

Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis

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Purpose: To report the occurrence of conjunctivitis associated with the use of dupilumab in patients with atopic dermatitis.

Methods: A retrospective small case series.

Results: The first case was a 56-year-old man who developed conjunctivitis 2 weeks after starting dupilumab. The second case was a 19-year-old man who developed blepharoconjunctivitis 3 months after starting dupilumab. The ocular inflammation in both cases resolved rapidly and remained controlled with topical steroid drops without necessitating the discontinuation of dupilumab. However, the second patient had already developed conjunctival cicatrization in 1 eye at the time of presentation.

Conclusions: The pathophysiology and the risk factors for the development of conjunctivitis in patients who take dupilumab for atopic dermatitis are not completely understood. However, topical steroid treatment halts the inflammation effectively without discontinuation of dupilumab therapy.

Key Words: dupilumab, atopic dermatitis, conjunctivitis, conjunctival cicatrization, symblepharon

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Dupilumab is a fully human monoclonal antibody targeting the alpha subunit of the interleukin-4 receptor. It was approved by the US Food and Drug Administration in 2017 for the treatment of adult patients with moderate-to-severe atopic dermatitis, whose disease is not adequately controlled with topical therapies. During the initial clinical trials, the incidence of conjunctivitis was noted to be higher in the subjects with atopic dermatitis who received dupilumab as compared to subjects with atopic dermatitis who received placebo. The rate of conjunctivitis was 28% in the groups receiving dupilumab every 2 weeks versus 11% in the group receiving placebo in the LIBERTY AD CAFÉ phase 3 clinical trial.¹ After the drug was released into the market, a number of publications have reported the development of

conjunctivitis in association with the use of dupilumab for atopic dermatitis. Most of those publications appeared in dermatology or allergy and immunology journals, whereas only a few publications have appeared thus far in ophthalmic journals.^{2–4} Herein, we present 2 cases of conjunctivitis associated with the use of dupilumab with 1 of the cases having already developed conjunctival cicatrization in 1 eye. We seek to highlight the importance of ophthalmological evaluation in patients who develop ocular symptoms while on dupilumab.

CASE REPORTS

Case 1

The first case is a 56-year-old black man who presented with redness, itching, tearing, mucoid discharge, and eyelid crusting involving both eyes for a duration of 2 weeks. The ocular symptoms started 2 weeks after he began receiving dupilumab 300 mg every 2 weeks for atopic dermatitis. He was diagnosed with atopic dermatitis 20 years prior to presentation. He did not have any ocular symptoms before the initiation of dupilumab and pretreatment ophthalmological examinations were positive only for refractive errors. Before presentation he had tried artificial tears, ketotifen drops, tetrazoline drops, and eyelid wipes without any relief. In addition to atopic dermatitis, his medical history was significant for asthma and hypertension. His other systemic medications included amlodipine, esomeprazole, losartan-hydrochlorothiazide, albuterol, and budesonide/formoterol inhalers.

At presentation, his uncorrected visual acuity was 20/30 in each eye. His intraocular pressure (IOP) was 13 mm Hg in the right eye (OD) and 10 mm Hg in the left eye (OS). On external examination, he had edema of the eyelids in both eyes (OU) without erythema or crusting. On slit-lamp examination, he had a 3+ injection of the bulbar conjunctiva, giant papillary reaction of inferior tarsal conjunctiva, and superficial punctate keratopathy OU. He had 1+ nuclear sclerotic cataract in both eyes. At his initial visit, he was started on 0.05% difluprednate 4 times a day in both eyes.

When he returned for a follow-up 4 days later, his ocular symptoms were improved and his conjunctival injection decreased. Conjunctival swabs were taken for cultures during this follow-up visit. The cultures were negative for chlamydia, respiratory syncytial virus, influenza A virus, influenza B virus, parainfluenza 1 virus, parainfluenza 2 virus, parainfluenza 3 virus, and adenovirus. An aerobic bacterial culture yielded a low growth of *Staphylococcus aureus*; he was treated with 0.3% ofloxacin drops; however, this growth on the culture was likely a contaminant. His symptoms and signs had resolved when he came for a follow-up 3 weeks after initial presentation, during which time he began tapering the dose of his difluprednate drops to once daily in both eyes. At his last follow-up

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visit, 7 weeks after presentation, his conjunctivitis remained controlled in both eyes, and he was advised to stay on difluprednate every other day in both eyes.

