Clinical & Experimental Allergy

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Dupilumab-Associated Ocular Surface Disease in Paediatric Atopic Dermatitis Patients: Results From the BioDay Registry

Lisa P. van der Rijst[1,2] | Chantal M. van Luijk[3] | Sara van der Kamp[2] | Nicolaas P. A. Zuithoff[4] | Joke H. de Boer[3] | 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 University, Utrecht, the Netherlands | [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Correspondence: Marlies de Graaf (m.degraaf-10@umcutrecht.nl)

Received: 20 November 2024 | **Revised:** 5 February 2025 | **Accepted:** 20 February 2025

Funding: Patients included in this manuscript participated in the BioDay registry sponsored by Sanofi, Regeneron Pharmaceuticals, Lilly and Company, Pfizer, and LEO Pharma. Data collection, analysis, and publication of this article were not funded.

Keywords: atopic dermatitis | children | conjunctivitis | dupilumab | ocular surface | paediatric | type 2 inflammation

ABSTRACT

Background: Dupilumab-associated ocular surface disease (DAOSD) is a common side effect in paediatric atopic dermatitis (AD) patients treated with dupilumab. However, long-term real-world safety data is limited. Therefore, this study investigates the incidence of DAOSD in paediatric AD patients treated with dupilumab and identifies associated risk factors.

Methods: This prospective study included paediatric AD patients (aged 3–17 years) treated with dupilumab. Ocular symptoms were assessed every 4–12 weeks. DAOSD was initially treated with lubricating eye drops, antihistamine eye drops, and/or tacrolimus ointment for the external eyelids. Persistent symptoms were treated with ocular anti-inflammatory therapy. Ophthalmological examination was performed in patients with DAOSD requiring ocular anti-inflammatory therapy. Univariable and multivariable regression analyses were conducted to identify predictors for developing DAOSD.

Results: A total of 104 patients (11.7 ± 4.0 years) with a median follow-up of 70.5 weeks were included. Overall, 34.6% (36/104) of patients developed DAOSD, of which 30.6% (11/36) required ocular anti-inflammatory therapy. The development of DAOSD was not age-dependent, nor was it associated with pre-existing allergic conjunctivitis. The most common ocular symptoms were pruritus (75.0%), redness (72.2%), and tearing (58.3%). Ophthalmological examination revealed tarsal conjunctivitis in all patients with DAOSD requiring ocular anti-inflammatory therapy. Baseline serum IgE levels of ≥ 3000 kU/L were independently associated with the development of DAOSD (OR 4.65; 95% CI 1.43–15.11, $p = 0.011$). DAOSD led to dupilumab discontinuation in 3.8% (4/104) of patients.

Conclusions: This prospective, long-term, real-world study shows that 34.6% of paediatric AD patients treated with dupilumab develop DAOSD. Elevated baseline serum IgE (≥ 3000 kU/L) may predict the development of DAOSD. The high incidence of DAOSD underscores the importance of awareness of ocular symptoms during dupilumab treatment, especially in (young) paediatric patients, where reporting ocular symptoms can be challenging and may lead to delayed diagnosis.

Abbreviations: AD, Atopic dermatitis; CI, confidence interval; DAOSD, Dupilumab Associated Ocular Surface Disease; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IL, interleukin; IQR, interquartile ranges; OR, odds ratio; OSD, ocular surface disease; TARC, thymus- and activation-regulated chemokine.

Summary

- DAOSD occurred in 34.6% of dupilumab-treated paediatric AD patients, of which 30.6% required ocular anti-inflammatory therapy.
- This high incidence rate underscores the importance of awareness during dupilumab treatment in paediatric patients.
- Elevated baseline serum IgE levels (≥3000 kU/L) may predict DAOSD development in paediatric AD patients.

