SHORT COMMUNICATION

High Prevalence of Lash Collarettes in Patients with Atopic Dermatitis Treated with Dupilumab

Ilaria TRAVE[1#], Ilaria SALVI[1#], Rei CANAMERI[1], Carlo Alberto CUTOLO[2], Chiara BONZANO[2], Matteo BALDI[2], Carolina BOLOGNA[2], Gabriele DRAGO[2], Giorgio BATTAGLIA[3], Aurora PARODI[1], Michele IESTER[2] and Emanuele COZZANI[1]
[1]Section of Dermatology, Dipartimento di Scienze della Salute (DISSAL) University of Genoa and IRCCS Ospedale Policlinico San Martino, Genoa, [2]Clinica Oculistica DiNOGMI, University of Genoa, IRCCS Ospedale Policlinico San Martino, Genoa, and [3]Department of Law, University of Turin, Turin, Italy. E-mail: ilaria.trave@gmail.com. [#]These authors share first authorship.
Submitted Mar 7, 2025. Accepted after revision Jul 9, 2025
Published Aug 18, 2025. DOI: 10.2340/actadv.v105.43322. Acta Derm Venereol 2025; 105: adv43322.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that represents a significant burden for both patients and the healthcare system. Dupilumab, an interleukin-4 and interleukin-13 inhibitor approved for the treatment of AD, has a favourable safety profile and is generally well tolerated. However, several adverse events have been reported in clinical trials and in real-world data (RWD) (1). While ocular complications were frequently reported in clinical trials investigating dupilumab for the treatment of AD, they were not as common in clinical trials regarding other indications, such as asthma and nasal polyposis (2). The ocular surface is generally involved and the most frequently reported signs and symptoms include conjunctivitis, dry or watery eyes, blepharitis, keratitis, eyelid dermatitis,, and palpebral oedema (2). Interestingly, the reported prevalence of dupilumab-associated ocular surface disease (OSD) was much higher in prospective and real-world evidence (RWE) (25.1%) than in randomized controlled trials (10.9%) (2). The exact pathogenesis of dupilumab-associated OSD is currently unknown with some studies pointing to alterations of the tear film due to functional changes of goblet cells (3) or meibomian gland dysfunction (4) during treatment with dupilumab.

The aim of this study was to focus on the prevalence and characteristics of ophthalmological alterations in patients affected by AD during treatment with dupilumab.

MATERIALS AND METHODS

This cross-sectional study was conducted from January to November 2024 at the Dermatology and Ophthalmology Units of San Martino University Hospital, Genoa, Italy. Adults (≥18 years) with AD treated with dupilumab for at least 6 months were enrolled. Patients under ophthalmological treatment or unable/unwilling to provide informed consent were excluded. Written informed consent was obtained from all participants.

Demographic and clinical data (age, gender, disease and treatment duration, ophthalmological comorbidities) were collected from clinical records. Each patient underwent a simultaneous dermatological and ophthalmological evaluation.

Dermatological assessment included full-body examination, EASI scoring (5), and DLQI (Italian version) (6). Ophthalmological evaluation included best corrected visual acuity, slit-lamp examination with grading of bulbar conjunctival hyperaemia (0–4) (7), collarettes (0–4) (8), eyelid margin erythema (0–3) (7), corneal fluorescein staining (Oxford scale) (9), and completion of the OSDI questionnaire (10).

Descriptive statistics were expressed as means, counts, and percentages. Associations between quantitative variables were analysed using linear correlation; Fisher's exact test was used for categorical variables. Linear regression and a Generalized Linear Mixed Model (GLMM) were applied to assess the impact of explanatory variables. Analyses were performed in R v4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 53 patients were recruited of whom 34 were male (64.2%) and 19 female (35.8%). The average (SD) age was 34.1 (16.8) years (range 18–75). The average (SD) duration of treatment with dupilumab was 94.8 weeks (72.1). The distribution of disease was: head and neck in 29/53 patients (54.7%), upper limbs in 17/53 patients (32.1%), lower limbs in 15/53 patients (28.3%), trunk in 14/53 patients (26.4%), and hands in 10/53 patients (18.9%). The average (SD) EASI score was 6.5 (7.8). The ophthalmologic comorbidities of the enrolled participants are summarized in **Table I**. Signs of OSD were found in a total of 49/53 patients (92.5%). The different prevalent signs of OSD are summarized in **Table II**.

