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CASE REPORT



Two differing presentations of periocular dermatitis as a side effect of dupilumab for atopic dermatitis

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ABSTRACT

Dupilumab is a monoclonal antibody used to treat atopic dermatitis. Worsening of atopic dermatitis and conjunctivitis following dupilumab use are reported adverse effects; however, there is little reported on the nature and mechanism of these complications. Here, we describe two patients with chronic atopic dermatitis who developed new or severely worsened periocular dermatitis, believed to be a side effect of dupilumab injections, and resolution after its discontinuation. We explore the possibility of dupilumab-induced suppression of Th2 mediated inflammation and upregulation of Th1 and IFN γ mediated inflammation as a possible mechanism.

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Dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals, Inc.) was approved by the Food and Drug Administration and European Medicine Agency in 2017 for use in adults with moderate-to-severe atopic dermatitis (AD) with inadequate response to topical therapies following a series of randomized, double-blind, placebo controlled studies.^{1,2} It is a monoclonal antibody that binds to the alpha subunit of the interleukin (IL)-4 receptor, thus inhibiting signalling of IL-4 and IL-13. These cytokines are key mediators in CD4+ Th2 cell dependent processes involved in the pathogenesis of many allergic diseases such as AD, asthma, and nasal polyposis. The most frequently reported adverse effects of dupilumab in phase 3 trials for AD include worsening of AD (10–18%) and conjunctivitis (14%).^{3,4}

We describe two phenotypically differing cases of periocular dermatitis believed to be caused by dupilumab. This study was performed with Institutional Review Board approval and is HIPAA compliant.

Case 1

A 66 year-old female with a history of chronic AD presented with severe periocular dermatitis following a single subcutaneous injection of dupilumab 600 mg (Figure 1a). At baseline, her AD was localized to the flexor surfaces of her elbows, tops of her feet, hands, and mouth. Periocular involvement included mild skin thickening and eyelid fissures that were treated with moisturizers and hydro

cortisone cream as needed. Past ophthalmic history was pertinent for bilateral upper and lower lid blepharoplasty 14 years prior to presentation. The patient reported an allergy to benzalkonium chloride (BAK) confirmed with patch testing. Seven days after her first and only dupilumab injection, she developed severe periocular dermatitis, unlike previous AD symptoms, with exacerbation of her perioral AD. She denied new dermatologic exposures. An outside physician placed her on dexamethasone/neomycin/polymyxin B drops four times daily and ointment twice daily (BID) and oral azithromycin for a skin culture growing *Staphylococcus*, without improvement. On initial examination, visual acuity was 20/20–3 in the right eye (OD) and 20/20 in the left eye (OS). External examination was significant for severe periocular erythema with skin thickening, peeling, and secondary ectropion. A slit-lamp examination was positive only for trace inferior injection and rare superficial punctate keratitis bilaterally (OU). Given her allergy history, she was instructed to discontinue all ocular drops and periocular ointment and to use preservative free artificial tears and aquaphor ointment over the affected sites. The patient initially noticed improvement with this intervention, but attempted an over the counter eye cleansing treatment once, followed by worsening dermatitis. Upon examination 3 weeks later, the patient's periocular dermatitis now extended to the lateral temples and was nearly confluent over the bridge of her nose (Figure 1b). Anterior segment examination showed diffuse 1+ chemosis and 2+ conjunctival injection OU. Over the following

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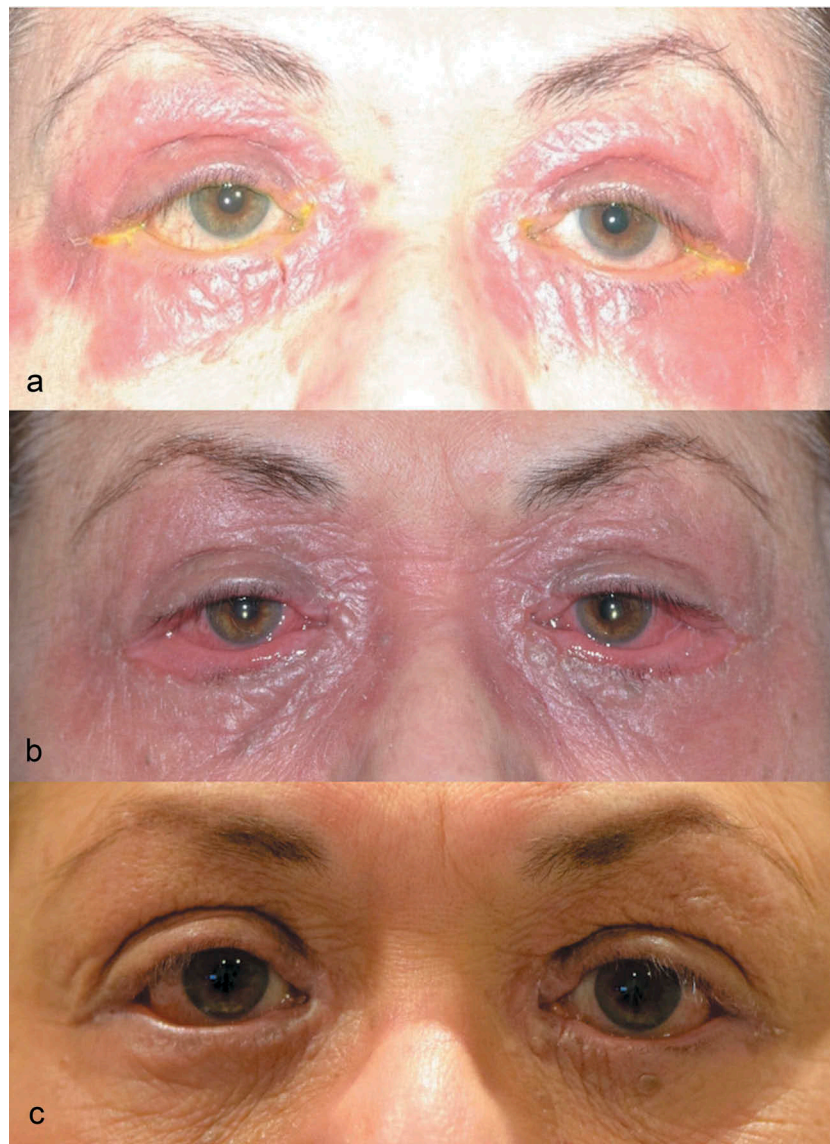


