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LETTER

WILEY

Ocular surface disease in pediatric patients with moderate-to-severe atopic dermatitis

To the Editor,

Ocular surface disease (OSD), an umbrella term encompassing various ocular conditions such as conjunctivitis and blepharitis, is a known comorbidity in patients with atopic dermatitis (AD).[1] Previous studies performing ophthalmological examination in adult patients with moderate-to-severe AD showed high prevalence rates of OSD (81.2%–91.3%).[2–4] Interestingly, only half of adult patients with OSD (53.6%) reported ocular symptoms.[2] These findings are important for the further understanding of treatment-emergent OSD, such as dupilumab-associated ocular surface disease (DAOSD), which is a frequently observed side effect in both dupilumab-treated adult and pediatric patients.[5–7] However, the prevalence of OSD in pediatric patients with moderate-to-severe AD remains unknown. As pre-existing ocular pathology may be a risk factor for ocular side effects such as DAOSD, and symptoms of OSD may be challenging to report, further understanding of pre-existing OSD in pediatric patients is needed.[2,5,6] Therefore, this prospective cohort study aimed to investigate the prevalence and severity of OSD in pediatric moderate-to-severe AD patients.

Pediatric patients (<18 years) with moderate-to-severe AD starting dupilumab treatment were included between August 2019 and July 2024. The study was conducted at the Wilhelmina Children's Hospital (University Medical Center Utrecht), the Netherlands. This study did not fall under the scope of the Medical Research Involving Human Subjects Act (METC 18/239) and has been performed according to the Declaration of Helsinki. All patients/parents provided written informed consent and participated in the prospective BioDay registry.

All patients were examined by an ophthalmologist and a dermatologist. Ophthalmological examination was performed before or within 2 weeks of starting dupilumab treatment. Medical ocular history, previous and current use of ophthalmic medication, ocular symptoms, and ophthalmological characteristics were assessed. The Utrecht Ophthalmic Inflammatory and Allergic disease (UTOPIA) score was used to objectively assess the presence and severity of OSD, including the severity of eyelid inflammation, bulbar and tarsal conjunctivitis, and limbal inflammation. The UTOPIA score was classified into no (0), mild (1–4), moderate (5–8), or severe (≥9) OSD, based on the most affected eye.[2,8] To assess the prevalence of OSD within age groups, patients were stratified by age (0.5–5 years, 6–11 years, and 12–17 years). The severity of AD was assessed by the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI). Laboratory testing included serum total immunoglobulin E (IgE), aeroallergen-specific IgE levels, eosinophil levels, and thymus- and activation-regulated chemokine (TARC). Characteristics of patients with and without OSD were compared using the Mann–Whitney U test for continuous variables, and Pearson's chi-squared test or (where applicable) Fisher's exact test for categorical variables. Data were analyzed using IBM SPSS Statistics version 29.0.1.

A total of 50 pediatric patients (52.0% female, median age 10.0 years [IQR 6.0–13.3]) were included (Table 1). Median EASI was 15.8 (IQR 12.1–20.9). Overall, 72% (36/50) of patients reported to have AD eyelid involvement in the past year. Self-reported allergic conjunctivitis was reported in 70.0% (35/50) of patients, and 10.0% (5/50) of patients had a history of nonallergic ocular disease. Among nonatopic chronic comorbidities, three patients reported autoimmune disorders (coeliac disease, alopecia areata, and lichen sclerosus). Concomitant ocular medication was used in 14.0% (7/50) of patients, and 26.0% (13/50) of patients previously used ocular medication.

OSD was observed in 74.0% (37/50) of patients (Table 1). Regarding prevalence by age group, OSD was observed in 28.6% (2/7) patients aged 0.5–5 years, 69.2% (18/26) patients aged 6–11 years, and 100.0% (17/17) patients aged 12–17 years. The development of OSD was significantly correlated with age (Spearman's correlation 0.609, $p < .001$). Moreover, OSD was significantly associated with EASI ($p = .015$), pre-existing allergic conjunctivitis ($p = .040$), and total IgE level ($p = .019$). OSD was mostly classified as mild (94.6%, 35/37), with a median UTOPIA score of 2.0 (IQR 1.0–3.0) (Table 2). No significant difference in UTOPIA score was found within age groups. No cases of severe OSD (UTOPIA score ≥9) were identified. In patients with OSD, 56.8% (21/37) reported ocular symptoms. Pruritus was the most frequently reported ocular symptom (64.9%, 24/37). Notably, 43.2% (16/37) of patients (median age 13.5 years [IQR 10.0–16.8]) did not report any ocular symptoms.

