

Treatment of refractory conjunctivitis associated to dupilumab with topical pimecrolimus applied to the eyelid skin

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Abstract

Patients with atopic dermatitis commonly experience ophthalmic complications, and a higher incidence of conjunctivitis has been observed during treatment with dupilumab.

We present the case of a 49-year-old woman with persistent severe atopic dermatitis who complained of refractory conjunctivitis associated with dupilumab. Ocular examination showed features of atopic conjunctivitis for which an external topical application to the eyelids of pimecrolimus 10 mg/g cream was prescribed. The patient showed substantial clinical remission after only 12 days. This case was remarkable as the medication applied externally to the eyelid skin was effective in treating the conjunctival involvement possibly due to penetration of pimecrolimus through the eyelid layers. Further studies are needed to support the use of this drug for dupilumab-related conjunctivitis.

Introduction

Dupilumab is a monoclonal antibody targeting the receptor subunit for IL-4 and IL-13, these are the cytokines of the main signaling pathways implied in atopic dermatitis and in other Th2-mediated disorders (Gandhi et al., 2016). This drug is the first biologic agent approved for the treatment of atopic dermatitis (AD) in adult patients who are candidates for systemic therapy (Thaçi et al., 2019).

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Patients with AD commonly experience ophthalmic complications, namely allergic conjunctivitis, blepharitis, and keratitis with an incidence of 32.4-55.8% that increases with the severity of skin disease (Bielory & Bielory, 2010; Thyssen et al., 2017).

In most clinical trials concerning AD, a higher incidence of conjunctivitis was observed in patients treated with dupilumab (8.6-22.1%) compared to those receiving a placebo (2.1-11.2%) (Akinlade et al., 2019).

The pathogenesis of ocular adverse events observed in the course of dupilumab therapy is still speculative and indications for its prevention and treatment still require standardization.

We present a case of successful treatment of refractory conjunctivitis associated to dupilumab with topical application of calcineurin inhibitor pimecrolimus to the eyelids.

Case presentation

A 49-year-old Caucasian female was diagnosed with persistent severe atopic dermatitis shortly after birth. Topical and systemic treatments, including cyclosporine, were employed in an attempt to control the disease, but with poor results and a negative impact on the quality of life. In June 2018 she was started on dupilumab with an EASI score of 24.1. Some weeks after the initiation of biologic therapy the patient reported the onset of conjunctivitis and independently consulted an ophthalmologist. She was diagnosed with filamentous conjunctivitis and treated with steroid eye drops, ketotifen eye drops, and artificial tears. However, all therapies had to be discontinued due to inefficacy.

Sixteen weeks after the start of dupilumab therapy a routine dermatological assessment revealed decent skin clearance and an EASI of 1. Despite this the patient had unfortunately worsening of her ocular symptoms. At this time our ophthalmology department became involved in this case.

We found that the patient complained of persistent eye redness with itching, a foreign body sensation, and watery discharge of the eye.

An ocular examination showed eczematoid blepharitis, caruncular edema, lacrimal punctum swelling, severe conjunctival injection, chemosis, papillary hypertrophy, perilimbal corneal injection and intense watery discharge (Figure 1).

A diagnosis of steroid resistant atopic conjunctivitis was made.

An initial management strategy was agreed with the patient, consisting of application of topical pimecrolimus 10mg/g cream twice daily to the external eyelid; this was continued until resolution of symptoms.

The patient was reassessed after twelve days of treatment; physical examination showed substantial conjunctivitis regression with only mild residual conjunctival injection and there was dramatic improvement of the erythema and lichenification of the eyelids (Figure 2).

With consideration to the improvement seen at this time a clinical decision was made to continue therapy at a frequency of twice daily applications for thirty days, followed by a once daily application for another thirty days. After this course there was complete resolution of symptoms.

Discussion

Our case is remarkable as we achieved clinical resolution of the patient's ocular condition by applying pimecrolimus dermatologic cream to the periocular area.

Delivery to the conjunctiva and lacrimal film has been demonstrated to occur after eyelid skin penetration of drug molecules. Bioavailability to ocular tissues becomes high due to a small volume of distribution. The high drug permeation through the eyelid skin could be associated with reduced thickness of the epithelium and the associated stratum corneum. This makes it a prospective site for ophthalmic medications (See, Sagesaka, Sugasawa, Todo, & Sugibayashi, 2017). We hypothesize that the eyelid structure allows for pimecrolimus penetration to the conjunctiva, but further studies are needed.

Ocular application of calcineurin inhibitors is an effective therapy for various inflammatory conditions of the eye and tacrolimus 0.1%, 0.03% and 0.02% eye ointments have been used successfully in the treatment of allergic conjunctivitis and vernal keratoconjunctivitis (Fukushima et al., 2014; Ohashi et al., 2010). However, ocular preparations have not been approved.

In a recent report, four patients with dupilumab-related conjunctivitis were treated with tacrolimus 0.03% eye ointment (Wollenberg et al., 2018), and in another recent case series (Ivert, Wahlgren, Ivert, Lundqvist, & Bradley, 2019) six out of ten patients showed some improvement after local treatment with daily applications of tacrolimus 0.1% ointment at the border of the eyelid with or without glucocorticoid eye drops. However, in this latter case series full clinical outcomes have not been described.

We are not currently aware of any previous case whereby refractory conjunctivitis has been resolved with only the application of pimecrolimus to the periocular skin. Dupilumab is a treatment for chronic AD and associated iatrogenic conjunctivitis requires a protracted treatment period. As calcineurin inhibitors do not influence intraocular pressure and do not induce glaucoma or cataract, topical pimecrolimus applied to the eyelids could be safe even in cases where long term treatment is necessary.

Pimecrolimus cream is commercially available and represents an advantageous alternative in comparison with off-label uses of other calcineurin inhibitor preparations which have been reported in recent literature. Additionally, by avoiding direct application to the ocular surface the patient's eye may not be compromised by the combination of local administration of an immune modulating agent in combination with systemic blockade of IL-4/IL-13 pathways. This can theoretically impair viral defenses and expose the patient to potential infectious complications such as viral keratitis and uveitis (Ivert et al., 2019).

Furthermore, application of a cream to the eyelid is a simpler administration route and is likely to be better tolerated by patients leading to better compliance. This would also avoid potential complications in patients with pre-existing ocular pathology already requiring regular eye drop therapy.

Ultimately, the benefits of systematic use will need to be supported by clinical trials and additional case reports.

Conclusion

For cases of refractory conjunctivitis associated with dupilumab treatment we recommend periocular application of pimecrolimus cream and referral to an ophthalmic specialist to undergo detailed ocular assessment.

This particular calcineurin inhibitor and the external route of administration could be an advantageous alternative to tacrolimus eye ointment; especially in cases of chronic refractory conjunctivitis, steroid allergy, or in parallel with concurrent regular eye drop therapy.

Eye examination should be conducted by a specialist at enrollment and during therapy with dupilumab in order to characterize the clinical phenotype of ocular involvement and to develop the most appropriate and timely management strategies.

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Author contributions

All authors made substantive intellectual contributions to the published study, and each author listed on the manuscript has seen and approved the submission of the manuscript.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

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Figure 1. Dupilumab-related conjunctivitis. Slit lamp photography shows caruncular edema, lacrimal punctum swelling, severe conjunctival injection, chemosis, peri-limbal corneal injection and intense watery discharge at the first assessment.

Figure 2. Slit lamp photography after 12 days of pimecrolimus periocular skin application shows substantial conjunctivitis regression with only mild residual conjunctival injection.



