

Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis

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IMPORTANCE Clinical trials of dupilumab for atopic dermatitis (AD) have reported an increased incidence of conjunctivitis in patients who received dupilumab compared with those who received placebo.

OBJECTIVE To describe the characteristics of patients who develop conjunctivitis secondary to dupilumab treatment for AD.

DESIGN, SETTING, AND PARTICIPANTS Case series of 12 patients who reported development of conjunctivitis from a cohort of 142 patients treated with dupilumab for AD at a secondary care center from March 14, 2017, to March 29, 2018.

EXPOSURES Patients received a 600-mg injection of dupilumab as a loading dose and a 300-mg injection every 2 weeks thereafter.

MAIN OUTCOMES AND MEASURES Primary outcome measures were severity of AD as measured by the Investigator Global Assessment (IGA) score, a 5-point scale from 0 (clear) to 4 (severe), at the time of dupilumab initiation and at conjunctivitis onset.

RESULTS Of the 12 patients included in this series, 7 (58%) were male. The mean (SD) age of patients was 30 (8.1) years at the time conjunctivitis developed. All patients showed improvement of their AD at the time of conjunctivitis diagnosis, with a mean (SD) 1.9 (0.8)-point decrease in IGA score and 47.8% (11.2%) decrease in body surface area affected. Nine of the 12 patients (75%) had severe baseline AD with an IGA score of 4. All patients who discontinued treatment had severe AD at the time of initial dupilumab administration and had at least 1 atopic condition in addition to AD.

CONCLUSIONS AND RELEVANCE Conjunctivitis that develops after administration of dupilumab to treat AD may be severe enough to necessitate stopping therapy. Severe conjunctivitis was more likely to develop in patients with more severe baseline AD who had a good response to dupilumab and an increased atopic phenotype. Studies are needed to confirm risk factors associated with development of conjunctivitis and to determine effective treatment.

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Clinical trials evaluating dupilumab treatment for atopic dermatitis (AD) have reported rapid improvement in patients with moderate to severe disease; however, an increased incidence of conjunctivitis has been detected in patients who received the drug compared with those who received placebo.^{1,2} Risk factors for the development of conjunctivitis have yet to be identified. With this case series, we describe characteristics of patients in whom conjunctivitis developed after dupilumab administration and note the distinctions in those severe enough to warrant discontinuation of dupilumab secondary to the conjunctivitis.

Methods

From March 14, 2017, to March 29, 2018, we retrospectively identified 12 cases of conjunctivitis diagnosed in a cohort of 142 patients in our clinic who were treated for AD with a 600-mg loading dose and subsequent biweekly 300-mg injections of dupilumab. All patients were warned of this and other potential adverse effects and instructed to contact the clinic if symptoms developed. Conjunctivitis was confirmed by conjunctival inflammation on clinical examination. Because this was a case series and patients were deidentified, we did not consult an institutional review board for approval. All patients signed a general consent stating that their information in the medical record may be used for research.

We retrospectively collected data on patients' age, sex, age at onset of AD, and history of other atopic or eye ailments. Investigator Global Assessment (IGA) score (based on a 5-point scale from 0 [clear] to 4 [severe]) and body surface area of AD involvement were recorded at the time of dupilumab initiation and at the office visit closest to the development of con-

Key Points

Question What factors are associated with the development of conjunctivitis in patients treated with dupilumab for atopic dermatitis?

Findings In this case series of 12 adults in whom conjunctivitis developed during dupilumab treatment for atopic dermatitis, 9 had severe atopic dermatitis at baseline. Severe conjunctivitis was seen only in patients with severe atopic dermatitis at baseline and in those with another atopic condition in addition to atopic dermatitis.

Meaning Baseline atopic dermatitis severity and history of atopic conditions should be considered when stratifying the risk for conjunctivitis development secondary to dupilumab administration for patients with atopic dermatitis.

junctivitis. A single dermatologist (P.A.L.) assigned all IGA scores and determined the severity of conjunctivitis (mild, moderate, or severe) based on the intensity of bulbar or palpebral hyperemia, whichever was worse. All reported symptoms, eye treatments prescribed for conjunctivitis, and ophthalmology notes that were available are listed in **Table 1**. Microsoft Excel for Mac, Version 15.25.1 (Microsoft) software was used for statistical calculations.

