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Staying ahead of dupilumab-associated ocular surface disease

Patricia-Ann Laughrea, MD, FRCSC and Mélanie Hébert, MD, MSc

INTRODUCTION

Dupilumab is an immunomodulatory medication blocking interleukins. This biologic drug is an injectable human monoclonal antibody targeting the α subunit of interleukin (IL)-4 which affects the IL-4 and IL-13 pathways. Since its approval by the United States Food and Drug Administration and Health Canada in 2017,[1] it has been used extensively for the treatment of multiple diseases, including chronic rhinosinusitis with nasal polyposis, asthma, and most notably atopic dermatitis. In patients with moderate-to-severe atopic dermatitis (AD), dupilumab has significantly improved patients' quality of life. In the pivotal SOLO 1 and SOLO 2 trials involving patients aged 18 years and older, dupilumab was compared with placebo and demonstrated a significant reduction in Investigator Global Assessment (IGA) atopic dermatitis score down to "clear" or "almost clear" (i.e., 0 or 1) and a ≥ 2-point improvement from baseline in that same score at week 16. This primary endpoint was achieved in 36-38% of patients on dupilumab compared with 8-10% of patients on placebo.[2] However, these outcomes are not without drawbacks.

The emergence of dupilumab-associated ocular surface disease (DAOSD) or dupilumab-induced ocular surface disease (DIOSD) is now commonly reported by both dermatologists and ophthalmologists who treat AD patients using dupilumab.[3–5] Interestingly, dupilumab has not been associated with increased conjunctivitis rates in studies in other diseases, including asthma and chronic rhinosinusitis with nasal polyposis, which suggests that the increased rates of conjunctivitis in AD studies may reflect a unique interaction between AD and dupilumab-related mechanisms.[6] The SOLO 1 and SOLO 2 trials were the first to detect a higher rate of conjunctivitis in dupilumab-treated patients with 3-5% of the dupilumab-treated patients developing "conjunctivitis of an unspecified cause" compared to 1% in the placebo groups,[2] with 1 of 920 patients discontinuing dupilumab because of conjunctivitis in SOLO 1.[6] The highest rate among dupilumab trials was in LIBERTY AD CAFÉ where conjunctivitis was reported in 16%, 28% and 11% of patients in the weekly dupilumab + topical corticosteroid (TCS), every two weeks + TCS and placebo + TCS groups, respectively; all but one event were mild or moderate.[7,8] However, in those trials patients did not undergo complete ophthalmological examinations to characterize the type of ocular involvement that was reported. Subsequent research and real-world experience has since detailed the variety of findings associated with DAOSD. With more studies now published, including those which involve subjects examined by ophthalmologists, we have a better idea of the incidence of DAOSD. A recent Canadian study reported a rate of DIOSD at 37% over a 52-week follow-up period, with 19% of these patients requiring a consultation in ophthalmology.[9] Most of the time, only the most severe cases will be referred to ophthalmologists, while milder cases will be treated by dermatologists or primary care providers through the use of artificial tears.

The aim of this article is to provide a basic framework for clinicians to understand the pathophysiology of DAOSD, how to diagnose DAOSD, and the optimal treatment strategy for these patients.

PATHOPHYSIOLOGY AND RISK FACTORS

The exact pathophysiological mechanism leading to DAOSD has not yet been clearly elucidated. However, two hypotheses are worthy of mention. First, IL-13 inhibition may induce loss of conjunctival goblet cells, which are responsible for lubrication and production of mucin.[10,11] These are essential components of the tear film and deficiency can lead to dry eye disease.[5,10] Second, an increase in Th1-mediated inflammatory response, in relation with the chronicity of atopic disease, is another mechanism to be considered.[12,13]

The time to onset of clinically apparent DAOSD seems to require a few months. This may be related to the achievement of a steady-state concentration of dupilumab in the blood by the four month timepoint. Alternatively, the onset of DAOSD could also be related to the time required for deterioration of the ocular surface, and for the patient to become symptomatic. In studies which examined symptomatic patients referred by dermatologists, the average time to diagnosis of DAOSD by an ophthalmologist varied between 1 and 10 months.[14,15] This differs from studies with patients examined earlier and more systematically where signs of ocular surface disease could be detected within two weeks of dupilumab treatment being initiated.[16]