1 | Introduction

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin disease, with a physician-diagnosed 1-year prevalence varying from 1% to 23% worldwide [1]. A complex interaction of predominantly type 2 inflammation, characterised by dysregulation of the T helper 2 pathway, and a dysfunctional epidermal barrier results in the development of severely pruritic skin lesions [2–4]. Dupilumab, a human monoclonal antibody that blocks the interleukin (IL)-4 and IL-13 signalling pathway, was the first biologic approved for the treatment of (moderate to) severe AD, and is currently available for patients aged ≥6 months [5–7]. Dupilumab has demonstrated clinical effectiveness and a tolerable safety profile in the treatment of paediatric AD, with dupilumab-associated ocular surface disease (DAOSD) being the most frequently reported adverse event. Incidence rates of DAOSD in paediatric patients vary between 8.8%–14.6% in long-term clinical trials and 5.6%–17.3% in real-world studies [5–13]. Nevertheless, real-world studies in paediatric patients are scarce and often limited to a short follow-up period.

Long-term real-world studies in adult AD patients have reported higher DAOSD incidence rates of up to 39.6%. Interestingly, Achten et al. found that approximately half of adult AD patients who developed DAOSD did not report symptoms [14]. Recognising symptoms of DAOSD can be even more challenging for (young) children, potentially leading to delayed diagnosis and/or referral to an ophthalmologist. This delay increases the risk of more severe and persistent ocular surface disease (OSD), which could progress to (chronic) ocular surface damage, including limbitis, and may result in irreversible long-term visual impairment [15]. Early detection of OSD is especially important in young children (<6 years), who are at an increased risk of developing keratoconus—a condition that can lead to visual impairment and may contribute to amblyopia [16].

Notably, DAOSD is less frequently described in patients treated with dupilumab for other type 2 inflammatory disorders, such as asthma and chronic rhinosinusitis with nasal polyposis, indicating that AD may play an important role in the development of ocular side effects [17]. Although the exact pathomechanism of DAOSD remains unclear, several hypotheses have been proposed for the mechanisms underlying the development of DAOSD in AD patients, including the effects of IL-4 and IL-13 inhibition on the reduced number and function of conjunctival goblet cells, and potential pre-existent epithelial barrier dysfunction of the eyelids in AD patients [17–19]. Furthermore, pre-existing ocular pathology and increased AD severity have been identified as risk factors for the development of DAOSD in adult AD patients [9, 17, 20–24]. However, risk factors for the development of DAOSD in paediatric patients remain unknown.

Given the lack of long-term real-world data in the paediatric population, this study aimed to investigate the incidence of DAOSD in paediatric patients with (moderate to) severe AD treated with dupilumab, and to identify potential risk factors associated with the development of DAOSD.

2 | Methods

2.1 | Study Design and Population

This prospective observational cohort study consecutively included paediatric patients (3–17 years) with (moderate to) severe AD who were treated with dupilumab for at least 16 weeks at the Department of Dermatology, Wilhelmina Children's Hospital (University Medical Center Utrecht), the Netherlands, between August 2019 and March 2024 (Figure 1). 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 participated in the BioDay registry and (parents) provided written informed consent.

2.2 | Treatment With Dupilumab

According to the labelling for treatment of (moderate to) severe AD, dupilumab was administered subcutaneously at a dose of 200 or 300 mg every 2 or 4 weeks, including a loading dose of 400 or 600 mg at baseline or 200 or 300 mg on day 15 of treatment, depending on age and weight [5–7]. If applicable, the dosage regimen was prolonged after 52 weeks of treatment in accordance with the BioDay protocol [25]. In addition, dosage regimen prolongation was permitted if required in patients developing an adverse event.

2.3 | Clinical Measurements

Data collected at the start of treatment (baseline) included demographics, AD severity, and laboratory measurements. AD severity was assessed by the Eczema Area and Severity Index (EASI) and Investigator's global Assessment (IGA) [26]. Laboratory measurements included total immunoglobulin E (IgE) levels, aeroallergen-specific IgE levels, eosinophil levels, and thymus- and activation-regulated chemokine (TARC) levels. Follow-up visits took place at 4 weeks and every 12 weeks thereafter. Changes in medication use, AD severity, and the presence of ocular symptoms were assessed at each visit. In patients who reported ocular symptoms, DAOSD was distinguished from self-reported episodes of (seasonal) allergic conjunctivitis, which included symptoms that were present prior to the start of dupilumab, had a seasonal pattern, or occurred after exposure to pets or pollen. Ocular symptoms requiring