Abbreviations: AD, atopic dermatitis; DAOSD, dupilumab-associated ocular surface disease; EASI, Eczema Area and Severity Index; IgE, immunoglobulin E (IgE); IL, interleukin; IQR, interquartile ranges; OSD, ocular surface disease.

TABLE 1 Patient characteristics.

Characteristics	Total cohort N = 50 (100.0%)	OSD + N = 37 (74.0%)	OSD − N = 13 (26.0%)	p Value[a]
Patient characteristics				
Sex (female), *n* (%)	26 (52.0)	20 (54.1)	6 (46.2)	.624
Age (years), median (IQR)	10.0 (6.0–13.3)	11.0 (9.0–15.0)	6.0 (4.5–7.0)	<.001
0.5–5 years, *n* (%)	7 (14.0)	2 (5.4)	5 (38.5)	.009[b]
6–11 years, *n* (%)	26 (52.0)	18 (48.6)	8 (61.5)	.424
12–17 years, *n* (%)	17 (34.0)	17 (45.9)	0 (0.0)	.002[b]
Age of AD onset (months), median (IQR)	0.0 (0.0–12.0)	0.0 (0.0–12.0)	0.0 (0.0–3.0)	538
Patient reported atopic comorbidity, *n* (%)	42 (84.0)	33 (89.2)	9 (69.2)	.181[b]
Allergic rhinitis	37 (74.0)	29 (78.4)	8 (61.5)	.281[b]
Asthma	25 (50.0)	18 (48.6)	7 (53.8)	.747
Allergic conjunctivitis	35 (70.0)	29 (78.4)	6 (46.2)	.040[b]
Food allergy	20 (40.0)	14 (37.8)	6 (46.2)	.599
Atopic diseases in first-degree relatives, ≥1, *n* (%)	49 (98.0)	36 (97.3)	13 (100.0)	1.000[b]
Atopic dermatitis	42 (84.0)	30 (81.1)	12 (92.3)	.662[b]
Allergic rhinitis	27 (54.0)	19 (51.4)	8 (61.5)	.526
Asthma	23 (46.0)	14 (37.8)	9 (69.2)	.051
Food allergy	9 (18.0)	7 (18.9)	2 (15.4)	1.000[b]
EASI score, median (IQR)	15.8 (12.1–20.9)	16.2 (13.2–23.0)	11.1 (8.0–17.1)	.015
Mild, *n* (%)	2 (4.0)	2 (5.4)	0 (0.0)	1.000[b]
Moderate, *n* (%)	39 (78.0)	26 (70.3)	13 (100.0)	.046[b]
Severe, *n* (%)	9 (18.0)	9 (24.3)	0 (0.0)	.089[b]
IGA score, median (IQR)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0)	.093
Mild, *n* (%)	6 (12.0)	4 (29.7)	2 (15.4)	.643[b]
Moderate, *n* (%)	30 (60.0)	20 (54.1)	10 (76.9)	.148
Severe, *n* (%)	13 (26.0)	12 (32.4)	1 (7.7)	.141[b]
Very severe, *n* (%)	1 (2.0)	1 (2.7)	0 (0.0)	1.000[b]
AD facial involvement in the past year, *n* (%)	45 (90.0)	34 (91.9)	11 (84.6)	.595[b]
AD eyelid involvement in the past year, *n* (%)	36 (72.0)	29 (78.4)	7 (53.8)	.078[b]
Medical history of nonallergic ocular disease[c], *n* (%)	5 (10.0)	5 (13.5)	1 (7.7)	1.000[b]
Visited an ophthalmologist before, *n* (%)	11 (22.0)	10 (27.0)	1 (7.7)	.248[b]
Allergic eye disease	2 (4.0)	1 (2.7)	1 (7.7)	.464[b]
Nonallergic eye disease	8 (16.0)	8 (21.6)	0 (0.0)	.090[b]
Medication use				
Previous use of ocular medication, *n* (%)	13 (26.0)	11 (29.7)	2 (15.4)	.469[b]
Lubricants	0 (0.0)	NA	NA	NA
Antihistamine eye drops	11 (22.0)	9 (24.3)	2 (15.4)	.275[b]
Anti-inflammatory ointment for the external eyelids	1 (2.0)	0 (0.0)	1 (7.7)	.260[b]
Anti-inflammatory eye drops/ointment	3 (6.0)	2 (5.4)	1 (7.7)	1.000[b]
Unknown	1 (2.0)	1 (2.7)	0 (0.0)	NA
Concomitant use of ocular medication[d], *n* (%)	7 (14.0)[e]	6 (16.2)	1 (7.7)	.660[b]
Lubricants	0 (0.0)	NA	NA	NA
Antihistamine eye drops	4 (8.0)[f]	3 (8.1)	1 (7.7)	1.000[b]
Anti-inflammatory ointment for the external eyelids	3 (6.0)[g]	3 (8.1)	0 (0.0)	.558[b]