Results

The mean (SD) age of patients was 30 (8.1) years at the time of development of conjunctivitis, and 7 of the 12 patients (58%) were male. All patients were noted to have a history of childhood AD, and none reported a history of eye conditions. Nine

Table 1. Conjunctivitis Severity and Outcomes^a

Patient No.	Conjunctivitis Severity	Eye Symptoms	Conjunctivitis Treatment	Ophthalmology Visit	Dupilumab Outcome
1	Severe	Hyperemia, blepharitis, irritation, dryness, pruritus, decrease in acuity, yellow discharge	Bromfenac, cyclosporine, loteprednol	Yes	Discontinued
2	Mild	Hyperemia, yellow discharge, swelling	Oral doxycycline, tobramycin-dexamethasone	No	Continuing
3	Unavailable	Hyperemia, eyelid irritation	Azithromycin	No	Continuing
4	Mild	Hyperemia, epiphora	Artificial tears, oral doxycycline	No	Continuing
5	Mild	Hyperemia	No treatment	Yes	Continuing
6	Severe	Hyperemia, discharge, swelling, irritation	Loteprednol-tobramycin	Yes	Discontinued
7	Moderate	Hyperemia, dryness	Erythromycin ointment, oral doxycycline	No	Continuing
8	Severe	Hyperemia, blepharitis, epiphora, sensitivity	Azithromycin, diclofenac, erythromycin ointment, eyelid cleanser, loteprednol, oral doxycycline, prednisolone	Yes	Continuing
9	Moderate to Severe	Hyperemia, irritation, dryness	Artificial tears, azithromycin, eyelid cleanser, tobramycin-dexamethasone	Yes	Continuing
10	Moderate	Hyperemia	No treatment	No	Temporarily discontinued
11	Moderate	Hyperemia, pruritus, irritation, discharge	Artificial tears, loteprednol-tobramycin, loteprednol, olopatadine	Yes	Continuing
12	Moderate	Hyperemia	Fluorometholone	Yes	Continuing

^a Severity was assessed by an ophthalmologist, ideally as soon as possible after symptoms of conjunctivitis appeared, but often several weeks after first reporting symptoms to the prescribing dermatologist.

Table 2. Patient Demographics and Severity of Atopic Dermatitis at First Dupilumab Administration and Onset of Conjunctivitis

Patient No./Sex/Age, y	Race/Ethnicity	Other Atopic Conditions	Before Treatment		At Conjunctivitis Onset ^a					Duration of Dupilumab Treatment, wk
			IGA Score ^b	BSA, %	IGA Score ^c	BSA, %	AD Location	Δ IGA ^c	Δ BSA, % ^c	
1/M/30s	White	Hay fever	4	70	2	20	Arms	-2	-50	11
2/F/20s	Asian	Asthma	4	60	1	10	Arms	-3	-50	12
3/M/20s	White	Asthma	4	80	1	15	Perioral, neck, arm,	-3	-65	22
4/F/40s	Asian	None	4	60	2	25	Arm, trunk, legs	-2	-35	16
5/M/30s	Asian	None	3	55	1	10	Cheek, trunk	-2	-45	21
6/M/30s	White	Asthma, hay fever	4	65	2	NR	Cheek, neck, trunk	-2	NA	11
7/M/30s	White	None	3	55	2	10	Arms	-1	-45	8
8/M/20s	White	Asthma	4	55	3	15	Legs	-1	-40	11
9/F/20s	White	None	4	NR	3	60	Face, neck, trunk, arm, hand	-1	NA	9
10/M/20s	Asian	Asthma	4	85	NR	NR	NR	NA	NA	20
11/F/20s	Hispanic	Asthma	4	75	1	10	Forehead, arms	-3	-65	8
12/F/30s	Asian	None	3	65	2	30	Forehead, cheek, neck, arms	-1	-35	41
All/30 (8.1) ^d	NA	NA	3.8 (0.5)	65.9 (10.4)	1.8 (0.8)	20.5 (15.5)	NA	-1.9 (0.8)	-47.8 (11.2)	15.8 (9.4)

Abbreviations: AD, atopic dermatitis; BSA, body surface area; Δ BSA, change in BSA; Δ IGA, change in IGA; IGA, Investigator Global Assessment; NA, not applicable; NR, not recorded.

^a Indicates at the clinic visit closest to conjunctivitis onset.

^b The IGA is a 5-point scale scored from 0 (clear) to 4 (severe).

^c Indicates time from before treatment to the time of conjunctivitis onset.

^d Data in this row given as mean (SD) values calculated from all patients with available data.

patients were noted to have had severe AD (IGA score, 4) and 3 to have moderate AD (IGA score, 3) at the time of initial dupilumab administration (Table 2), with 1 patient having baseline eyelid involvement.

Conjunctivitis developed after a mean (SD) of 15.8 (9.4) weeks of treatment (range, 8-41 weeks). All patients showed improvement of their AD at the time of conjunctivitis diagnosis, with a mean (SD) 1.9 (0.8)-point decrease in IGA score and 47.8% (11.2%) decrease in body surface area affected (Table 2).

One patient temporarily discontinued and 2 permanently discontinued dupilumab therapy because of severe conjunctivitis. All 3 of these patients had severe baseline AD and at least 1 atopic condition in addition to AD, and both patients who permanently discontinued use of the drug had a history of hay fever, a diagnosis not found in any other patient in the cohort (Tables 1 and 2).

