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Case report

Dupilumab-associated facial redness not responsive to antifungal therapy successfully treated with tralokinumab

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Abstract. Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and intense itching. Dupilumab, was the first biological drugs approved for this disease. Dupilumab-associated facial redness (DFR), characterized by facial and/or neck erythema, was never reported during pivotal clinical trials. A twenty-one-year-old male developed non-pruritic erythematous patches in the frontal, palpebral, malar, latero-cervical, and nuchal areas after about eight weeks of treatment with Dupilumab. Since the patient did not perform patch test before starting dupilumab, to rule out possible allergic contact dermatitis (ACD), patch tests were performed using standard and personal product series, which yielded negative results. A skin scraping and a microscopic examination with negative result were performed in order to rule out possible Demodicosis and head and neck dermatitis due to Malassezia species. After conducting a literature review, it was decided to discontinue Dupilumab and start fluconazole therapy. However, this approach did not significantly improve the EASI score for the head/neck region. Due to the negative impact that the Dupilumab therapy-related manifestation had on the patient's quality of life, a decision was made to switch to systemic therapy based on Tralokinumab. The regimen of 300 mg every other week with this molecule resulted in the resolution of DFR after only three administrations while maintaining excellent disease control in other affected sites. Tralokinumab also demonstrated an excellent safety profile even after sixteen weeks of treatment. This paper presents what could be the first case of DFR to be successfully treated with Tralokinumab. (www.actabiomedica.it)

Key words: atopic dermatitis, Dupilumab, Tralokinumab, Dupilumab-associated facial redness, antifungal therapy

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and intense itching. Although it is more prevalent during infancy, it occasionally also occurs in adulthood. The pathogenesis of AD is defined by a genetically determined dysfunction of the epidermal barrier, immune dysregulation and alteration of the skin microbiome(1). Available and approved therapies for this condition include topical non-pharmacological therapies (moisturizers, wet-wrap therapy); topical pharmacological therapies (corticosteroids and topical calcineurin inhibitors) phototherapy (UVA/UVB); systemic immunosuppressive drugs (systemic corticosteroids, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil); biological drugs (Dupilumab, Tralokinumab); JAK inhibitors (Upadacitinib, Baricitinib)(2). Dupilumab, in particular, was the first biological drugs approved for this disease. It is a monoclonal antibody of the recombinant human IgG4 class, which specifically targets the signal transduction of interleukin-4

(IL-4) and interleukin-13 (IL-13) effectively blocking key factors in human type 2 inflammatory diseases(3,4). Dupilumab was also the first systemic agent made available for pediatric patients and gained approval in 2019 for treating moderate to severe AD in children over 12 years of age(5). In 2020, its usage was expanded to children aged six years and over(6), and most recently, in 2022, it was approved for use in children aged six months and older(7). A number of randomized-controlled clinical studies have confirmed that dupilumab is both effective and safe when used to treat AD(8–12). Frequently occurring adverse events (AEs) (experienced by at least 5% of them) included the following: conjunctivitis, injection-site reactions, nasopharyngitis, AD, upper respiratory tract infection, headache and oral herpes(8). Dupilumab-associated facial redness (DFR), characterized by facial and/or neck erythema, was never reported during pivotal clinical trials. It has been observed in 4-10% of patients treated with dupilumab in real-life settings. DFR is an adverse event that can manifest as a new onset or paradoxical flare-up of pre-existing facial dermatitis, which may occur at any time after initiating treatment with dupilumab. The latency period reported in studies ranges from 2-9 months(13–15). Tralokinumab, instead, is a human IgG4 monoclonal antibody designed to bind with specific affinity to IL-13, thus preventing its binding to IL-13α1 and IL-13α2 receptors(16). Randomized-controlled clinical trials have shown that this molecule, in combination with topical corticosteroids as needed, is effective and well tolerated in patients with moderate-to-severe AD(17–19). The most common AEs reported are similar to Dupilumab, except for conjunctivitis where tralokinumab appears to have lower rates of ocular complications than dupilumab(19,20). To date, there have been no reports of facial redness associated with this treatment. This paper presents what could be the first case of DFR to be successfully treated with Tralokinumab.

