

Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab—clinical characteristics and treatment



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Clinical Implications

- A clinically characteristic inflammation of the anterior conjunctiva and hyperemia of the limbus were observed during dupilumab treatment of patients with atopic dermatitis, which can be treated successfully with commercially available fluorometholone 0.1% eye drops or off-label with tacrolimus 0.03% eye ointment.

TO THE EDITOR:

Atopic dermatitis (AD) is a common, highly pruritic, chronic, inflammatory skin disease with a high burden of disease to the patient.¹ Established therapeutic options include emollient therapy, topical anti-inflammatory therapy with corticosteroids, and calcineurin inhibitors, as well as (mostly off-label) use of systemic immunosuppressive drugs.² Dupilumab is an antibody directed against the IL-4 receptor alpha subunit, which blocks the signaling activity of both IL-4 and IL-13. It has recently been approved by the FDA for the treatment of adult patients affected by moderate-to-severe AD. During clinical trials, conjunctivitis adverse events were reported in a minority of patients, but more often in dupilumab-treated patients (5% to 28%) compared with placebo (2% to 11%).³⁻⁵

It was hypothesized that the blockage of IL-4 and IL-13 would increase the activity of the specific ligands involved in atopic keratoconjunctivitis, such as the OX40 ligand, in the eye.⁶ However, the pathogenesis, clinical characteristics, and treatment options of this conjunctivitis are still not characterized well. Severe AD, preexisting conjunctivitis, and low serum concentrations of dupilumab are reported to be associated with the occurrence of conjunctivitis, which is more frequently observed in AD trial patients only, but not in asthma or nasal polyposis trials.⁷

Here, we report our experience with this clinically relevant complication of dupilumab-treated AD seen in 25% and 50% of patients from our 2 centers from April 2016 to February 2017, and give treatment recommendations based on our personal experience with 13 moderate-to-severe dupilumab-treated patients with AD developing conjunctivitis as an adverse event. This conjunctivitis is reported in temporal association with dupilumab treatment, but a causal relation is not established.

The prominent feature in all of these patients was redness of the conjunctiva in both eyes. In most, but not all patients, typical symptoms included itch, stinging, burning, tearing, foreign body sensation, and depending on the severity of tearing, also some decrease in bilateral visual acuity.

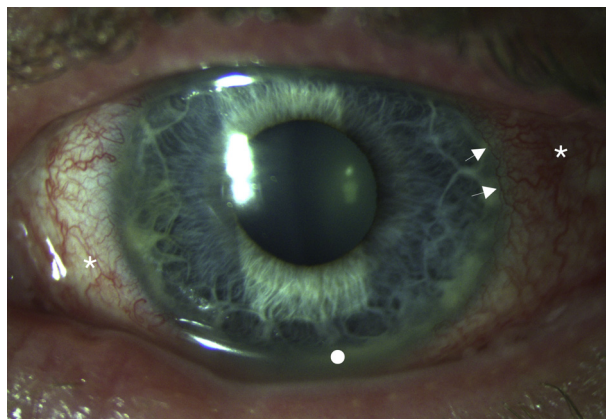


FIGURE 1. Dupilumab-induced conjunctivitis showing conjunctival hyperemia (white asterisks), limbal hyperemia (white triangles) and tearing (white dot).

Specifically, the prominent feature of dupilumab-related conjunctivitis is the predominant involvement of the conjunctiva, and especially a hyperemia of the limbus (Fig 1). In the most severe cases, this included nodular swelling of the limbus resembling the picture of Tantras' dots, but being located a little more anteriorly on the limbus. Characteristics of conjunctivitis are summarized in Table I. Of the 13 patients, 9 did not have a history of conjunctivitis before participating in the dupilumab clinical trials. In 4 patients, conjunctivitis reoccurred or worsened after onset of dupilumab. New signs of blepharitis developed in 10 patients during dupilumab treatment. Blepharitis symptoms were mild in the majority of patients. The dupilumab-related conjunctivitis was generally manageable, and the benefit-risk profile remained largely favorable in patients who developed this condition; therefore, this was not a side effect limiting dupilumab treatment.

We have applied a number of different treatment options to our patients depending on the preference of the managing clinician in each case. In 2 patients, the severity of conjunctivitis was too mild to warrant the use of topical steroids. These patients received either hyaluronic acid eye drops or no topical treatment at all.

However, in our limited experience, antihistamine eye drops and artificial tears did not confer any alleviation in this type of conjunctivitis (data not shown). In 11 patients, dupilumab-related conjunctivitis was treated with topical tacrolimus or steroids, leading to clinically significant improvement or full recovery in all 11 patients treated. Two treatment options were particularly successful, and we would recommend these for future patients.

In 5 patients, conjunctivitis was treated with fluorometholone 0.1% eye drops, leading to significant improvement. Fluorometholone was used because it is approved for allergic inflammation of the anterior eye segment and because of its relatively poor penetration into the anterior chamber of the eye compared with other available topical steroids, resulting in a lower risk of complications like cataract and glaucoma. Clinically significant improvement was achieved in all 5 fluorometholone-treated patients. In 2 patients, signs and symptoms resolved completely.