TABLE 1 (Continued)

Characteristics	Total cohort N = 50 (100.0%)	OSD + N = 37 (74.0%)	OSD − N = 13 (26.0%)	p Value[a]
Anti-inflammatory eye drops/ointment	1 (2.0)[h]	1 (2.7)	0 (0.0)	1.000[b]
Concomitant immunosuppressives/modulants for AD[i], *n* (%)	6 (12.0)	6 (16.2)	0 (0.0)	.319[b]
Oral corticosteroids	1 (2.0)	1 (2.7)	0 (0.0)	1.000[b]
Cyclosporine A	4 (8.0)	4 (10.8)	0 (0.0)	.561[b]
Methotrexate	1 (2.0)	1 (2.7)	0 (0.0)	1.000[b]
Laboratory measures				
Eosinophil levels ($\times 10^9$/L), median (IQR)	0.5 (0.3–0.9)	0.5 (0.3–0.8)	0.7 (0.3–1.0)	.211
Eosinophilia ($\geq 0.5 \times 10^9$/L), *n* (%)	27 (54.0)	18 (48.6)	9 (69.2)	.200
TARC levels (pg/mL), median (IQR)	1085.5 (637.0–2015.0)	1140.0 (495.0–2093.0)	1046.0 (664.0–1509.0)	.894
Total IgE levels (kU/L), median (IQR)	1702.5 (685.3–4590.8)	2874.5 (1089.3–5000.8)	952.0 (122.5–1759.8)	.019
Missing, *n* (%)	6 (12.0)	5 (13.5)	1 (7.7)	NA
Aeroallergen-specific IgE (kU/L), *n* (%)[j]	40 (80.0)	29 (78.4)	11 (84.6)	NA
Positive for ≥1 inhalant allergens	37 (92.5)	27/29 (93.1)	10/11 (90.9)	1.000[b]
House dust mite	32/36 (88.9)	25/27 (92.6)	7/9 (77.8)	.255[b]
Birch pollen	34/36 (94.4)	24/26 (92.3)	10/10 (100.0)	1.000[b]
Timothy grass pollen	31/36 (86.1)	23/27 (85.2)	8/9 (88.9)	1.000[b]
Mugwort	16/26 (61.5)	14/20 (70.0)	2/6 (33.3)	.163[b]
Aspergillus fumigatus	22/30 (73.3)	18/23 (78.3)	4/7 (57.1)	.345[b]
Cat	33/35 (94.3)	26/26 (100.0)	7/9 (77.8)	.061[b]
Dog	36/37 (97.3)	27/27 (100.0)	9/10 (90.0)	.270[b]
Negative inhalant allergy screening	3 (7.5)	2/29 (6.9)	1/11 (9.1)	1.000[b]
Missing	10 (20.0)	8 (21.6)	2 (15.4)	NA

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; IgE, immunoglobulin E; IQR, Interquartile range; SD, standard deviation; TARC, thymus- and activation-regulated chemokine.

[a]*p* Values indicate differences in characteristics between patients with and without OSD. *p* Values of <0.05 were considered as statistically significant.

[b]Fisher's exact test was used due to low expected counts.

[c]*n* = 2 diplopia, *n* = 1 requirement of prednisone injections for eyelids, *n* = 1 strabismus surgery, and *n* = 1 tear duct surgery.

[d]Medication started prior to ophthalmological examination.

[e]*n* = 5 used ocular medication as needed, *n* = 2 used it on a daily basis.

[f]*n* = 3 used antihistamine eye drops as needed, *n* = 1 used it on a daily basis.

[g]*n* = 2 used anti-inflammatory treatment for the external eyelids as needed, *n* = 1 used it on a daily basis.

[h]*n* = 1 used corticosteroid eye drops as needed.

[i]Concomitant use of systemic immunosuppressive treatment for AD was recorded as using prednisolone or cyclosporine A within 1 week and methotrexate within 4 weeks prior to the start of dupilumab treatment.