Figure 1. Periocular dermatitis following a single dupilumab injection 600 mg. (a) Initial presentation showing severe periocular erythema, skin thickening, and secondary ectropion. (b) Follow-up three weeks later also showing diffuse injection and chemosis OU. (c) Resolved dermatitis 12.5 weeks after dupilumab injection.

5 weeks, she was treated with two rounds of methylprednisolone 4 mg dose pack, topical periocular tacrolimus BID, hydrocortisone 1% cream to the eyelids PRN, and daily oral loratadine or cetirizine. The patient declined repeat patch testing. Her periocular and perioral dermatitis returned to baseline and conjunctival chemosis and injection resolved 12.5 weeks after her single dupilumab injection (Figure 1c).

Case 2

A 28 year-old female with a 6 year history of hand and upper extremity AD presented with periocular dermatitis following 11 dupilumab injections. Her hand and extremity dermatitis had previously been treated with topical triamcinolone, fluocinonide, clobetasol, and

phototherapy without relief. She was treated with cyclosporine A for 3 months with improvement and transitioned to xenon chloride excimer laser. Her AD was well-controlled on weekly laser treatments for 1 year. She was then started on dupilumab, with an initial dose of 600 mg subcutaneously and 300 mg every other week thereafter. Five and a half months after starting dupilumab therapy, she experienced an AD flare of her hands and arms, but also, for the first time, eye redness, excess tearing, and a raised rash around her eyes. For 2 days prior to presentation, the patient experienced yellowish discharge OU and awoke with her eyes crusted and glued shut. She reported multiple allergies, including pimecrolimus, chromium, nickel, ragweed, trees, and ibuprofen confirmed with

prior patch testing, but denied new recent exposures. On initial ophthalmologic evaluation, visual acuity was 20/20 OU. External examination was significant for bilateral periocular erythema and edema, most prominent at the medial aspect of her eyelids, with bilateral upper and lower skin crease thickening. She had a fine, erythematous rash at her lateral canthi and nose, consistent with her other eczema sites (Figure 2). Slit lamp examination showed mild conjunctival injection and intense pre-tarsal papillary reaction of the upper and lower lids OU. She was diagnosed with bilateral periocular dermatitis and conjunctivitis in the setting of dupilumab use. She was treated with ketotifen drops BID OU, topical Vaseline, and fluorometholone topical ointment daily; ketotifen was discontinued due to irritation. The patient was referred for further allergy testing, but elected not to pursue this. After 15 treatments, dupilumab injections were discontinued due to injection site pain and ocular symptoms, and her periocular dermatitis fully resolved within 13 weeks.

Discussion

AD is a common and debilitating disease affecting 10% of the U.S. adult population, and it can have significant quality of life effects including those related to physical and mental health.⁵ AD treatment traditionally involves topical moisturizers, steroids, and calcineurin inhibitors; if these are unsuccessful, phototherapy, or systemic immunosuppressive treatments such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, are used, but with potential for significant side effects.^{3,6} Dupilumab is the first approved systemic

biologic drug for AD.⁷ In the SOLO1 and SOLO2 phase 3 trials, after 16 weeks of treatment, 37–38% patients with AD who received dupilumab weekly or every other week achieved a 75% improvement in the Eczema Area and Severity Index compared to 10% who received placebo treatment.² Similarly, the LIBERTY AD CHRONOS phase 3 trial showed that 39% of patients who received dupilumab (weekly or every other week) plus topical steroids achieved the aforementioned endpoints at 16 weeks compared to 12% of patients receiving placebo plus topical steroids.¹ However, worsening of AD (10–18%) and conjunctivitis (14%) were reported as common adverse events in these phase 3 trials.³ One of these patients developed blepharoconjunctivitis with AD of the peri-orbital region.⁸ An additional report of bilateral conjunctivitis with cicatricial ectropion associated with dupilumab use indicated an eczematous reaction of the lower eyelids and cheeks that resolved after dupilumab discontinuation.⁷