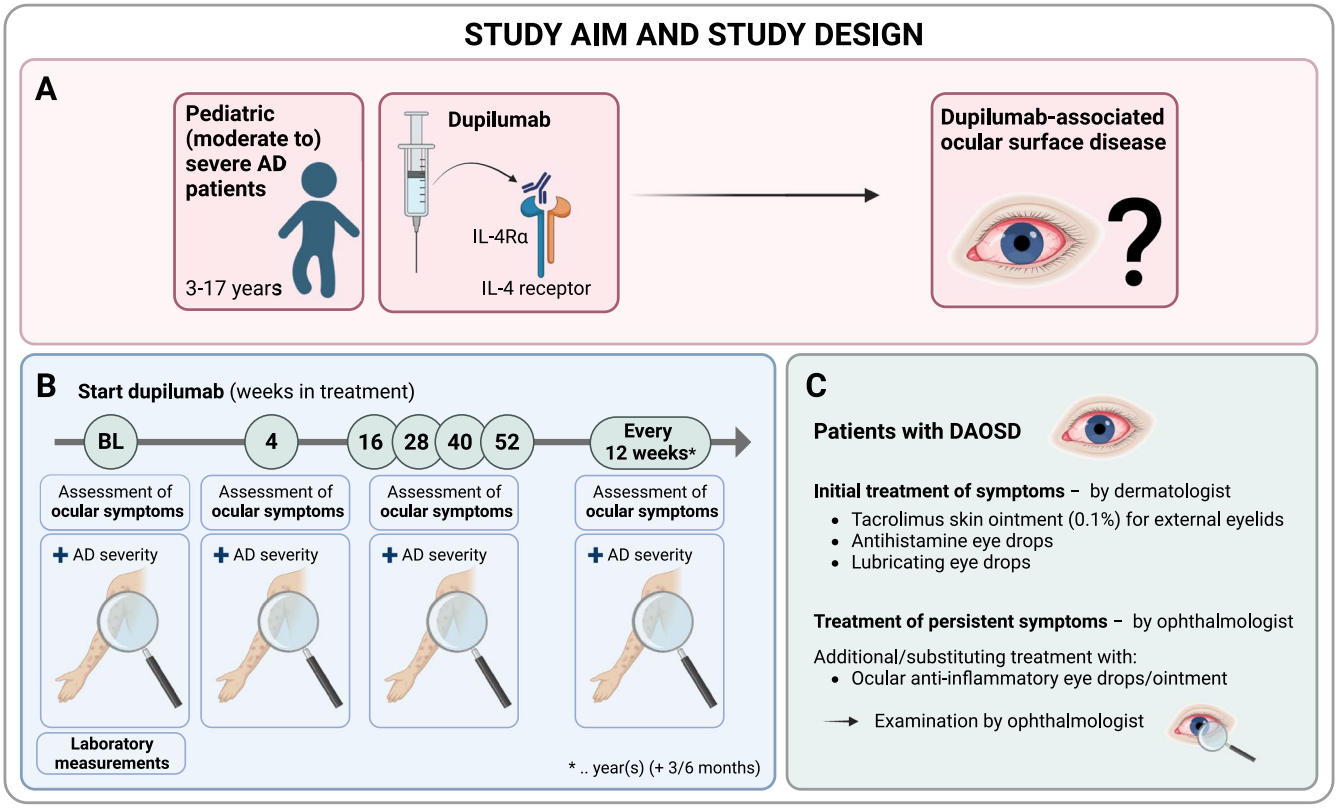


FIGURE 1 | Graphical method of the present study. AD, atopic dermatitis; BL, baseline; DAOSD, dupilumab-associated ocular surface disease; IL, interleukin. Figure created with BioRender.

treatment were initially treated by the dermatologist, including treatment with lubricating eye drops, antihistamine eye drops, and/or tacrolimus ointment for the external eyelids.