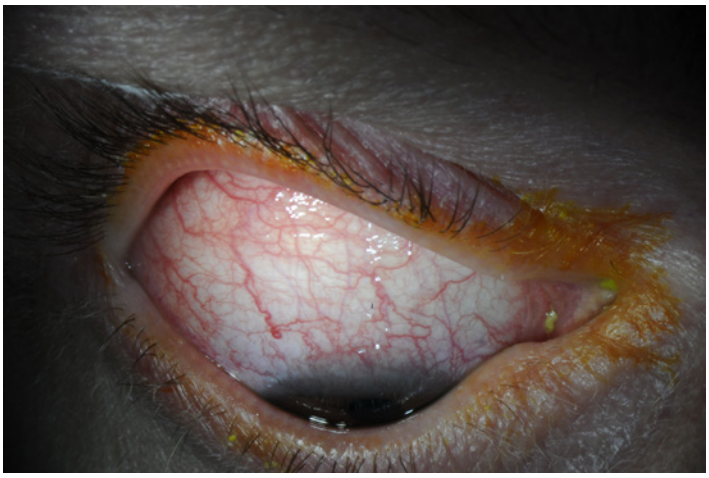
The relationship between the severity of atopic dermatitis and of previous atopic facial or palpebral involvement remains uncertain but these may be predisposing factors.[8,15,16]

CLINICAL SIGNS AND SYMPTOMS

Patients who develop DAOSD often complain of redness, burning, tearing, and foreign body sensation. Patients may also complain of crusting and discharge with occasionally worsening of periocular atopic dermatitis-like findings.

On ophthalmological examination, visual acuity is usually preserved, though patients can complain of blurred vision. Ocular findings are most often bilateral but can be asymmetric and are usually limited to the anterior segment.

The associated redness is the most frequent sign and is often striking. This could be described as an episcleritis-like, inflammatory conjunctivitis (**Figure 1**). Diffuse or sectoral hyperemia of the limbus with nodular swelling and Horner-Trantas-like dots can also be found.. Infrequently, the inflammation will lead to conjunctival scarring, cicatricial symblepharon, punctal stenosis, or ectropion.[17–20]



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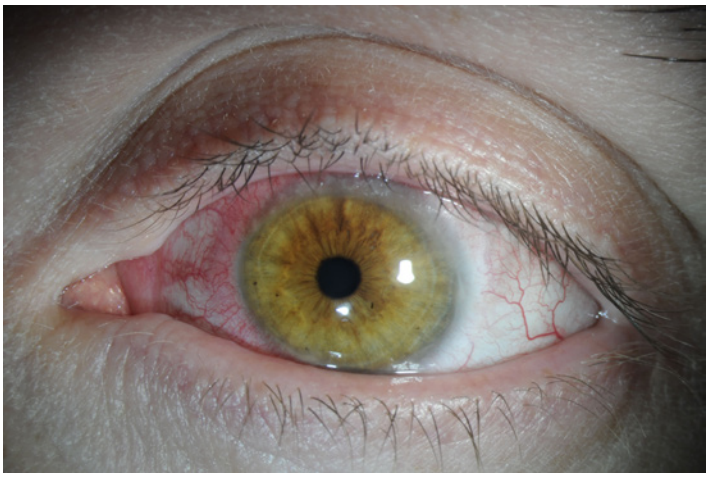

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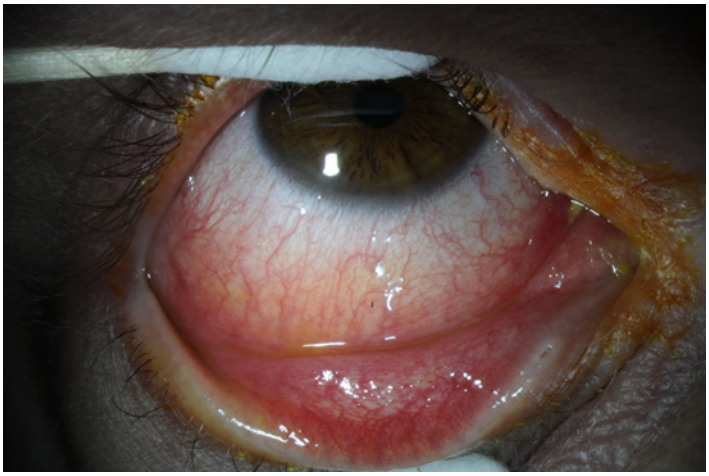

