Ocular surface disease is common in moderate-to-severe atopic dermatitis patients

To the Editor,

High rates of ocular surface disease (OSD) in atopic dermatitis (AD) patients have been reported during dupilumab treatment. One of the hypotheses about the pathomechanism to be responsible for its development is focal scarcity of intraepithelial goblet cells.\(^1\) An association between moderate-to-severe AD patients and low goblet cell density (GCD) has also been reported previously.\(^2\) Despite the association between AD and OSD reported in previous literature, moderate-to-severe AD patients do not commonly undergo ophthalmological evaluation.\(^2\) To better understand the pathomechanism of dupilumab-associated OSD (DAOSD), more insight in the occurrence of OSD in moderate-to-severe AD population is needed. Therefore, we investigated the frequency, severity, and pathogenesis of OSD in moderate-to-severe AD patients before the start of dupilumab.

This prospective study included adult moderate-to-severe AD patients treated with topical corticosteroids on the skin, between February 2020 and September 2021 from the University Medical Centre Utrecht, the Netherlands. The patients provided informed consent and were registered in the BioDay registry, which is co-funded by the manufacturer of dupilumab.\(^3\) Ethics approval was obtained by the local Medical Research Ethics Committee.

All patients were examined by a dermatologist and an ophthalmologist before starting dupilumab treatment. AD severity was assessed by the Eczema Area and Severity Index (EASI). Clinical ophthalmological characteristics and symptoms of OSD were reported.

The patients were divided into having no, mild, moderate or severe OSD based on the Utrecht Ophthalmic Inflammatory and Allergic disease (UTOPIA) score, and the severity classification of the most severely affected eye was used.\(^3\)

 Conjunctival impression cytology (CIC) by using the Eyeprim device was performed to investigate the number of conjunctival goblet cells (GCs) and its major secretory mucin, which is Mucin5AC (MUC5AC). The CIC from the left eye was stained with Periodic Acid-Schiff and haematoxylin following the Eyeprim protocol.\(^4\) Afterwards, the GCD per sample was calculated. Flow cytometry analyses of CIC of the right eye were performed in a representative subgroup of the included patients. CIC is further explained in the online access repository following [https://zenodo.org/record/6275350](https://zenodo.org/record/6275350).

Differences between no or mild OSD and moderate-to-severe OSD were calculated with the chi-square test and with the Mann–Whitney U test. CIC results were reported per severity category of OSD. Statistical analyses were conducted with SPSS Statistics version 25.0.0.2 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows). Figures were created by using Prism (version 9 GraphPad Software).

A total of 70 moderate-to-severe AD patients (median EASI 15.0 (IQR 10.8–20.9)) were included (Table 1). Mild, moderate, and severe OSD were reported in 32/70 (45.7%), 24/70 (34.3%), and 7/70 (10.0%) patients respectively. Only 7/70 (10.0%) patients showed no signs of OSD. Significantly higher EASI scores were found in patients with moderate-to-severe OSD compared to patients with no or mild OSD (17.7 (IQR 13.7–24.9) vs. 11.8 (IQR 9.0–16.7), p = <.001). Additionally, occurrence of both AD eyelid involvement and AD facial involvement in the past year was significantly higher in patients with moderate-to-severe OSD compared to patients with no or mild OSD (n = 28 (90.3%) vs. n = 18 (46.2%), p = <.001 and n = 31 (100.0%) vs. n = 33 (84.6%), p = .030 respectively). Of all patients with moderate-to-severe OSD, 23/31 patients (74.2%) experienced OSD symptoms.

A lower conjunctival GCD median was found in patients with OSD compared to patients without OSD (Figure 1A). Flow cytometry analyses of CIC showed a trend of higher median fluorescence intensity (MFI) of MUC5AC within MUC5AC + GCs in patients with more severe OSD (Figure 1B). This indicates that patients with more severe OSD had more MUC5AC production by GCs.

This prospective study demonstrates that OSD is very frequent in adult patients with moderate-to-severe AD (90%) and is associated with lower conjunctival GCD compared with GCD of healthy controls reported in the literature.\(^5\) Moderate-to-severe OSD was found in 44.3% of the AD patients and was associated with more severe AD.