2.4 | Referral to an Ophthalmologist

Patients with persistent ocular symptoms were examined by an ophthalmologist. The Utrecht Ophthalmic Inflammatory and Allergic disease (UTOPIA) score was used to assess the severity of ocular inflammation. Severity following UTOPIA was graded separately for each eye on a scale from no inflammation (score 0), mild (score 1–4), moderate (score 5–8), and severe (score ≥ 9) [14]. If the severity of inflammation differed between eyes, the classification of the most affected eye was used for further analysis. Ocular anti-inflammatory treatment for managing more severe symptoms included corticosteroid eye drops (fluorometholone, dexamethasone, hydrocortisone, prednisolone), other intraocular anti-inflammatory treatments (tacrolimus eye ointment, cyclosporine A eye drops), and combined anti-inflammatory and antimicrobial eye drops/ointments (oxytetracycline/hydrocortisone, dexamethasone/tobramycin).

2.5 | Ocular Adverse Events

An ocular adverse event was defined as new ocular symptoms or pre-existing ocular symptoms that worsened during dupilumab treatment and required ocular treatment. As not all patients were routinely examined by an ophthalmologist, which is required to assess ocular inflammation with the standardised UTOPIA score, the severity of DAOSD was classified based on the required ocular therapy [14]. This classification differentiates between symptoms of DAOSD managed with lubricating eye drops, antihistamine eye drops, and/or tacrolimus ointment for the external eyelids (indicative of mild DAOSD) and ocular symptoms requiring ocular anti-inflammatory treatment (indicative of moderate-to-severe DAOSD). Adverse event discontinuation date was recorded as the date of resolution of ocular symptoms. If this date was unclear, the discontinuation date was documented as the next visit without ocular symptoms. Data lock was set for 12 March 2024.

2.6 | Statistical Analysis

Descriptive statistics were used to analyse patient characteristics. To assess the incidence of DAOSD within age groups, patients were stratified by age (< 6 years, 6–11 years, and 12–17 years). Potential risk factors were selected based on findings from previous literature [9, 17, 20, 21, 23, 24]. A detailed explanation of the risk factor selection is provided in the Supporting Information. Univariable and multivariable logistic regression analyses were performed to identify risk factors contributing to the development of DAOSD using all selected potential predictors [27]. As the number of patients developing DAOSD was relatively low for the number of predictors to be evaluated, we applied Firth's correction in the estimation of the multivariable logistic regression model [28]. The discriminative ability of the model was assessed with a Receiver Operating Characteristic curve and its corresponding area under the curve, included to evaluate the overall

discriminative ability of the combined predictors rather than to develop a clinically actionable prediction model [29]. *p* values of < 0.05 were considered statistically significant.

3 | Results

3.1 | Study Population

A total of 104 patients (11.7 ± 4.0 years; 41.3% male) with a median follow-up of 70.5 weeks (interquartile range (IQR): 46.3–113.0) were included (Table 1). During dupilumab treatment, 34.6% (36/104) of patients developed DAOSD, of which 69.4% (25/36) were managed with lubricating eye drops, antihistamine eye drops, and/or tacrolimus ointment for the external eyelids, while 30.6% (11/36) required ocular anti-inflammatory therapy. The onset of associated ocular symptoms occurred after a median treatment duration of 13.0 weeks (IQR 4.0–27.3) and resolved at a median duration of 24.5 weeks (IQR 10.5–50.8). DAOSD occurred in 52.8% (19/36) of patients within the first 16 weeks and 86.1% (31/36) within the first 52 weeks of treatment. Five patients (13.9%) developed DAOSD after 52 weeks of treatment. DAOSD occurred in 30.0% (3/10) of young children (< 6 years), 28.6% (10/35) of children (6–11 years), and 39.0% (23/59) of adolescents (12–17 years). Ocular anti-inflammatory therapy for DAOSD was required in 10.0% (1/10) of young children (< 6 years), 11.4% (4/35) of children (6–11 years), and 10.2% (6/59) of adolescents (12–17 years). Spearman correlation did not show significant correlation with age and the development of DAOSD ($r = 0.175$, $p = 0.076$). Overall, an episode of allergic conjunctivitis was recorded in 10.6% (11/104) of patients, of whom none developed DAOSD.