Cases report

A twenty-one-year-old male with a history of relapsing-remitting severe AD presented to our clinic for a recent flare-up. In his medical history, the patient reported onset of illness at the age of thirteen, with no family history of atopy. He had an allergy to milk and dairy products until the age of eleven, and allergic rhino-conjunctivitis due to dust mites and grasses, but no other comorbidities. The patient's atopic dermatitis (AD) was refractory to several lines of treatment, including topical corticosteroids, topical calcineurin inhibitors, systemic corticosteroids, and cyclosporine, which were all discontinued due to failure or inadequate response. Due to the severity of the disease (EASI: 30, DLQI: 21, NRS pruritus: 10, NRS sleep: 10) and the pharmacological history, therapy with Dupilumab 300 mg every fortnight was started, resulting in marked improvement in all affected areas and in quality of life. However, after about eight weeks of treatment, the patient developed non-pruritic erythematous patches in the frontal, palpebral, malar, latero-cervical, and nuchal areas (Figure 1). Since the patient did not perform patch test before starting dupilumab, to rule out possible allergic contact dermatitis (ACD), patch tests were performed using standard and personal product series pediatric series, which yielded negative results. A skin scraping and a microscopic examination with negative result were performed in order to rule out possible Demodicosis and head and neck dermatitis due to Malassezia species. After conducting a literature review, it was decided to discontinue Dupilumab and start weekly fluconazole 150 mg for four weeks(21–24). However, this approach did not significantly improve the EASI score for the head/neck region. Due to the negative impact that the Dupilumab therapy-related manifestation had on the patient's quality of life (DLQI: 20, EASI: 5), a decision was made to switch to systemic therapy based on Tralokinumab. This highly selective interleukin-13 inhibitor is characterized by high affinity and specificity. This reduces its toxicity and increases its tolerability. The regimen of 300 mg every other week with this molecule (after an appropriate induction dose of 600 mg) resulted in the resolution of DFR after only three administrations while maintaining excellent disease control in other affected sites (EASI: 4, DLQI: 3) (Figure 2). Tralokinumab also demonstrated an excellent safety profile even after sixteen weeks of treatment.

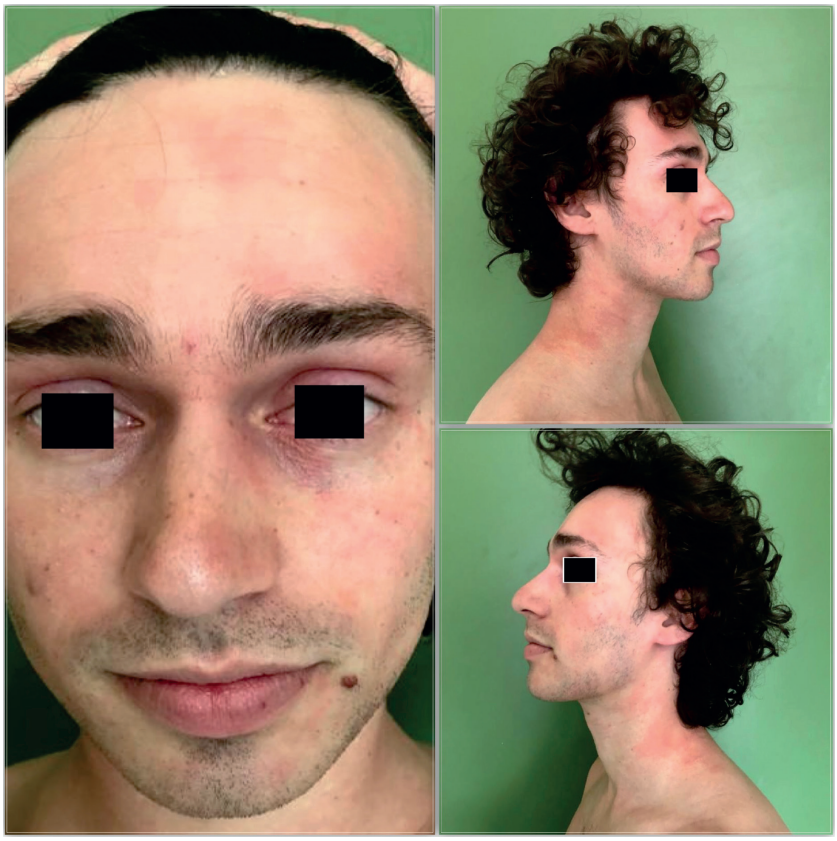

Figure 1. Dupilumab-associated facial redness (DFR). Erythematous patches in the frontal, palpebral, malar, latero-cervical, and nuchal areas.