Our results show higher rates of OSD in AD patients (90%) than previous studies, reporting an incidence of 32.4%–55.8% of OSD in severe AD patients.\(^1\) All of our patients were examined by an ophthalmologist following a standardized protocol, which is more reliable than patient-reported diagnosis and explain the higher rates of OSD. In our study, 25% of the patients with moderate-to-severe OSD did not report OSD symptoms. Bortoluzzi et al.\(^6\) reported low Ocular Surface Disease Index, which focusses partly on symptoms of OSD, in patients with severe ocular surface involvement. These findings are comparable to our results and explain the underreporting of ocular comorbidity in AD based on patient-reported...
diagnosis. Furthermore, significantly more of our included patients with moderate-to-severe OSD reported the presence of eyelid and facial eczema in the past year compared to patients with no or mild OSD. Dogru et al.\textsuperscript{2} reported also that OSD in AD patients was associated with facial and eyelid eczema and that patients with facial atopy had higher grades of conjunctival squamous metaplasia. Additionally, patients from our study with moderate-to-severe OSD had more severe AD based on EASI and serum Thymus and Activation-Regulated Chemokine (TARC) levels, shown in Table 1, suggesting that more severe AD is associated with moderate-to-severe OSD. The abovementioned points underline the importance of early intervention for patients with moderate-to-severe AD.

**Key Messages**
- In a single-centre study, we assessed ocular surface disease prevalence in moderate-to-severe atopic dermatitis.
- Before starting dupilumab, 60/70 (90%) of patients already had ocular surface disease.
- Ocular surface disease was associated with lower conjunctival goblet cell density and more severe AD.

**Table 1** Patient, dermatological and ophthalmological characteristics

|                      | Total cohort (n = 70) | No or mild OSD (n = 39) | Moderate-to-severe OSD (n = 31) | p-Value |
|----------------------|----------------------|-------------------------|---------------------------------|---------|
| **Age (years), median (IQR)\textsuperscript{a}** | 38.5 (27.0–53.3)     | 41.0 (27.0–59.0)        | 32.0 (24.0–46.0)                 | .090    |
| **Men, n (%)**       | 35 (50.0)            | 15 (38.5)               | 20 (64.5)                       | .030    |
| **Age of onset of AD, n (%)** |                      |                         |                                 |         |
| Childhood            | 62 (88.6)            | 32 (82.1)               | 30 (96.8)                       | .135    |
| Adolescence          | 5 (7.1)              | 4 (10.3)                | 1 (3.2)                         | n/a     |
| Adult                | 3 (4.3)              | 3 (7.7)                 | 0 (0.0)                         | n/a     |
| **History of self-reported episodic acute allergic conjunctivitis, n (%)** | 55 (78.6)            | 28 (71.8)               | 27 (87.1)                       | .121    |
| **Allergic asthma, n (%)** | 35 (50.0)            | 18 (46.2)               | 17 (54.8)                       | .470    |
| **Allergic rhinitis, n (%)** | 51 (72.9)            | 28 (71.8)               | 23 (74.2)                       | .823    |
| **Food allergy, n (%)** | 34 (48.6)            | 21 (53.8)               | 13 (41.9)                       | .322    |
| **History of rosacea, n (%)** | 2 (2.9)              | 1 (2.6)                 | 1 (3.2)                         | 1.000   |
| **EASI score, median (IQR)\textsuperscript{a}** | 15.0 (10.8–20.9)     | 11.8 (9.0–16.7)         | 17.7 (13.7–24.9)                | .001    |
| **IGA score, median (IQR)\textsuperscript{a}** | 3 (3–3)              | 3 (2–3)                 | 3 (3–4)                         | .002    |
| **AD eyelid involvement in the past year, n (%)** | 46 (65.7)            | 18 (46.2)               | 28 (90.3)                       | <.001   |
| **AD facial involvement in the past year, n (%)** | 64 (91.4)            | 33 (84.6)               | 31 (100.0)                      | .030    |
| **TARC (pg./ml), median (IQR)\textsuperscript{a}** | 1564 (811–2716)      | 1411 (787–1975)         | 1919 (1348–3154)                | .026    |
| **Missing, n (%)**   | 1 (1.4)              | 0 (0)                   | 1 (3.2)                         | n/a     |
| **Peripheral blood eosinophils (×10\textsuperscript{9}/L), median (IQR)\textsuperscript{a}** | 0.29 (0.16–0.51)     | 0.29 (0.14–0.50)        | 0.31 (0.20–0.52)                | .624    |
| **Eosinophilia (≥0.45 × 10\textsuperscript{9}/L), n (%)** | 21 (30.4)            | 12 (30.8)               | 9 (30.0)                        | .945    |
| **Missing, n (%)**   | 1 (1.4)              | 0 (0)                   | 1 (3.2)                         | n/a     |
| **Visited an ophthalmologist before, n (%)** | 36 (51.4)            | 19 (48.7)               | 17 (54.8)                       | .611    |
| **Previous use of ophthalmic medication, n (%)** | 45 (64.3)            | 24 (61.5)               | 21 (67.7)                       | .591    |
| **Lubricant eye drops** | 23 (32.9)            | 8 (20.5)                | 15 (48.4)                       | .014    |
| **Antihistamine eye drops** | 22 (31.4)            | 13 (33.3)               | 9 (29.0)                        | .700    |
| **Anti-inflammatory ointment for the external eyelids** | 5 (7.1)              | 2 (5.1)                 | 3 (9.7)                         | .649    |
| **Anti-inflammatory therapy (eye drops or eye ointment)** | 14 (20.0)            | 4 (10.3)                | 10 (32.3)                       | .022    |
| **Other**            | 15 (21.4)            | 6 (15.4)                | 9 (29.0)                        | .167    |
| **Wearing contact lenses, n (%)** | 6 (8.6)              | 4 (10.3)                | 2 (6.5)                         | .687    |
of ophthalmological examination in patients with moderate-to-severe AD, especially in patients with the presence of eyelid eczema or severe AD including the face, in which low-threshold referral to an ophthalmologist is recommended. Diagnosing OSD is important since it may be associated with chronic limbitis, possibly leading to irreversible limbal stem cell deficiency and subsequently to irreversible long-term visual loss.