A maximum serum concentration of dupilumab is achieved 1 week after a 600 mg loading dose, and steady state concentrations are reached at 16 weeks regardless of whether subsequent treatments are weekly or every other week. Drug elimination to non-detectable levels takes 10 to 13 weeks, depending on whether injections are every 2 weeks or weekly, respectively.⁹ In the two cases presented herein, time to resolution of periocular dermatitis after dupilumab discontinuation was in accordance with drug clearance rates. Interestingly, the first patient developed severe periocular dermatitis about 1 week after her loading dose, correlating with the maximum serum concentration; the second patient



Figure 2. Periocular dermatitis following 5.5 months of dupilumab injections. Bilateral periocular erythema with skin thickening, most prominent at medial eyelids, and fine erythematous rash at the lateral canthi and nose.

developed a milder fine periocular rash over 5 months after receiving regular treatments, at which time one could assume steady state concentration.

The underlying aetiology of dermatitis after dupilumab treatment is unclear, whether worsened (as in Case 1) or new (as in Case 2). In the setting of dupilumab use, dermatitis may represent atopy, increased allergen sensitivity, or a combination of both aetiologies.

Dupilumab exerts its anti-inflammatory effects by inhibiting IL-4R α , which both IL-4 and IL-13 use for signalling via the transcription factor STAT6. These cytokines are effectors of Th2-mediated inflammation, including IgE class switching, epidermal hyperplasia, eosinophil recruitment, and activation of dendritic cells.⁵ Dupilumab changes the gene expression profile in treated skin, with a downregulation in the AD transcriptome, including Th2 associated chemokines (CCL17, CCL18, CCL22, CCL26) and markers of keratinocyte proliferation (K16 and MK167) without significant change in Th1-related genes.^{3,5} However, studies with STAT6 deficient mice, who inherently lack a Th2 response, have shown similar rates of AD lesions with prominent Th1 cell differentiation and IFN γ expression.¹⁰ As patients treated with dupilumab have suppressed STAT6 signalling, it is possible that new or worsened AD lesions may develop through a Th1-dependent mechanism. In allergic contact dermatitis, while CD8+ T-cells are the primary effector cells, CD4+ T-cells, both Th1 and Th2, aid in the expression of inflammatory cytokines, chemokines, and adhesion molecules that promote massive T-cell recruitment.¹¹ In contact hypersensitivity reactions, Th2 cells and cytokines inhibit the Th1 response.¹² It is thus possible that dupilumab-induced inhibition of Th2 effectors may lead to an increased Th1 response and therefore an increased tendency towards contact hypersensitivity.

The cases presented here suggest that properties specific to periocular skin may contribute to dupilumab-induced dermatitis. The eyelids have the thinnest epidermis on the body, even compared to other areas of the face (0.55 mm versus 2.0 mm).¹³ Therefore, it is easier for antigens to cross the skin barrier of the eyelid than other parts of the face. Interestingly, isolated periocular allergic contact dermatitis is often driven by allergens in contact with other unaffected cutaneous sites.¹³ Both patients in this series were offered repeat patch testing to identify potential new or more severely reactive allergens in the setting of dupilumab use, but both refused additional allergen testing.

In addition to periocular dermatitis, both of our patients developed conjunctivitis. It has been postulated that downregulation of IL-4 and IL-13 leads to increased

OX40, a ligand involved in atopic keratoconjunctivitis (AKC).^{4,8} Interestingly, conjunctivitis has not been reported as a complication of dupilumab used for asthma or nasal polyposis.⁴ In our cases, the primary involvement was periocular skin rather than the cornea or conjunctiva. However, as AKC can present with some degree of eyelid dermatitis, it is possible that the symptoms experienced by these patients are part of an AKC spectrum.

In conclusion, dupilumab has set a precedent for biologic therapy of AD. However, it does demonstrate an ability to incite conjunctivitis and, as seen here, periocular dermatitis. In the cases presented here, the periocular dermatitis only resolved with discontinuation of the dupilumab and presumed systemic clearance of the drug. We have proposed mechanisms through which dupilumab may lead to worsened AD or ACD through upregulation of Th1 mediated inflammation despite Th2 suppression. However, further elucidation of dupilumab's immunologic effects is needed to better understand the underlying pathophysiology of ocular and periocular side effects.

Disclosure statement

Dr. Belsito has served as an advisor to Sanofi, the US marketer for dupilumab. Ms. Yamane and Dr. Dagi Glass have no financial interests to disclose. The authors alone and responsible for the content and writing of the paper.

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