3.2 | Baseline Characteristics of Patients Developing DAOSD

Mean EASI was comparable between patients with (19.4 ± 11.6) and without (17.4 ± 10.1) DAOSD (Table 1). However, patients with DAOSD tended to have more severe AD compared to those without DAOSD based on categorical EASI and IGA severity scores (36.1% vs. 19.1% for severe AD based on EASI and 41.7% vs. 23.5% for (very) severe AD based on IGA). In addition, concomitant use of oral corticosteroids at baseline was considerably higher in patients with DAOSD compared to patients without DAOSD (8.3% vs. 0.0%). The presence of AD eyelid involvement was comparable between patients with and without DAOSD. Notably, prior use of antihistamine eye drops and baseline IgE levels were higher in patients with DAOSD compared to patients without DAOSD.

Baseline characteristics of patients who developed DAOSD requiring ocular anti-inflammatory therapy are shown in Table S1. Consistent with findings in the cohort of patients with DAOSD, a higher rate of prior ocular medication use (mainly antihistamine eye drops for pre-existing (seasonal) allergic conjunctivitis) was observed in patients who developed DAOSD requiring ocular anti-inflammatory therapy compared to those without DAOSD (45.5% vs. 14.7%).

3.3 | Symptoms and Ocular Characteristics of DAOSD

The most frequently reported ocular symptoms were pruritus (75.0%), redness (72.2%), and tearing (58.3%) (Table 2). Ophthalmological examination revealed that tarsal conjunctivitis (100.0%), meibomian gland dysfunction (87.5%), and blepharitis (75.0%) were the most common ocular characteristics in patients with DAOSD requiring ocular anti-inflammatory therapy. New-onset limbitis was reported in 6/104 (5.8%) patients. In two of these patients, UTOPIA scores were missing. In patients with DAOSD requiring ocular anti-inflammatory therapy, the median UTOPIA score was 9.5 (IQR 3.0–11.5, range: 2.0–12.0), indicating severe DAOSD following UTOPIA classification.

3.4 | Treatment of DAOSD

The most frequently prescribed ophthalmological treatment for DAOSD included antihistamine eye drops (37.5%), lubricating eye drops (34.6%), and tacrolimus skin ointment for the external eyelids (29.8%) (Table S2). Among patients who developed DAOSD, 25.0% (9/36) were treated with ocular corticosteroids, 19.4% (7/36) with combined anti-inflammatory and antimicrobial treatment, and 13.9% (5/36) with other intraocular anti-inflammatory treatment. Overall, dupilumab dosing interval prolongation was required in 13.9% (5/36) of patients with DAOSD (4.8% of total cohort), resulting in improvement of ocular symptoms in three patients and unknown effects in two patients. Dupilumab treatment was discontinued in 11.1% (4/36) of patients with DAOSD (3.8% of total cohort) due to persistent ocular symptoms, resulting in improvement of ocular symptoms in all four patients, with three patients achieving complete remission at data lock.

3.5 | Univariable and Multivariable Regression Analyses

Univariable and multivariable regression analyses showed that baseline serum total IgE level ≥ 3000 kU/L was the only characteristic associated with the development of DAOSD (Odds Ratio (OR) 5.24; 95% CI 1.95–14.05, $p = 0.001$ and OR 4.65; 95% CI 1.43–15.11, $p = 0.011$, respectively) (Figure 2). Although not statistically significant, multivariable regression analyses indicated a minor increased OR for age at baseline (OR 1.07; 95% CI 0.94–1.21, $p = 0.306$) and a decreased OR for male sex (OR 0.59; 95% CI 0.22–1.57, $p = 0.289$). Moreover, increased ORs were observed for comorbid allergic rhinitis (OR 2.60; 95% CI 0.60–11.19, $p = 0.200$), prior use of ocular medication (OR 1.98; 95% CI 0.57–6.87, $p = 0.285$), and baseline eosinophil levels (OR 1.57; 95% CI 0.48–5.12, $p = 0.452$). AD severity, reflected by EASI and immunosuppressant use at baseline, showed minor increased ORs (OR 1.02; 95% CI 0.96–1.07, $p = 0.571$ and OR 1.04; 95% CI 0.33–3.32, $p = 0.943$, respectively). The area under the Receiver Operator Characteristic curve for the multivariate regression model was 0.830 (95% CI 0.751–0.910), indicating excellent discriminative ability (Figure S1) [29].

TABLE 1 | Baseline patient characteristics.