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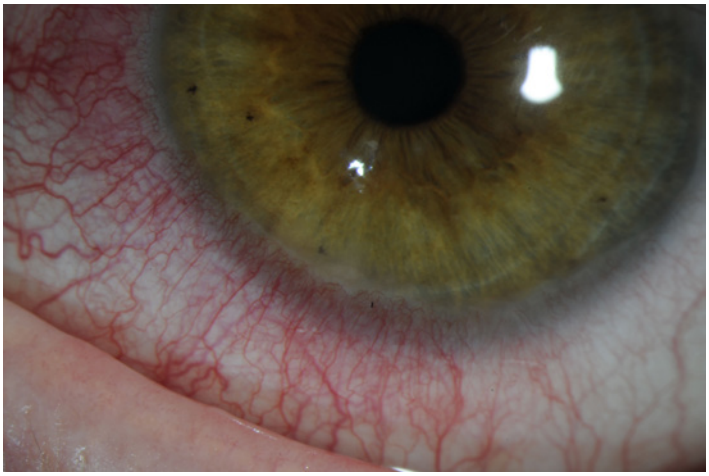

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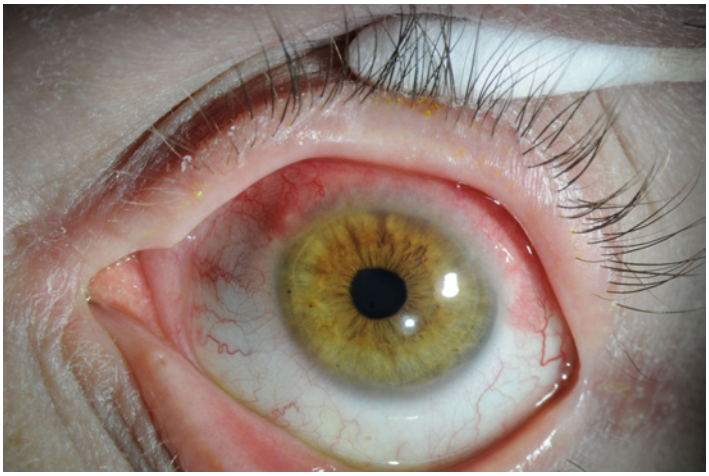

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Figure 1: *Photographic examples of dupilumab-associated ocular surface disease (DAOSD), including (A, B) diffuse, inflammatory conjunctival hyperemia, (C, D) limbitis with Horner-Trantas-like dots in the absence of significant eyelid disease, and (E) magnified view of concomitant peripheral sterile corneal infiltrates; photos courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD*

SIGNS OF DAOSD	RELATIVE FREQUENCY
Conjunctival hyperemia	very frequent, typical sign
Inflammatory conjunctivitis	very frequent, typical sign
Dry eye disease	very frequent, typical sign
Limbal inflammation / limbitis (including nodules and Horner-Trantas-like dots)	frequent
Blepharitis (atopic dermatitis-like)	frequent
Peripheral or central corneal infiltrates	rare sign, association less clear
Episcleritis	rare sign, association less clear
Corneal ulceration (up to perforation)	very rare sign, few case reports
Cicatricial conjunctivitis (including punctal stenosis, fornix shortening, symblepharon, ectropion)	very rare sign, few case reports

Table 1: *Clinical findings in dupilumab-associated ocular surface disease (DAOSD) by relative frequency; courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD*

On the cornea, inferior punctate epithelial erosions are common. Other signs of dry eye disease can be expected such as decreased tear breakup time (TBUT) and reduced tear meniscus. Inflammatory, marginal keratitis-like sterile infiltrates can be found in the periphery of the cornea, or centrally. These tend not to be very dense, contrary to infectious ulcers but can be confounding in establishing a differential diagnosis. A few isolated cases of corneal ulceration and thinning with possible perforation and cases of intraocular or posterior involvement have been reported (e.g., posterior scleritis, anterior uveitis, placoid chorioretinitis, macular edema).[20–22] Further studies and cases are needed to confirm these findings. See **Table 1** for common signs of DAOSD and their relative frequency.

DIAGNOSIS

DAOSD remains a clinical diagnosis relying on a complete ophthalmological exam with slit-lamp biomicroscopy. Other tests such as Schirmer's test and TBUT can be useful but are less likely to differentiate DAOSD from other types of ocular surface diseases. To properly identify patients with possible DAOSD, probing for a history of dupilumab use is crucial as this could otherwise go unnoticed. At consultation, the clinician should determine the duration in months and dosing interval (e.g., every week or every two weeks) of dupilumab use. Additionally, some patients may report worsening of their symptoms shortly following dupilumab injection, which would be more specific for DAOSD.