[j]sIgE levels of ≥0.35 kU/L were considered as positive and levels of >100 were defined as 101 kU/L. Levels of total IgE >5000 were defined as 5001 kU/L.

This prospective real-world study provides insight in the prevalence of OSD in 50 moderate-to-severe pediatric AD patients. Although our study demonstrates a high prevalence of OSD (74.0%), this rate is lower than those reported in adult AD patients (81.2%–91.3%).[2–4] Notably, the prevalence of OSD in our cohort increased significantly with age, although its severity was comparable within age groups. Interestingly, almost all pediatric patients (94.6%) had mild OSD, while mild OSD is only seen in 45.7%–53.6% of adult AD patients.[2–4] The increased prevalence of OSD with age in our study, together with the increased severity of OSD in adults, may reflect the cumulative effects of prolonged OSD duration and/or the chronicity of AD. In addition, the presentation of OSD may differ at different stages of life, as vernal keratoconjunctivitis is more common in children, while it is thought to evolve into the more chronic atopic keratoconjunctivitis in adulthood.[9]

Severity of AD, based on EASI, was significantly associated with the presence of OSD, which is consistent with findings in

TABLE 2 Ophthalmological characteristics.

Ophthalmological characteristics	Total cohort *N* = 50	OSD + *N* = 37
Presence of ocular symptoms (patient-reported), *n* (%)	21 (42.0)	21 (56.8)
Redness	4 (8.0)	4 (10.8)
Tearing	4 (8.0)	4 (10.8)
Pruritus	24 (48.0)	24 (64.9)
Pain	0 (0.0)	0 (0.0)
Photophobia	0 (0.0)	0 (0.0)
Burning	0 (0.0)	0 (0.0)
UTOPIA-score, median (IQR)		
Total cohort	2.0 (0.0–3.0)	2.0 (1.0–3.0)
Patients aged 0.5–5 years	0.0 (0.0–1.0)	1.5 (1.0-NA)
Patients aged 6–11 years	1.5 (0.0–3.0)	3.0 (1.3–3.8)
Missing, *n* (%)	2 (4.0)	2 (5.4)
Patients aged 12–17 years	2.0 (1.0–3.0)	2.0 (1.0–3.0)
OSD severity, *n* (%)		
No OSD	13 (26.0)	NA
Mild OSD	35 (70.0)	35 (94.6)[a]
Moderate OSD	2 (4.0)	2 (5.4)
Severe OSD	0 (0.0)	0 (0.0)
Presence of characteristics of OSD, *n* (%)	37 (74.0)	37 (100.0)
Blepharitis	13 (26.0)	13 (35.1)
Meibomian gland dysfunction	18 (36.0)	18 (48.6)
Missing	1 (2.0)	0 (0.0)
Tarsal conjunctivitis	28 (56.0)	28 (75.7)
Bulbar conjunctivitis	11 (22.0)	11 (29.7)
Limbitis	0 (0.0)	0 (0.0)
Limbal vascularization	8 (16.0)	8 (21.6)
Punctate corneal lesions	4 (8.0)	4 (10.8)
Missing	2 (4.0)	2 (5.4)
Hurricane fluorescein staining	0 (0.0)	0 (0.0)
Missing	2 (4.0)	2 (5.4)

Abbreviations: IQR, interquartile range; NA, not applicable; OSD, ocular surface disease; UTOPIA, Utrecht ophthalmic inflammatory and allergic disease.

[a]*n* = 2 classified as mild OSD based on available OSD characteristics, despite lacking information about punctate corneal lesions and hurricane fluorescein staining.

studies in adult moderate-to-severe AD patients.[2] Furthermore, a significantly higher prevalence of self-reported allergic conjunctivitis was observed in patients with OSD (78.4%) compared to those without OSD (46.2%), indicating a higher rate of pre-existing ocular pathology in patients with OSD. In contrast to findings in adult patients, our study did not find a significant association between eyelid dermatitis in the past year and OSD, despite the comparable prevalence of eyelid dermatitis in our pediatric cohort (72.0%) and the previously reported adult cohort (68.1%).[3] Moreover, higher serum total IgE levels were associated with the presence of OSD, which may reflect the presence of co-existing atopic conditions.[10]