	Total cohort	DAOSD+	DAOSD−
	N **= 104**	***N*** **= 36**	***N*** **= 68**
Patient characteristics			
Sex (male), *n* (%)	43 (41.3)	13 (36.1)	30 (44.1)
Age (years), mean (SD)	11.7 (4.0)	12.6 (4.0)	11.2 (4.0)
< 6 years, *n* (%)	10 (9.6)	3 (8.3)	7 (10.3)
6–11 years, *n* (%)	35 (33.7)	10 (27.8)	25 (36.8)
12–17 years, *n* (%)	59 (56.7)	23 (63.9)	36 (52.9)
Age of AD onset (years), mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Patient reported atopic comorbidity, ≥ 1, *n* (%)	93 (89.4)	33 (91.7)	60 (88.2)
Allergic rhinitis, *n* (%)	83 (79.8)	31 (86.1)	52 (76.5)
Asthma, *n* (%)	55 (52.9)	23 (63.9)	32 (47.1)
Allergic conjunctivitis, *n* (%)	65 (62.5)	23 (63.9)	42 (61.8)
Food allergy, *n* (%)	47 (45.2)	15 (41.7)	32 (47.1)
Atopic diseases in first-degree relatives, ≥ 1, *n* (%)	94 (90.4)	33 (91.7)	61 (89.7)
Atopic dermatitis, *n* (%)	78 (75.0)	28 (77.8)	50 (73.5)
Allergic rhinitis, *n* (%)	62 (59.6)	25 (69.4)	37 (54.4)
Asthma, *n* (%)	45 (43.3)	18 (50.0)	27 (39.7)
Food allergy, *n* (%)	14 (13.5)	5 (13.9)	9 (13.2)
EASI score, mean (SD)	18.1 (10.6)	19.4 (11.6)	17.4 (10.1)
Mild (1.0–7.0), *n* (%)	8 (7.7)	4 (11.1)	4 (5.9)
Moderate (7.1–21.0), *n* (%)	70 (67.3)	19 (52.8)	51 (75.0)
Severe (21.1–72.0), *n* (%)	26 (25.0)	13 (36.1)	13 (19.1)
IGA score, *n* (%)			
Mild (IGA 2)	13 (12.5)	6 (16.7)	7 (10.3)
Moderate (IGA 3)	60 (57.7)	15 (41.7)	45 (66.2)
(Very) Severe (IGA ≥ 4)	31 (29.8)	15 (41.7)	16 (23.5)
AD eyelid involvement in the past year, *n* (%)	64 (61.5)	21 (58.3)	43 (63.2)
Missing, *n* (%)	2 (1.9)	0 (0.0)	2 (2.9)
AD facial involvement, *n* (%)	92 (88.5%)	33 (91.7)	59 (86.8)
History of non-allergic eye disease[a], *n* (%)	3 (2.9)	2 (5.6)	1 (1.5)
Missing, *n* (%)	3 (2.9)	0 (0.0)	3 (4.4)
Medication use			
Prior use of ocular medication, *n* (%)	20 (19.2)	10 (27.8)	10 (14.7)
Lubricating eye drops, *n* (%)	1 (1.0)	0 (0.0)	1 (1.5)
Antihistamine eye drops[b], *n* (%)	17 (16.3)	10 (27.8)	7 (10.3)
Corticosteroids, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Missing, *n* (%)	1 (1.0)	0 (0.0)	2 (2.9)

(Continues)

TABLE 1 | (Continued)

