

Dupilumab-induced ocular surface disease: A systematic review

To the Editor: Dupilumab is a monoclonal antibody approved for moderate-to-severe atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis.¹ Ocular surface disease was reported as an adverse event in AD dupilumab clinical trials, but not in non-AD clinical trials.¹ Since then, numerous published studies have reported dupilumab-induced ocular surface disease (DIOSD) in patients with AD. This systematic review aims to summarize the current available data regarding DIOSD, including its risk factors, course, and treatment options.

A literature review was conducted using the PubMed, Embase, Cochrane, and ClinicalTrials databases. Publications up to July 29, 2020 were screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Fig 1 available via Mendeley at <https://doi.org/10.17632/y4yxmmjmzs.1>). A total of 77 clinical studies met the inclusion criteria, including 13 case reports, 11 case series, 28 retrospective studies, 11 prospective studies, 13 randomized controlled trials (RCTs), and a single meta-analysis of RCTs, encompassing 11,189 patients treated with dupilumab. Because the detailed characteristics of DIOSD were described primarily in case reports and series and less often in retrospective studies, results are presented separately for each category of clinical studies (Tables I and II).

DIOSD was unique to AD, but was also reported in AD-related dermatologic disorders, such as nummular and dyshidrotic eczema, prurigo nodularis, and allergic contact dermatitis. The incidence of DIOSD was higher in prospective (25.1%) and real-life retrospective trials (20.6%) than in RCTs (10.9%). Most DIOSD cases appeared in the first weeks to months of treatment, were mild to moderate, and resolved with continued dupilumab treatment. Various ophthalmic disorders were described, other than conjunctivitis, including dry or watery eyes, blepharitis, keratitis, eyelid dermatitis, and palpebral edema.

Cessation of dupilumab due to DIOSD was reported in 86 patients (4.5% of patients with DIOSD). Permanent sequelae were even rarer, involving several cases of cicatricial changes.^{2,3} Possible DIOSD risk factors were previous ophthalmic disorders, high baseline AD severity, and elevated IgE levels.

Several beneficial treatment options for DIOSD included warm compresses, artificial tears, topical antihistamines/mast cell stabilizers, topical antibiotics, topical corticosteroids, cyclosporine eye drops, tacrolimus ointment, and lifitegrast eye drops.

Table I. Characteristics of patients with dupilumab-induced ocular surface disease in case reports and case series (n = 86)

Characteristic	No. (% or range)
Mean age in years (range)	40.3 (18-83)*
Female:male ratio (numerical)	2:3 (30:45) [†]
Indication	
Atopic dermatitis	84 (97.6%)
Allergic contact dermatitis	1 (1.1%)
Chronic actinic dermatitis	1 (1.1%)
Severity of atopic dermatitis	
Mild to moderate	8 (9.3%)
Severe [‡]	43 (50%)
Comorbidities	
Ophthalmologic predisposition [§]	9 (10.4%)
Other atopic conditions	30 (34.8%)
Course	
Conjunctivitis	83 (96.5%)
Keratitis	4 (4.6%)
Blepharitis	21 (24.4%)
Dry eyes	5 (5.8%)
Watery eyes	4 (4.6%)
Other	4 (4.6%)
Severe conjunctivitis	20 (23.2%)
Mean latency period to onset of conjunctivitis in weeks (range)	14.75 (1-55)
Patients referred to ophthalmologists	33 (38.7%)
Termination of dupilumab treatment	12 (13.9%)
Treatment [¶]	
Topical anti-inflammatory agents	43 (50%)
Systemic anti-inflammatory agents	3 (3.4%)
Topical moisturizers	23 (26.7%)
Topical antibacterial agents	15 (17.4%)
Systemic antibacterial agents	6 (6.9%)
Other	17 (19.7%)

*For 11 patients, ages were not given; for 6 patients, only the median age was reported.

[†]Eleven patients were not reported with a male:female ratio.

[‡]Fourteen patients were described as having moderate-to-severe atopic dermatitis.

[§]Including dryness, atopic blepharoconjunctivitis, herpes uveitis and secondary glaucoma, keratoconus, corneal transplantation, marginal keratitis, bacterial keratitis, iridocyclitis, and blepharoplasty.

^{||}In 1 patient, dupilumab was temporarily discontinued.

[¶]Some patients received a combination of treatments. Only efficacious treatments are included. Anti-inflammatory agents included corticosteroids, calcineurin inhibitors, and nonsteroidal anti-inflammatory drugs. Moisturizers included artificial tears, trehalose, and petroleum jelly. Antibacterial agents included antibiotics and antiviral agents. Other treatments included topical (12 patients) and systemic (1 patient) antihistamines, lifitegrast (1 patient), and eye cleansers (4 patients).

The main limitation of this systematic review is the vast heterogeneity among the included studies. Nevertheless, this review confirms that an increased incidence of DIOSD is observed almost exclusively

Table II. Rates of DIOSD reported in clinical studies, including retrospective, prospective, open-label studies, and RCTs

Study	Total treated; n	Patients with DIOSD; n	Rate of DIOSD; %	Latency to DIOSD; weeks	Severe DIOSD; n (% of patients with DIOSD)
Real life retrospective	1860	385	20.6	10.1	14 (15.2)*
Prospective and open label	4735	1187	25.1	-	38 (3.6)*

RCT	Total treated; n	Patients and rate of DIOSD in treatment group; n (%)	Total treated with placebo; n	Patients and rate of ocular surface disorders in placebo group; n (%)	Severe DIOSD; n (% of patients with DIOSD)
Atopic dermatitis indication	2,532	276 (10.9)	1325	59 (4.5)	8 (6)*
Nonatopic dermatitis indication	2030	12 (0.59)	953	7 (0.73)	0

DIOSD, Dupilumab-induced ocular surface disease; RCT, randomized controlled trial.

*Of the total number of patients for which data on severity and discontinuation were known.

in patients with AD and AD-related dermatologic disorders. The higher incidence of DIOSD in prospective and real-life retrospective trials than in RCTs may be due to the increased awareness of this adverse effect, which may have been overlooked in earlier RCTs.

The pathogenic mechanisms responsible for DIOSD remain obscure. By blocking interleukin 13, dupilumab may cause goblet cell hypoplasia, resulting in decreased mucin secretion and mucosal epithelial barrier dysfunction, leading to DIOSD.⁴ Alternatively, upregulation of Th1 response due to the effect of dupilumab on Th2 signaling may contribute to DIOSD pathogenesis.⁵

In conclusion, DIOSD is a common adverse effect of dupilumab in AD, which tends to resolve with topical treatment and continuation of dupilumab. Long-term sequelae are rare. Predisposing factors of DIOSD and its pathomechanisms should be further investigated.

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Conflicts of interest

None disclosed.

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Racial disparities in mortality among patients with prurigo nodularis: A multi-center cohort study



To the Editor: Prurigo nodularis (PN) is a chronic inflammatory skin condition characterized by intensely pruritic and hyperkeratotic nodules on the torso and extremities.¹ Studies to date have shown that PN is associated with many systemic and psychiatric comorbidities, and racial/ethnic minorities are affected disproportionately.² Although the morbidity of PN is well documented, there are no available data on the mortality associated with PN. We sought to investigate the mortality among patients with PN and stratify by race/ethnicity to identify racial disparities.