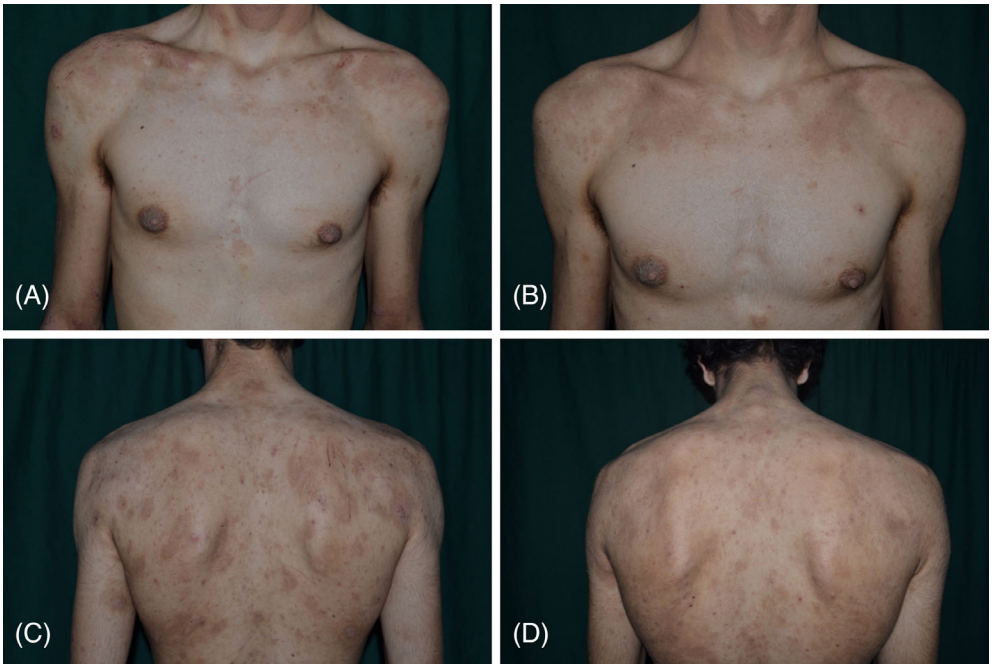

FIGURE 2 A-D, Atopic eczema of the upper trunk before, A and C, and after, B and D, 3 months of therapy with Omalizumab. Reduction of active lesions and scratching signs with the prevalence of postinflammatory hyperpigmentation can be noted

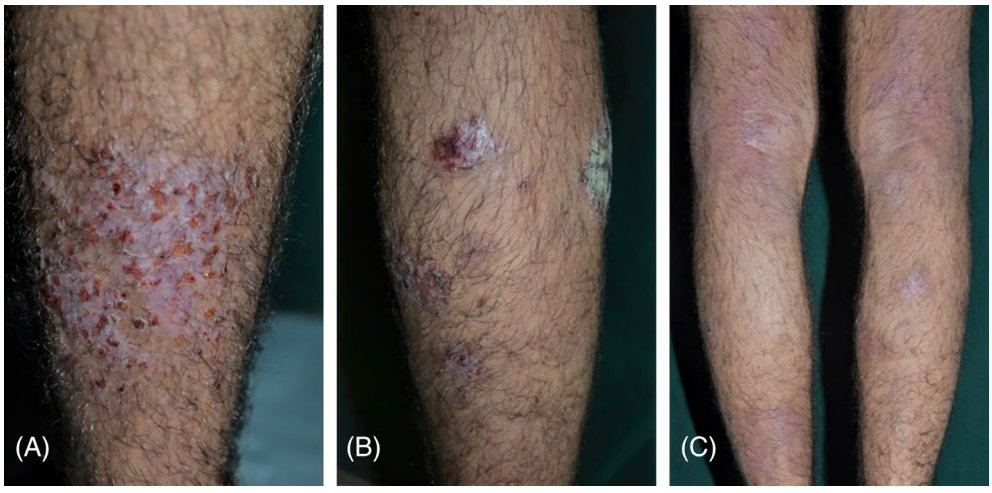

FIGURE 3 A-D, Significant improvement of lower limbs before, A and B, and after, C, therapy with persistence of lichenification but complete disappearance of exudation

studies define this therapy as an effective and useful concomitant therapy in pediatric refractory severe AD,[10,11] especially improving the quality of life, reducing the severity of skin lesions and the need for systemic therapies (steroids, immunosuppressors) with their potential side-effects.

It is used off-label in the treatment of severe refractory atopic dermatitis to topical and/or systemic therapy of first, second, and third level, as recent several studies and literature reviews demonstrate,[11] with a good profile of safety.[12,13]

The literature data on the effectiveness of Omalizumab in the AD are not unique. The results would look better in children, transient and partial in adults. Our experience in both adolescent patients is in line with what has emerged from the literature about drug safety and clinical efficacy in respiratory pathology. There was no satisfactory AD check-up at 3 and 6 months from the start of therapy.

In our experience, Omalizumab cannot be compared to Dupilumab (anti-IL-4 and IL-13) in terms of efficacy and disease control in AD. The use of this molecule is off-label in childhood at the moment.[14,15] However, from real-life use of this drug in pediatric patients, we expect to get what we usually observe in adults. Healing time of skin lesions depends on their severity and time of onset. Chronicity features (eg, lichenification) disappear over time, since they depend on settled inflammation and repeated scratching. Rapid disappearance of itch, starting from first administrations, occurs in most patients and long-term efficacy is the rule.

Regarding Omalizumab, the comparison between the EASI scores at the baseline and at the 3-month follow-up shows a slight improvement. Despite not having observed a complete remission, the reduction of asthma attacks and of about, respectively, 33% and 34% of EASI scores in our patients, meant an increase in their quality of life. Furthermore, it should not be forgotten that visible skin lesions, especially during adolescence, can heavily afflict relational life, causing a state of malaise far more serious than the disease itself. Therefore, Omalizumab represents a therapeutic option for severe AD unresponsive to conventional therapies in patients with allergic comorbidities, since the benefit on asthma can be accompanied by the improvement (albeit partial) of the skin condition with positive effects on the well-being of young patients.

Nowadays studies of Omalizumab for the treatment of severe-refractory AD in children are limited and the results obtained are conflicting. To date, published articles include only three clinical trials, one with positive and two with negative outcome and a number of single case reports or small case series.[16] This lack of "real life" data is particularly evident for which concerns pediatric patients. Also, many dosing regimens have been used by different authors, in association or not with other drugs (antihistamines, potent topical corticosteroids) and the definition of clinical and/or laboratory criteria (age, sex, ethnicity, baseline clinical disease severity, history of concomitant asthma, IgE levels) which should drive the decision is still a matter of debate.

Our experience on the use of Omalizumab as single therapy in adolescent patients indicated a good efficacy and safety profile, with no adverse effects.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Mario Vaccaro https://orcid.org/0000-0003-3787-5145

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