In particular, collarettes were found in 45/53 patients (84.9%), with a total of 90/106 eyes, grade 2 or worse collarettes (>10 lashes with collarettes per eyelid) were found in 45/106 eyes (42.5%). Eyelid margin erythema was found in 42/53 patients (79.2%), with a total of 82/106 eyes; moderate–severe grade eyelid margin erythema was found in 16/106 eyes (15.1%).

Bulbar conjunctivitis was found in 31/53 patients (58.5%), with a total of 60/106 eyes, 2 cases were unilateral and 29 bilateral; moderate–severe grade bulbar conjunctivitis was found in 16/106 eyes (15.1%).

Table I. Prevalence of different ophthalmologic comorbidities in the study population

Comorbidity	Patients, *n* (%)
Myopia	4 (7.5)
Astigmatism	1 (1.9)
Recurrent conjunctivitis	7 (13.2)
Chronic conjunctivitis	4 (7.5)
Allergic blepharitis	4 (7.5)
Keratoconus	1 (1.9)
Chalaza	2 (3.8)
Cataract	1 (1.9)
Choroidal nevus	1 (1.9)
Hypermetropy	1 (1.9)
Photoreactive keratectomy	1 (1.9)
Corneal ulcers	1 (1.9)
Dry eye	1 (1.9)

Table II. Prevalence of different signs of OSD in the study population

Sign	Patients, *n* (%)	Eyes, *n* (%)
All signs	49 (92.5)	99 (93.4)
Collarettes	45 (84.9)	90 (84.9)
Grade 1	24 (45.3)	45 (42.5)
Grade 2	14 (26.4)	25 (23.6)
Grade 3	6 (11.3)	12 (11.3)
Grade 4	4 (7.5)	8 (7.5)
Eyelid margin erythema	42 (79.2)	82 (77.4)
Grade 1	35 (66.0)	66 (62.3)
Grade 2	7 (13.2)	12 (11.3)
Grade 3	2 (3.8)	4 (3.8)
Bulbar conjunctivitis	31 (58.5)	60 (56.6)
Grade 1	24 (45.3)	44 (41.5)
Grade 2	6 (11.3)	12 (11.3)
Grade 3	3 (5.7)	4 (3.8)
Grade 4	0 (0)	0 (0)
Corneal fluorescein staining	13 (24.5)	22 (20.8)
Grade 1	8 (15.1)	12 (22.6)
Grade 2	6 (11.3)	10 (18.9)
Grade 3	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)

A positive association was found between collarettes and eyelid erythema ($t = 2.773$; $p = 0.007$), between eyelid erythema and conjunctivitis ($t = 4.557$; $p = 0.00002$), and between collarettes and conjunctivitis ($t = 2.025$; $p = 0.047$).

Mild (grade II) corneal fluorescein staining was found in 10/106 eyes (9.4%). The average Oxford score (SD) was 0.31 (0.63).

Dry eye symptoms (OSDI score ≥ 13) were found in 10/53 patients (18.9%). In particular, mild symptoms (OSDI score 13–22) were present in 9/53 patients (16.9%) and severe symptoms (OSDI score 33–100) were reported by 1/53 patients (1.9%). The average OSDI score (SD) was 6.8 (6.8).

The OSDI score was not associated with collarettes, eyelid erythema, or conjunctivitis ($p > 0.05$).

The localization of disease was not associated with the presence of any sign of OSD ($p > 0.05$).