After 2 months of discontinuation, patient 10 restarted treatment with dupilumab, with no further evidence of conjunctivitis; this patient's AD did not improve until approximately 8 weeks into the second course of dupilumab. As of this writing, the patient continues to receive dupilumab and is doing well.

Both patients who permanently discontinued the drug experienced an improvement in conjunctivitis severity after cessation of dupilumab treatment, although symptoms persisted at the most recent ophthalmologist visit. Ten weeks after drug cessation, patient 1 was noted to have 1+ bulbar hyperemia and 2+ palpebral hyperemia bilaterally on a scale of increasing severity of 0 to 4. This patient was also found to have limbal edema and corneal scarring, and blepharitis and atopic keratoconjunctivitis (AKC) were diagnosed, although other

causes of conjunctivitis cannot be excluded. Eight weeks after drug cessation, patient 6 was noted to have bilateral 2+ palpebral hyperemia and received a diagnosis of acute conjunctivitis.

Discussion

Phase 2b and 3 trials have found a combined 8% incidence of conjunctivitis in participants who received dupilumab; however, a 14% incidence of conjunctivitis was found in the longest trial to date (52 weeks).^{2,3} In our patient population, the mean (SD) time from treatment initiation to the development of conjunctivitis was 15.8 (9.4) weeks; however, in 4 patients, conjunctivitis developed after 20 weeks, suggesting that the 16-week end point of select trials may have missed cases that developed later. We propose that a short treatment time for some patients and reliance on patient self-report underestimates at 8.5% the incidence of conjunctivitis in our cohort of 142 patients with AD treated with dupilumab.

In previous trials, more than 90% of conjunctivitis cases were mild or moderate in severity, and a single patient discontinued treatment with dupilumab after AKC developed.² Our patient population differed in that a greater percentage (3 of 12 [25%]) experienced severe conjunctivitis (1 with AKC), and 2 patients permanently discontinued dupilumab treatment owing to the severity. Although it has been reported that treatment with antibiotic, cyclosporine, or medium- to high-dose corticosteroid eyedrops leads to improvement in conjunctivitis secondary to dupilumab,⁴ both patients were treated with corticosteroid eyedrops and 1 with corticosteroid plus an-

tibiotic without sufficient relief. Furthermore, in these 2 patients, conjunctivitis developed earlier than the mean time for all patients, suggesting a need for vigilance in conjunctivitis detection early in treatment.

It is unclear what predisposes patients with AD to the development of severe conjunctivitis secondary to dupilumab; AD severity and history of additional atopic conditions should be considered. Previous studies have noted that patients with conjunctivitis were more likely to have severe AD.¹ In this patient population, 9 of the 12 patients, including all patients with severe conjunctivitis, had an IGA score of 4 before the initiation of dupilumab treatment. Patients with conjunctivitis seemed to have a good cutaneous response to dupilumab despite conjunctivitis development.

In addition to increased severity of AD, the results of this series suggest that certain atopic phenotypes may increase the propensity for conjunctivitis development. Both patients who permanently discontinued dupilumab treatment had a history of hay fever. In addition, our patient population had an increased atopic phenotype 7 of the 12 cases (58%) compared with population studies, in which 31.1% of patients with AD have an additional atopic condition,⁵ although these results may be confounded by severe disease.

Currently, the pathogenesis of conjunctivitis secondary to dupilumab administration is not understood. One suggestion is that *Demodex* mites may thrive in decreased ocular cytokines, leading to interleukin 17 (IL-17)-mediated inflammation and a disease similar to ocular rosacea.⁶ Some authors refute this suggestion, noting that IL-17 is decreased in treated

patients and that the conjunctivitis is too short lived.⁷ Others have suggested that dupilumab may increase AKC-specific ligands and, subsequently, rates of AKC. Still others point to an increase in eosinophil counts after drug administration, noting that eosinophilic factors are elevated in the tears of patients with allergic conjunctivitis.⁸ Perhaps most striking are the potential implications of IL-13 inhibition. In a phase 2 trial of lebrikizumab, a monoclonal antibody against IL-13, a trend for increased conjunctivitis was identified.⁹ This association was not noted in previous trials for asthma.⁹ Although IL-13 has been implicated in ocular mucus production and immune function,¹⁰ it is unclear why inhibition of this cytokine would lead to conjunctivitis exclusively in patients with AD.

Conclusions

Although uncommon, the development of conjunctivitis can be severe enough to necessitate cessation of dupilumab in some patients.¹¹ This outcome is particularly distressing, as conjunctivitis seems to favor those with more severe baseline AD that responds well to the drug. Given the limitations of our study, including reliance on patient self-report of conjunctivitis and involvement of a single institution, future studies are needed to confirm the increased risk of conjunctivitis development associated with severe baseline AD and certain atopic phenotypes. There may be utility in early ophthalmology referral and prophylactic treatment for at-risk patients.

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