Overall, 56.8% of patients with OSD reported ocular symptoms, which is in line with studies performed in adults (53.6%–57.1%).[2,3] Achten et al. showed that adult patients with moderate-to-severe OSD were more likely to report symptoms (74.2%) than those with mild OSD (43.6%).[2] These results indicate that a substantial number of patients do not report symptoms, suggesting potential unreliability in patient-reported OSD. This could potentially lead to underdiagnosis of OSD, resulting in delayed diagnosis and treatment. This may be of particular concern in (young) children, who may have more difficulty recognizing and expressing ocular symptoms.[7]

Although previous studies in adult patients found an association between pre-existing ocular pathology and development of DAOSD,

it remains unclear whether the presence of OSD in pediatric patients—which is relatively mild compared to adult patients—increases the risk of developing DAOSD.[5,6] Future research, including ophthalmological examination during dupilumab treatment, is needed to elucidate whether OSD is also a risk factor for DAOSD in pediatric patients and to determine whether early treatment of OSD could prevent the development of DAOSD.

There are several limitations. First, as we did not have a control group, the prevalence of OSD in pediatric patients without AD remains unknown. Second, ophthalmological examination took place before or within 2 weeks of starting dupilumab, which may have influenced the results. Nevertheless, no differences were observed between assessments before and within 2 weeks of starting dupilumab (data not shown). Third, the cross-sectional design of the study may have resulted in an underestimation of OSD prevalence, particularly among patients with seasonal allergic conjunctivitis.

In conclusion, this prospective real-world study shows that OSD is common in pediatric patients with moderate-to-severe AD, with its prevalence increasing with age. OSD was mostly classified as mild, and only half of patients with OSD reported ocular symptoms. These findings highlight the potential underdiagnosis of OSD in pediatric moderate-to-severe AD patients, and may contribute to preventative strategies and earlier identification of ocular side effects in patients starting treatment with biologics.

KEYWORDS

atopic dermatitis, children, conjunctivitis, ocular surface disease, pediatric, type 2 inflammation

AUTHOR CONTRIBUTIONS

Lisa P. van der Rijst: Conceptualization; investigation; methodology; writing – original draft; project administration; visualization; writing – review and editing; formal analysis; data curation. **Nienke Veldhuis:** Conceptualization; investigation; writing – original draft; methodology; visualization; writing – review and editing; formal analysis; data curation; project administration. **Sara van der Kamp:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Roselie E. Achten:** Writing – review and editing. **Chantal M. van Luijk:** Investigation; methodology; writing – review and editing. **Elsbeth S. M. Voskuil-Kerkhof:** Investigation; writing – review and editing. **Inge M. Haeck:** Supervision; writing – review and editing. **Marjolein S. de Bruin-Weller:** Conceptualization; funding acquisition; methodology; project administration; resources; writing – review and editing; supervision. **Marlies de Graaf:** Conceptualization; writing – original draft; methodology; project administration; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

L.P. van der Rijst has been a speaker for AbbVie and Novartis. N. Veldhuis, S. van der Kamp, R.E. Achten, C.M. van Luijk, and E.S.M. Voskuil-Kerkhof have nothing to disclose. M.S. de Bruin-Weller has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Amgen, Aslan, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi. M. de Graaf has been a consultant, advisory board member, and/or speaker for AbbVie, ALK, Almirall, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi.

PEER REVIEW

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ETHICS STATEMENT

The study was approved by the institutional Medical Ethics Committee of the University Medical Center Utrecht (METC 18/239). All patients provided written informed consent.

Lisa P. van der Rijst[1,2]
Nienke Veldhuis[2]
Sara van der Kamp[2]
Roselie E. Achten[2]
Chantal M. van Luijk[3]
Elsbeth S. M. Voskuil-Kerkhof[3]
Inge M. Haeck[2]
Marjolein S. de Bruin-Weller[2]
Marlies de Graaf[1,2]

[1]*Department of Dermatology and Allergology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Department of Dermatology and Allergology, Utrecht University, Utrecht, The Netherlands*
[2]*Department of Dermatology and Allergology, National Expertise Center for Atopic Dermatitis, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[3]*Department of Ophthalmology, University Medical Center Utrecht, Utrecht, The Netherlands*

Correspondence
Marlies de Graaf, Department of Dermatology and Allergology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Department of Dermatology and Allergology, Utrecht University, Heidelberglaan 100, 3584CX Utrecht, The Netherlands.
Email: m.degraaf-10@umcutrecht.nl

Lisa P. van der Rijst and Nienke Veldhuis contributed equally.

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ORCID

Lisa P. van der Rijst https://orcid.org/0000-0002-5865-8986

Marlies de Graaf https://orcid.org/0000-0001-9004-5111

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