In our study, lower conjunctival GCD was found in patients with OSD, compared to patients without OSD. Since there were only seven patients without OSD, having a large variation in GCD, no significant differences in GCD could be found between these groups. However, median GCD of patients with OSD was much lower compared with mean GCD from normally covered conjunctival sites (973 cells/mm²) described in the literature, assuming that lower GCD is associated with OSD. In contrast, GC hyperplasia and mucin hypersecretion are reported in allergic conjunctivitis.

In our cohort, OSD was accompanied by low conjunctival GCD, which makes it different from (episodic) allergic conjunctivitis.

In addition to the lower GCD in patients with OSD, higher MFI of MUC5AC was found in patients with more severe OSD. MUC5AC is the major GC secretory mucin and protects and lubricates the ocular surface.

Dogru et al. investigated OSD in atopic patients and suggested that the increased expression of MUC5AC might be a defence response of the ocular surface to compensate for the ailing ocular surface condition, with eventually decreased expression of MUC5AC as a result of the progression of atopic OSD. This higher

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| TABLE 1 (Continued) | Total cohort (n = 70) | No or mild OSD (n = 39) | Moderate-to-severe OSD (n = 31) | p-Value |
|----------------------|----------------------|------------------------|---------------------------------|---------|
| Current use of ophthalmic medication, n (%) | | | | |
| Lubricant eye drops | 3 (4.3) | 0 (0.0) | 3 (9.7) | .082 |
| Antihistamine eye drops | 6 (8.6) | 4 (10.3) | 2 (6.5) | .687 |
| Anti-inflammatory ointment for the external eyelids | 2 (2.9) | 1 (2.6) | 1 (3.2) | 1.000 |
| Anti-inflammatory therapy (eye drops or eye ointment) | 2 (2.9) | 1 (2.6) | 1 (3.2) | 1.000 |
| Medical history of any eye disease, n (%) | 22 (31.4) | 9 (23.1) | 13 (41.9) | .091 |
| Medical history of allergic eye diseasea, n (%) | 3 (4.3) | 1 (2.6) | 2 (6.5) | .580 |
| Medical history of non-allergic eye disease b, n (%) | 12 (17.1) | 5 (12.8) | 7 (22.6) | .282 |
| Medical history of other eye disease, n (%) | 8 (11.4) | 3 (7.7) | 5 (16.1) | .452 |
| Presence of symptoms of OSD, n (%) | 40 (57.1) | 17 (43.6) | 23 (74.2) | .010 |
| Redness | 20 (28.6) | 5 (12.8) | 15 (48.4) | .001 |
| Pruritus | 35 (50.0) | 14 (35.9) | 21 (67.7) | .008 |
| Watery eyes | 20 (28.6) | 10 (25.6) | 10 (32.3) | .542 |
| Burning sense | 12 (17.1) | 4 (10.3) | 8 (25.8) | .086 |
| Pain | 6 (8.6) | 1 (2.6) | 5 (16.1) | .081 |
| Photophobia | 6 (8.6) | 3 (7.7) | 3 (9.7) | 1.000 |
| Presence of clinical characteristics of OSD, n (%) | | | | |
| Blepharitis | 50 (71.4) | 19 (48.7) | 31 (100.0) | <.001 |
| Meibomian gland dysfunction | 45 (64.3) | 15 (38.5) | 30 (96.8) | <.001 |
| Tarsal conjunctivitis | 57 (81.4) | 26 (66.7) | 31 (100.0) | <.001 |
| Bulbar conjunctivitis | 38 (54.3) | 11 (28.2) | 27 (87.1) | <.001 |
| Limbitis | 4 (5.7) | 0 (0.0) | 4 (12.9) | .034 |
| Limbal vascularization | 42 (60.0) | 13 (33.3) | 29 (93.5) | <.001 |
| Punctate corneal lesions | 20 (29.0) | 6 (15.4) | 14 (46.7) | .005 |
| Hurricane fluorescein staining | 0 (0.0) | 0 (0.0) | 0 (0.0) | n/a |

Note: Severity of OSD is based on the eye with the highest severity within a patient. p-values were calculated with the chi-square test.