A previous history of ophthalmological disease was not associated with the presence of any sign of OSD ($p > 0.05$).

DISCUSSION

In this cross-sectional study, 53 adult patients under long-term treatment with dupilumab underwent dermatological and ophthalmological examination in order to evaluate the prevalence and severity of different ocular alterations indicative of OSD.

A major finding of this study was the high prevalence of signs of OSD (92.5%), which is similar to that reported in a previous study conducted on patients with moderate–severe AD who were not treated with biologic drugs (91.3%) (3). This could signify that, regardless of their treatment, all patients with moderate–severe AD are at greater risk of developing OSD, which may not be induced, but rather exacerbated, by the treatment with dupilumab. However, it must be noted that the results reported by Achten et al. (3) and ours are not perfectly comparable because of the different diagnostic methods that were employed.

Another interesting finding was the high prevalence of collarettes in our cohort (84.9%). Collarettes are waxy cylindrical debris at the base of the eyelashes, which are considered a pathognomonic sign of Demodex blepharitis (11), a common chronic inflammatory condition affecting the eyelid margins linked to the proliferation of Demodex mites (11).

Noteworthy is that it has been previously hypothesized, albeit never confirmed, that Demodex colonization could have a role in the pathogenesis of dupilumab-associated conjunctivitis (12). In particular, as the role of type 2 immunity in the regulation of hair follicle commensalism by Demodex mites has been established (13), dupilumab-mediated inhibition of T helper (Th) cell 2 signalling may hypothetically compromise the immune response against helminth infections, thus promoting the proliferation of Demodex mites (12). This theory is supported by the findings of a 2016 study, which showed that Demodex mites rapidly colonize genetically modified mice (BALB/c-IL13/IL4) with impaired Th 2 response (14).

Eyelid margin erythema (79.2%) and bulbar conjunctivitis (58.5%) were frequently observed. These findings may be manifestations of Demodex blepharitis, as suggested by the association between collarettes, eyelid erythema, and conjunctivitis. Nonetheless, although no significant correlation was found between a history of allergic conjunctivitis and the presence of bulbar conjunctivitis at the visit, an allergic origin cannot be ruled out.

A corneal fluorescein staining test, which evaluates damage to the cornea, revealed only mild grade staining in 9.4% of all patients. This prevalence is comparable to that found in the general adult population (8.7%) (15).

Symptoms indicative of dry eye disease were present in 18.9% of all enrolled patients, a lower prevalence than that reported by another publication conducted on patients with AD after 6 months of treatment with dupilumab (33.3%) (16). However, in the cited study, dry eye disease was assed using objective methods (tear film breakup time test, osmolarity and Schirmer test), while our results are based on self-reported OSDI score.

Our study has several limitations. First, its cross-sectional design prevents the assessment of causality between dupilumab and the high prevalence of OSD observed. A prospective study evaluating patients before and after starting dupilumab would better clarify this point. Second, the absence of a control group limited our ability to compare OSD prevalence among patients with and without AD. A case-control study comparing both the presence of OSD and the prevalence of Demodex infestation in patients with AD and in healthy controls would certainly provide valuable information. Lastly, although collarettes are indicative of Demodex blepharitis, we did not confirm the presence of Demodex

mites, which would have strengthened the hypothesis of their involvement in OSD among dupilumab-treated patients. Future studies should focus on the demonstration of Demodex mite presence, for example by sampling eyelashes to be examined with optical microscopy.

The authors have no conflicts of interest to declare.