Case 2

The second case is a 19-year-old white man who presented with redness, photophobia, tearing, and burning sensation of both eyes for approximately 15 months duration. The patient was diagnosed with atopic dermatitis during his infancy. His atopic dermatitis worsened at age 2 and remained uncontrolled until he started dupilumab 300 mg every 2 weeks. Although the patient reported mild redness and itching of both eyes before the initiation of dupilumab, findings during pretreatment ophthalmological annual examinations were unremarkable. The patient developed severe ocular symptoms only 3 months after he started taking dupilumab. His presenting symptoms were not controlled with lubricant artificial tears, topical antibiotic drops, and naphazoline/pheniramine topical drops. He had started 0.05% cyclosporine drops 2 times per day OU several days before his presentation. In addition to atopic dermatitis, his medical history was also significant for asthma and herpes labialis.

At initial presentation, visual acuity was 20/40 in OD (improving to 20/20 with pinhole) and 20/30 in OS. His IOP was 8 mm Hg OD and 11 mm Hg OS. On external examination, he was noted to have erythema and edema of both the upper and lower eyelids of both eyes. On slit-lamp examination, he had a 2+ diffuse injection of bulbar conjunctiva associated with mild diffuse chemosis, papillary reaction of inferior and superior tarsal conjunctiva, and micropannus involving the inferior portion of the cornea in both eyes (Fig. 1A). In addition, he had a symblepharon in the right eye inferonasally. His lenses were clear, and the fundus examination was unremarkable in both eyes. The patient was started on 1% prednisolone acetate drops 6 times per day OU along with the continuation of 0.05% cyclosporine drops 2 times per day OU.

When he returned for the follow-up 4 weeks later, his ocular symptoms had improved. On examination, the erythema and edema of the eyelids and the injection and chemosis of the bulbar conjunctiva had disappeared and the micropannus regressed in both eyes (Fig. 1B). However, the symblepharon remained in OD.



FIGURE 1. External photographs of subject 2 at presentation (A) and after 4 weeks of treatment (B).

The regimen of his prednisolone acetate drops was decreased to 4 times per day in both eyes. Eight weeks after initial presentation, he remained asymptomatic and his conjunctivitis remained inactive. The prednisolone acetate drops were switched to loteprednol acetate 0.5% drops twice per day in both eyes for long-term maintenance. He continued cyclosporine drops twice per day in both eyes.

DISCUSSION

Ophthalmologists should be aware of the possibility of significant ocular surface inflammation associated with dupilumab treatment including potential irreversible changes of the ocular surface. The most common ocular adverse effect for dupilumab in clinical trials was unspecified conjunctivitis. The study protocols did not require any specific query about ocular symptoms in the key studies, and patient-reported ocular adverse effects were noted by the study team members.^{1,5–7} Other uncommonly reported manifestations were periocular dermatitis, infectious uveitis, and orbital varicella zoster infections.^{8,9} The highest rates for conjunctivitis were reported in the LIBERTY AD CAFÉ study.¹ The duration-adjusted incidence rates for the development of conjunctivitis with dupilumab compared with placebo were 81.13 per 100 patient years versus 38.94 patients per 100 patient years, respectively.¹⁰ The risk factors identified in the same study for developing conjunctivitis were severe atopic dermatitis at baseline, a history of conjunctivitis, and certain biomarkers (thymus and activation-regulated chemokine, IgE, and eosinophils).¹⁰ Studies using dupilumab for the treatment of conditions other than atopic dermatitis, included asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis, each of which showed no difference in the rate of conjunctivitis between treatment and placebo arms.^{11–16} Thus, atopic dermatitis is a risk factor for the development of conjunctivitis in patients treated with dupilumab.

To our knowledge, there are 2 cases of cicatricial changes previously reported in the literature. Levine et al¹⁷ reported a case of a 49-year-old man with severe atopic dermatitis who presented with cicatrizing blepharoconjunctivitis 8 weeks after starting dupilumab treatment. The patient was successfully managed with steroid drops and was able to continue dupilumab treatment. The second case was reported by Barnes et al¹⁸ of a 61-year-old man with cicatricial ectropion 2 months after starting dupilumab. He was treated with an oral steroid taper and his lid position recovered after 12 weeks of treatment, but his symptoms did not resolve and dupilumab treatment was discontinued. By contrast, the second case presented in this article had already developed a persistent symblepharon.