Exacerbation of pre-existing atopic keratoconjunctivitis can be a significant confounder for the diagnosis of DAOSD; however, in patients who had little or no symptoms of atopic keratoconjunctivitis prior to starting dupilumab, DAOSD becomes more likely. Other diagnoses may help in the differential diagnosis, including atopic keratoconjunctivitis, allergic keratoconjunctivitis, vernal keratoconjunctivitis, dry eye syndrome, bacterial blepharoconjunctivitis, meibomian gland dysfunction, marginal keratitis / staphylococcal hypersensitivity, viral keratoconjunctivitis, episcleritis, phlyctenulosis, superior limbic keratitis, contact lens-associated giant papillary conjunctivitis or keratitis, and infectious infiltrates.[23,24] Identifying possible factors leading to a deterioration of symptoms such as seasonal changes or contact lens wear may help differentiate from other etiologies.

GIven that DAOSD is generally a bilateral disease, when unilateral symptoms are present, careful examination of the fellow eye should always be performed, as it may reveal subtle signs of DAOSD as well. In the absence of signs in the fellow eye, an alternative diagnosis to DAOSD should be considered.

MANAGEMENT

A management flowchart for DAOSD is suggested in **Figure 2**. For mild disease, artificial tears and antihistamine-mast cell stabilizer eyedrops (e.g., olopatadine 0.2%) will help to control signs and symptoms associated with dry eye and allergic keratoconjunctivitis, respectively.[13,16] The initiation of prophylactic artificial tear treatment, before the onset of symptoms, has been documented in the literature and has resulted in a decreased incidence of DAOSD.[4,13,25] Artificial tears should ideally be preservative-free with a frequency that can be titrated up to every hour. Some patients may prefer a more viscous formula like a gel or ointment, especially at night. Warm compresses with or without lid hygiene to address meibomian gland dysfunction can be a useful adjunct.

If clinical response is not achieved, especially in the setting of severe and diffuse conjunctivitis or limbal inflammation, mild (e.g., fluorometholone 0.1%, fluorometholone 0.25%, loteprednol 0.2%, loteprednol 0.5%, rimexolone 1%) or strong (e.g., prednisolone 0.12%, prednisolone 1%, dexamethasone 0.1%, difluprednate 0.05%) corticosteroid eye drops can be used. This can be titrated depending on the severity of the symptoms and the degree of inflammatory involvement. Corticosteroid eyedrops are typically started q.i.d. with a taper of one drop every 2 to 4 weeks depending on treatment response. In the absence of clinical response, the strength and frequency of corticosteroid eyedrops can be increased. The taper of corticosteroids can be lengthy and require multiple adjustments. Prolonged corticosteroid eyedrop use necessitates close ophthalmologic follow-up as serious adverse events such as increased intraocular pressure, glaucoma, infection, and cataracts may appear, sometimes in just a few weeks. It can then be necessary to reduce the potency and frequency to the minimum tolerated dose.