Discussion

Epidemiologically, our case mirrors what has been reported in the literature where DFR has been found to be more common in the post-pubertal period and with increasing age in atopic patients treated with Dupilumab (13). Several hypotheses have been proposed to explain the pathogenesis of DFR: hypersensitivity reaction, site-specific failure, seborrheic dermatitis-like, allergic contact dermatitis (ACD). These hypotheses, along with the possibility of differential diagnoses such as ACD, rosacea, periorificial dermatitis, demodicosis, corticosteroid withdrawal, and head and neck dermatitis from Malassezia, have led to the most frequently reported diagnostic approaches in the literature. These include skin scraping to test for Malassezia yeast/Demodex mites, evaluation of serum Malassezia-specific immunoglobulin E, serological screening to rule out autoimmune connective-tissue diseases, skin biopsy with histological examination, and PATCH testing(13,25,26). In our case, the hypothesis of a hypersensitivity reaction is unlikely, considering that the patient remained on the treatment for weeks without progressing to a generalized reaction. The hypothesis of a site-specific failure is also unlikely, considering that the patient had never had involvement of the head and neck region. The hypothesis of a seborrheic-like dermatitis is discarded, considering the lack of response to antifungal drugs, while the hypothesis of a possible ACD is unlikely, considering the negative result of the PATCH tests performed. Finally, the hypothesis of a demodicosis or head and neck dermatitis caused by Malassezia was discarded after the negative result of the microscopic examination.

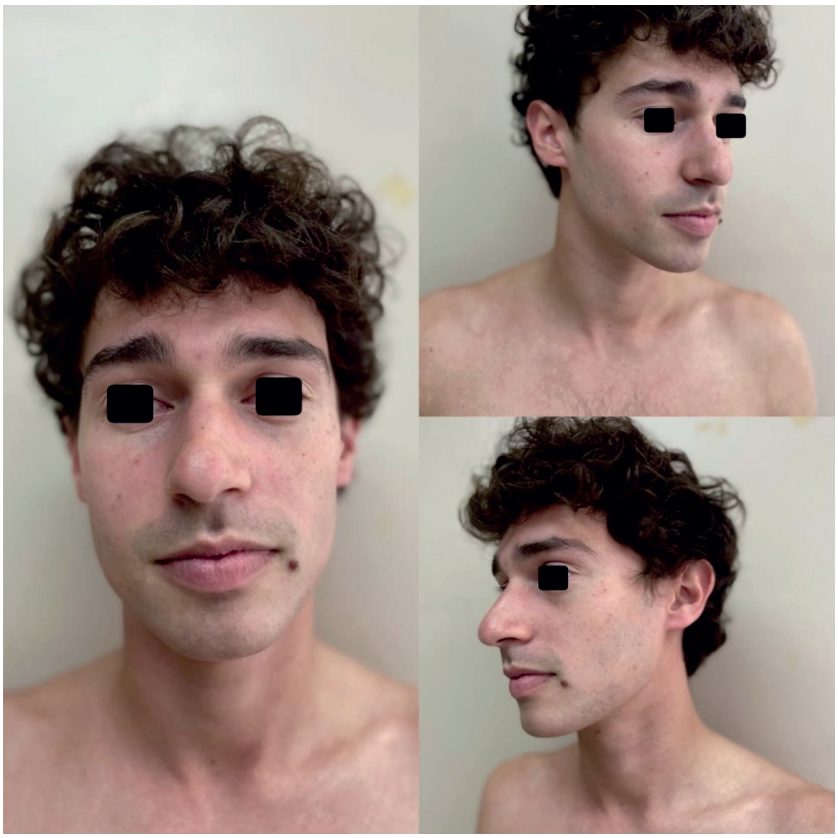

Figure 2. Resolution of DFR post treatment with Tralokinumab.

Dupilumab exerts its therapeutic effects by inhibiting the signaling of IL-4 through the type I receptor (IL-4Rα/γc), as well as the signaling of both IL-4 and IL-13 through the type II receptor (IL-4Rα/IL-13Rα). On the other hand, Tralokinumab works more selectively as it binds directly to IL-13, thereby preventing it from binding to the IL-13Ra1 and IL-13Ra2 receptors, and effectively blocking both IL-13 signaling and endogenous regulation of IL-13(27). The differences that characterize these drugs in terms of mechanism of action, pharmacokinetics and therapeutic schedule could therefore, at least in part, explain the difference in efficacy and side effects profile associated with each of them, including DFR. This is probably the first known case of dupilumab-associated facial redness not responsive to systemic/topical antifungal therapy solved with switch to Tralokinumab. The clinical definition and etiopathogenetic mechanism related to this manifestation still represent important unresolved issues. This particular clinical case raises doubts about the possible role of Malassezia in the etiology and that of seborrheic-like dermatitis in the pathogenesis of this condition. Based on the information provided, it seems that the possible differential diagnoses for the patient's condition have been thoroughly evaluated and ruled out, leaving the possibility of a drug reaction as the most likely explanation for the development of DFR as does the patient's rapid improvement following the switch to Tralokinumab therapy. Overall, more research is needed to better understand the mechanisms underlying DFR and to identify effective treatment options for this condition.

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