TABLE I. Patient characteristics

Patient no.	Age, sex	History of conjunctivitis	AD severity before dupilumab	Time to onset (d)	Conjunctivitis	Blepharitis	Limbal edema	Corneal vascularization	Effective treatment of conjunctivitis	Clinical outcome
1	61, F	—	Severe, EASI 26.8, IGA 4	27	OU: mild palpebral	—	—	—	Tacrolimus eye ointment 0.03%	Improvement
2	28, M	—	Moderate, EASI 16.2, IGA 3	181	OU: mild bulbar OU: moderate palpebral	OU: moderate	—	—	Tacrolimus eye ointment 0.03%	Complete resolution
3	53, M	—	Severe, EASI 44.2, IGA 4	25	OU: severe bulbar and palpebral	OU: severe	OU: yes	—	Tacrolimus eye ointment 0.03%	Improvement
4	52, F	—	Severe, EASI 30.4, IGA 4	30	OU: severe bulbar	OU: mild	OU: yes	—	Tacrolimus eye ointment 0.03%	Complete resolution
5	39, M	Yes	Severe, EASI 44.9, IGA 4	110	OU: mild palpebral	OU: mild	—	—	NA	Ongoing
6	44, M	—	Severe, EASI 34.5, IGA 4	20	OU: mild bulbar OU: moderate palpebral	OU: mild	—	—	Oxytetracycline and hydrocortisone eye drops	Improvement
7	35, M	Yes	Severe, EASI 27.9, IGA 4	42	OU: moderate palpebral	OU: mild	—	OS: deep vascularisation	Dexamethasone eye drops	Improvement
8	33, M	—	Moderate, EASI 25.1, IGA 3	34	OU: mild bulbar	OU: severe	—	—	NA	NA
9	42, M	—	Moderate, EASI 24, IGA 3	150	OU: moderate palpebral	OU: mild	—	—	Fluorometholone Liquifilm eye drops	Improvement
10	41, F	—	Severe, EASI 42, IGA 4	150	OU: severe palpebral	OU: moderate	OU: yes	—	Fluorometholone Liquifilm eye drops	Complete resolution
11	34, M	Yes	Severe, EASI 41.6, IGA 4	389	OU: moderate palpebral	OU: mild	OU: yes	—	Fluorometholone Liquifilm eye drops	Improvement
12	48, F	—	Moderate, EASI 22.7, IGA 3	163	OU: moderate palpebral	—	OU: yes	—	Dexamethasone and Fluorometholone Liquifilm eye drops	Improvement
13	59, M	Yes	Moderate, EASI 14.5, IGA 3	210	OU: mild bulbar	—	—	—	Fluorometholone Liquifilm eye drops	Complete resolution

AD, Atopic dermatitis; OD, right eye; OS, left eye; OU, both eyes; —, no; NA, not applicable.

In 4 patients, conjunctivitis was treated with tacrolimus 0.03% eye ointment (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). A calcineurin inhibitor was chosen because this substance does not induce glaucoma or cataract even on long-term use, and the special formulation was chosen to reduce the viscosity of the resulting ointment. Signs and clinical symptoms improved significantly in all patients, and in 2 patients, full recovery of conjunctivitis was achieved. Ocular application of tacrolimus is used in the treatment of various ocular inflammatory diseases. Ocular application of tacrolimus 0.1%, 0.03%, and 0.02% have been used successfully in patients with allergic conjunctivitis and vernal keratoconjunctivitis,^{8,9} but preparations have not been approved.

Dexamethasone or hydrocortisone eye drops or antibiotic combination therapies of medium to high potency were used in 3 patients leading to clinically significant improvement of conjunctivitis symptoms. As the long-term use of ocular steroids increases the risk of complications such as glaucoma and cataract, these can be considered for short term but are not suitable for prolonged treatment.

Tacrolimus 0.03% eye ointment can be safely used for prolonged treatment, as it does not influence intraocular pressure and there is no increased risk of glaucoma and cataract.

Because dupilumab is a long-term treatment option for AD, conjunctivitis occurring during dupilumab treatment may require therapy for a prolonged period of time. Therefore, we would recommend considering either fluorometholone 0.1% eye drops or off-label use of tacrolimus 0.03% eye ointment in the treatment of conjunctivitis occurring in patients with AD during dupilumab treatment.

In conclusion, a clinically characteristic inflammation of the anterior conjunctiva and hyperemia of the limbus was observed during dupilumab treatment, which can be treated successfully with fluorometholone 0.1% eye drops or tacrolimus 0.03% eye ointment.

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ONLINE REPOSITORY

TABLE E1. Compounding instruction for tacrolimus eye ointment 0.03%

<i>Rp.:</i>	
Tacrolimus ointment 0.1%	27.00 g
Cholesterol	0.63 g
<i>Paraffinum subliquidum</i>	26.77 g
<i>Vaselineum album</i>	35.60 g
<i>M.D.S.:</i> Tacrolimus eye ointment, dispense in 5 g tubes	