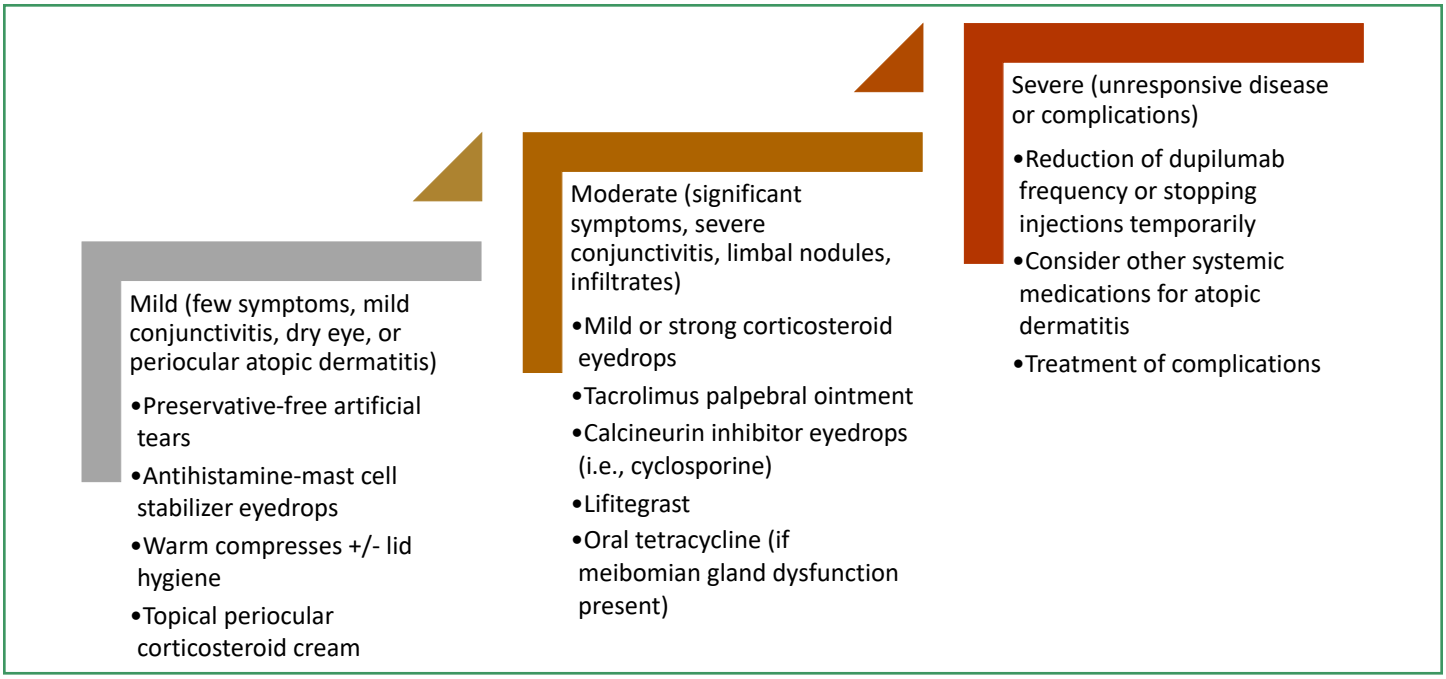

Figure 2: *Suggested management flowchart for patients with mild, moderate, and severe dupilumab-associated ocular surface disease; courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD*

Calcineurin inhibitor eyedrops such as cyclosporin 0.05% to 1%[13,26] or tacrolimus 0.03% eye ointment (off-label use)[27] and lifitegrast[3] have been tried, with authors reporting good response in a few small series and case reports. Tacrolimus ointment 0.03% or 0.1% applied to the lid margins has demonstrated improvement in some cases,[14,28] and has been proposed as a potential first-line therapy for moderate-to-severe dupilumab-induced blepharoconjunctivitis.[16] The addition of oral tetracycline antibiotics (e.g., doxycycline or minocycline) may be considered when meibomian dysfunction seems prominent. A discussion with the patient's dermatologist may be necessary if sufficient DAOSD control cannot be achieved with corticosteroid eyedrops or if the patient exhibits serious side effects such as steroid-response glaucoma. This could require reducing dupilumab frequency or discontinuing dupilumab temporarily or considering alternate atopic dermatitis medications including drugs that are currently in research protocols.

In DAOSD cases with corneal infiltrates and ulceration, an infectious cause should be ruled out first and broad-spectrum antibiotics such as a fluoroquinolone should be used to treat a presumed infectious ulcer. If the infiltrates are bilateral and do not have an associated epithelial deficit in a non-contact lens wearer, an ophthalmologist can more comfortably assume a sterile, inflammatory cause such as DAOSD or marginal keratitis and start the necessary corticosteroid eyedrops.

In certain patients, the eyelids and periocular skin may have findings like atopic dermatitis even with quiescent cutaneous disease. The body's response to dupilumab may be heterogenous with some systems (i.e., the skin) having a different response compared to others (i.e., the eyes). For example, de novo blepharitis may occur or existing blepharitis may worsen despite the excellent cutaneous response for the treatment and mangement of the underlying AD.[6] In these cases, periocular corticosteroids (e.g., hydrocortisone 0.5%) or periocular calcineurin inhibitors (e.g., tacrolimus 0.03%-0.1%) will often help. Again, a discussion with the patient's treating dermatologist may be necessary to select a more potent cream if these do not provide appropriate clinical response.

Clinicians should note that most DAOSD patients will improve while continuing dupilumab therapy. However, this may require ocular and palpebral topical treatment to be used for prolonged periods. Dupilumab will rarely need to be discontinued.

CONCLUSION

Dupilumab has solidified its place in the dermatology armamentarium and is likely to remain a staple in the treatment of moderate-to-severe atopic dermatitis. The conjunctivitis first reported in association with dupilumab treatment for atopic dermatitis is a complex entity. Early identification of DAOSD and prophylactic treatment with artificial tears appear to be beneficial. For moderate-to-severe cases, antihistamine/mast cell stabilizer eyedrops, topical ocular corticosteroids, and palpebral calcineurin inhibitors have demonstrated efficacy. Corticosteroid-sparing topical medication is a promising approach, but further studies are still needed. Most importantly, ophthalmologists, dermatologists, patients and caregivers should be alerted to the risk of DAOSD when using dupilumab. Prompt referral to ophthalmology should be considered for any suspicious ocular sign or symptom in a patient taking dupilumab. Collaboration between ophthalmologists, dermatologists, and primary care providers is crucial to maintaining ocular comfort and preventing ocular complications while still providing control of a patient's atopic dermatitis.

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