REFERENCES

1. Kychygina A, Cassagne M, Tauber M, Galiacy S, Paul C, Fournié P, et al. Dupilumab-associated adverse events during treatment of allergic diseases. Clin Rev Allergy Immunol 2022; 62: 519–533. https://doi.org/10.1007/s12016-022-08934-0
2. Fachler T, Shreberk-Hassidim R, Molho-Pessach V. Dupilumab-induced ocular surface disease: a systematic review. J Am Acad Dermatol 2022; 86: 486–487. https://doi.org/10.1016/j.jaad.2021.09.029
3. Achten R, Thijs J, van der Wal M, van Luijk C, de Graaf M, Bakker D, et al. Dupilumab-associated ocular surface disease in atopic dermatitis patients: clinical characteristics, ophthalmic treatment response and conjunctival goblet cell analysis. Allergy 2023; 78: 2266–2276. https://doi.org/10.1111/all.15717
4. Serino F, Dattilo V, Cennamo M, Roszkowska AM, Gola M, Magliulo M, et al. Dupilumab-associated blepharoconjunctivitis: clinical and morphological aspects. Biomedicines 2023; 11: 3104. https://doi.org/10.3390/biomedicines11123104
5. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001; 10: 11–18. https://doi.org/10.1034/j.1600-0625.2001.100102.x
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210–216. https://doi.org/10.1111/j.1365-2230.1994.tb01167.x
7. Schulze MM, Hutchings N, Simpson TL. The use of fractal analysis and photometry to estimate the accuracy of bulbar redness grading scales. Invest Ophthalmol Vis Sci 2008; 49: 1398–1406. https://doi.org/10.1167/iovs.07-1306
8. Yeu EL, Wirta DL, Karpecki P, Baba SN, Holdbrook M, Saturn I Study Group. Lotilaner ophthalmic solution, 0.25%, for the treatment of demodex blepharitis: results of a prospective, randomized, vehicle-controlled, double-masked, pivotal trial (Saturn-1). Cornea 2023; 42: 435–443. https://doi.org/10.1097/ICO.0000000000003097
9. Tappeiner C, Heiligenhaus A, Halter JP, Miserocchi E, Bandello F, Goldblum D. Challenges and concepts in the diagnosis and management of ocular graft-versus-host disease. Front Med (Lausanne) 2023; 10: 1133381. https://doi.org/10.3389/fmed.2023.1133381
10. Anh BTV, Thuy PT, Ngoc NTB, Hien NTT, Yen PH, Quyet D, et al. Dry eyes status on Des scale and related factors in outpatients at Vietnam National Institute of Ophthalmology. Open Access Maced J Med Sci 2019; 7: 4292–4296. https://doi.org/10.3889/oamjms.2019.377
11. Rhee MK, Yeu E, Barnett M, Rapuano CJ, Dhaliwal DK, Nichols KK, et al. Demodex blepharitis: a comprehensive review of the disease, current management, and emerging therapies. Eye Contact Lens 2023; 49: 311–318. https://doi.org/10.1097/ICL.0000000000001003
12. Thyssen JP. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with Demodex and increased interleukin-17 levels? Br J Dermatol 2018; 178: 1220. https://doi.org/10.1111/bjd.16330
13. Ricardo-Gonzalez RR, Kotas ME, O'Leary CE, Singh K, Damsky W, Liao C, et al. Innate type 2 immunity controls hair follicle commensalism by Demodex mites. Immunity 2022; 55: 1891–1908.e12. https://doi.org/10.1016/j.immuni.2022.08.001
14. Smith PC, Zeiss CJ, Beck AP, Scholz JA. Demodex musculi infestation in genetically immunomodulated mice. Comp Med 2016; 66: 278–285.
15. McCann P, Abraham AG, Mukhopadhyay A, Panagiotopoulou K, Chen H, Rittiphairoj T, et al. Prevalence and incidence of dry eye and meibomian gland dysfunction in the united states: a systematic review and meta-analysis, JAMA Ophthalmol 2022; 140: 1181–1192. https://doi.org/10.1001/jamaophthalmol.2022.4394
16. Marolo P, Ribero S, Caselgrandi P, Ghilardi A, de Sanctis U, Parisi G, et al. Ocular surface disease in patients with atopic dermatitis treated with dupilumab: a prospective case-control study. Cornea 2024; 43: 221–227. https://doi.org/10.1097/ICO.0000000000003341