Management should be based on a timely and accurate diagnosis. Evaluation for concomitant disease, such as infectious blepharitis, is crucial to exclude other causes of ocular surface inflammation. We believe that patients with severe atopic dermatitis or a history of conjunctivitis should be evaluated by an ophthalmologist by using a slit lamp before treatment initiation. The development of ocular symptoms should prompt a timely referral to manage this potentially complex disease. Being able to identify

cicatricial changes during early stages is critical to preventing progression.

The continued use of dupilumab must be evaluated jointly by the ophthalmologist and dermatologist based on the ocular risk versus systemic benefit. In most cases, local treatment of the ocular disease allows for continuation of dupilumab, given its efficacy in improving cutaneous symptoms of atopic dermatitis. The various modalities of treatment that have been reported in the literature include topical steroids, cyclosporine, lifitegrast, tacrolimus, and oral prednisone.^{17,18} In our opinion, topical steroids are the initial treatment of choice because of their rapid onset of action and efficacy. The steroid potency should be adjusted to the severity of inflammation at presentation. The authors would like to indicate that the use of difluprednate in case 1 and the use of loteprednol etabonate in case 2 were off-label. Once inflammation is controlled by topical steroids, changing to a less potent steroid, such as loteprednol, or topical steroid sparing agent, such as cyclosporine, can be made. This decision should be tailored to each patient, depending on individual risk factors including a history of IOP elevation because of a steroid response, risk for infection, cost, and risk of cataract formation.

In summary, the ocular manifestations of dupilumab-associated conjunctivitis can be severe. Identification of patients at higher risk is crucial and dermatologists play a fundamental role in prompting an early referral. Because more patients with atopic dermatitis are being treated with this medication, we expect an increase of the incidence of this complication. Thus, the ophthalmologist should be aware of and be ready to initiate treatment to prevent progression.

REFERENCES

1. de Bruin-Weller M, Thaçi D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol*. 2018;178:1083–1101.
2. Paulose SA, Sherman SW, Dagi Glass LR, et al. Dupilumab-associated blepharoconjunctivitis. *Am J Ophthalmol Case Rep*. 2019;16:100550.
3. Roca-Ginés J, Rahhal-Ortuño M, Torres-Navarro I, et al. Cyclosporine 0.1% (Ikervis®) treatment in steroid-dependent dupilumab-associated conjunctivitis. *Arch Soc Esp Ophthalmol*. 2019;94:396–399.
4. Shen E, Xie K, Jwo K, et al. Dupilumab-induced follicular conjunctivitis. *Ocul Immunol Inflamm*. 2019;27:1339–1341.
5. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389:2287–2303.
6. Thaçi D, L Simpson E, Deleuran M, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *J Dermatol Sci*. 2019;94:266–275.
7. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375:2335–2348.
8. Yamane MLM, Belsito DV, Glass LRD. Two differing presentations of periocular dermatitis as a side effect of dupilumab for atopic dermatitis. *Orbit*. 2019;38:390–394.
9. Ivert LU, Wahlgren C-F, Ivert L, et al. Eye complications during dupilumab treatment for severe atopic dermatitis. *Acta Derm Venereol*. 2019;99:375–378.
10. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol*. 2019;181:459–473.
11. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388:31–44.
12. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378:2475–2485.
13. Rabe KF, Nair P, Brusselle G, et al. Dupilumab in patients with corticosteroid-dependent severe asthma: efficacy and safety results from the randomized, double-blind, placebo-controlled phase 3 Liberty Asthma Venture study. *Am J Respir Crit Care Med*. 2018;197:A7712.
14. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378:2486–2496.
15. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315:469–479.
16. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active Eosinophilic Esophagitis. *Gastroenterology*. 2020;158:111–122.e10.
17. Levine RM, Tattersall IW, Gaudio PA, et al. Cicatrizing blepharoconjunctivitis occurring during dupilumab treatment and a proposed algorithm for its management. *JAMA Dermatol*. 2018;154:1485–1486.
18. Barnes AC, Blandford AD, Perry JD. Cicatricial ectropion in a patient treated with dupilumab. *Am J Ophthalmol Case Rep*. 2017;7:120–122.