Abbreviations: AD, atopic dermatitis; EASI, eczema area and severity index; IGA scale, Investigator’s Global Assessment Scale; IQR, interquartile range; OD, oculus dexter (right eye); OS, oculus sinister (left eye); OSD, ocular surface disease; SD, standard deviation; TARC, thymus and activation-regulated chemokine.

a Indicates p-values were calculated with Mann–Whitney U tests.

b Atopic keratoconjunctivitis; vernal keratoconjunctivitis; giant papillary conjunctivitis.

c Keratoconus; pellucid marginal degeneration; keratitis; uveitis; herpetic keratitis; blepharitis; glaucoma; cataract; macular oedema; amblyopia; Meibomian gland dysfunction; retinal detachment.
expression of MUC5AC protein as a defence response might explain the higher expression of MUC5AC protein found in our patients with more severe OSD.

The development of ocular side-effects during dupilumab treatment in AD patients emphasises the importance of gaining more insight into the ocular comorbidities in patients with moderate-to-severe AD. This current study shows that 90% of the moderate-to-severe AD patients have OSD before the initiation of dupilumab, at least in our centre, which leads to the question of what effect dupilumab will have on pre-existing OSD. Previously, we have shown scarcity of conjunctival GCD with increased local Th1-related cytokine production in a case series of patients with DAOSD. Inhibition of interleukin (IL)-4/IL-13 signalling by dupilumab, combined with increased local Th1-related cytokine production may be the basis for the loss of GCs and their important immunomodulatory function in the conjunctiva. Additionally, a small observational study by Barnett et al. reported a relative deficiency of MUC5AC in tear levels in AD patients with DAOSD. The abovementioned hypothesis and conclusions will be studied in future research, in which we will evaluate the included patients of this current study longitudinally during dupilumab treatment.

This study has some limitations. First, severity of only one eye was included, which might have led to loss of information. However, a preliminary analysis showed a very strong association (Spearman correlation) of 0.953 between severity of both eyes, assuming that this has not influenced our results. Second, due to the small number of patients without OSD having a large variation in GCD, no significant differences were found in GCD between patients with and without OSD. However, by comparing GCD of patients with OSD to GCD of healthy controls described in the literature, we can conclude that moderate-to-severe AD patients with OSD have lower GC counts. Third, since this is an explorative study in which two small subgroups were compared, we did not correct for multiple testing. Larger cohorts or other comparable studies are needed to support our results.

In conclusion, this prospective, single-centre cohort study shows that OSD is a common finding in adult patients with moderate-to-severe AD and is associated with low conjunctival GCD, more severe AD, and the presence of facial AD and/or eyelid eczema. As many patients with OSD did not report OSD symptoms, low-threshold referral to an ophthalmologist is recommended in patients with the mentioned risk factors. The results of this study provide an important basis for unravelling the pathomechanism of ocular side-effects associated with IL-4/IL-13 blocking treatment in future studies.

KEYWORDS
atopic dermatitis, goblet cell, ocular surface disease

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CONFLICT OF INTEREST
Roselle E. Achten has nothing to disclose. Daphne S. Bakker is a speaker for Sanofi Genzyme and LEO Pharma. Chantal M. van Luijk...
is a speaker for Sanofi Genzyme and Santen. Marlot van der Wal has nothing to disclose. Marlies de Graaf is a principal investigator and advisory board member and/or speaker for Sanofi Genzyme and Regeneron Pharmaceuticals and LEO Pharma. Femke van Wijk is a speaker and/or consultant for Janssen, Johnson & Johnson and Takeda. Nicolaas P.A. Zuijthoff has nothing to disclose. Lisa P. van der Rijst has nothing to disclose. Celeste M. Boesjes has nothing to disclose. Judith L. Thijs is a speaker for Sanofi Genzyme and LEO Pharma. Joke H. de Boer received research funding from Abbvie; this is outside the submitted work. Marjolein S. de Bruin-Weller is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Aslan, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron and Sanofi-Genzyme.

AUTHOR CONTRIBUTIONS
The authors confirm contribution to the paper as follows: data were collected by Roselie E. Achten and Chantal M. van Luijk. Flow cytometry analyses were performed by Marlot van der Wal. PAS staining was performed by Roselie E. Achten. Statistical analyses were conducted by Roselie E. Achten and Nicolaas P.A. Zuijthoff. Interpretation of data was performed by all authors. Roselie E. Achten and Daphne S. Bakker prepared the first draft manuscript. Critical comments on the draft and the manuscript and the final approval of the manuscript were given by all authors.

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