	Total cohort	DAOSD+	DAOSD−
	N **= 104**	***N*** **= 36**	***N*** **= 68**
Concomitant use of systemic immunosuppressants[c], *n* (%)	23 (22.1)	8 (22.2)	15 (22.1)
Oral corticosteroids, *n* (%)	3 (2.9)	3 (8.3)	0 (0.0)
Cyclosporine A, *n* (%)	16 (15.4)	5 (13.9)	11 (16.2)
Methotrexate, *n* (%)	4 (3.8)	0 (0.0)	4 (5.9)
Laboratory measures			
Eosinophil level (×10*9/L), median (IQR)	0.60 (0.3–0.9)	0.62 (0.30–0.91)	0.53 (0.34–0.85)
Eosinophilia (≥ 0.5 × 10*9/L), *n* (%)	56 (53.8)	20 (55.6)	36 (52.9)
TARC level (pg/mL), median (IQR)	1140.0 (668.5–2938.0)	1775.0 (672.5–5006.5)	1046.0 (663.0–1552.0) (287–36,210)
Missing, *n* (%)	3 (2.9)	2 (5.6)	1 (1.5)
Total IgE level[f] (kU/L), median (IQR)	1820.0 (720.5–5000.5)	3570.0 (1333.5–5001.0)	1430.0 (526.0–3898.5)
Missing, *n* (%)	23 (22.1)	8 (22.2)	15 (22.1)
Aeroallergen-specific IgE[d] (kU/L), *n* (%)	81 (77.9)	28 (77.8)	53 (77.9)
Positive for ≥ 1 inhalant allergens, *n* (%)[e]	76 (93.9)	26/28 (92.9)	50/53 (94.3)
House dust mite, *n* (%)	61/63 (96.8)	23/23 (100.0)	38/40 (95.0)
Birch pollen, *n* (%)	60/61 (98.4)	22/22 (100.0)	38/39 (97.4)
Timothy grass pollen, *n* (%)	64/65 (98.5)	24/24 (100.0)	40/41 (97.6)
Mugwort, *n* (%)	33/37 (89.2)	14/14 (100.0)	19/23 (82.6)
Aspergillus fumigatus, *n* (%)	43/45 (95.6)	12/12 (100.0)	31/33 (93.9)
Cat, *n* (%)	55/57 (96.5)	17/17 (100.0)	38/40 (95.0)
Dog, *n* (%)	65/65 (100.0)	20/20 (100.0)	45/45 (100.0)
Negative inhalant allergy screening, *n* (%)	5 (6.2)	2/28 (7.1)	3/53 (5.7)
Missing, *n* (%)	23 (22.1)	8 (22.2)	15 (22.1)

Abbreviations: AD, atopic dermatitis; DAOSD, Dupilumab Associated Ocular Surface Disease; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; IgE, immunoglobulin E; IQR, Interquartile range; N/A, not applicable; SD, Standard Deviation; TARC, thymus- and activation-regulated chemokine.
[a]Herpetic keratitis; blepharitis.
[b]Ocular antihistamines including ketotifen, cromoglicic acid, and levocabastine.
[c]Concomitant use of systemic immunosuppressive treatment for AD was recorded as the use of prednisolone, cyclosporine A, or small molecule inhibitors within 1 week, and methotrexate within 4 weeks prior to baseline.
[d]Specific IgE levels of ≥ 0.35 kU/L were considered positive, and levels of > 100 were defined as 101 kU/L.
[e]Several specific IgE measures were missing due to a lack of serum to measure all separate specific IgE levels.
[f]Levels of total IgE > 5000 were defined as 5001 kU/L.

4 | Discussion

This prospective cohort study shows that 34.6% of the 104 paediatric patients treated with dupilumab developed DAOSD, of which 30.6% required ocular anti-inflammatory therapy. Furthermore, this study demonstrated that the development of DAOSD was not age dependent and that baseline serum IgE levels ≥ 3000 kU/L were independently associated with the development of DAOSD. Despite being a burdensome side effect, primarily causing redness, tearing, and pruritus of the eyes, DAOSD rarely resulted in dupilumab treatment discontinuation (Video 1).

Although comparable to incidence rates in real-world adult AD studies (ranging from 2.6% to 42.3%, dependent on definition and region), our results show a higher incidence than reported in clinical trials and real-world paediatric AD studies, which report rates ranging from 5.6% to 17.3% [5–14, 19, 24, 30–32]. Factors shown to be associated with an increased risk of developing DAOSD—including severe AD, prior use of ocular medication, and elevated baseline IgE—were present in our patients with DAOSD and may have contributed to these higher rates [9, 17, 20–24, 33]. Second, the study design, which involved regular and proactive assessment of ocular symptoms by physicians focused on ophthalmological comorbidity in AD, combined

TABLE 2 | Ocular symptoms and characteristics in paediatric AD patients who developed dupilumab-associated ocular surface disease during dupilumab treatment.

Characteristics	DAOSD (total cohort) *N* = 36	DAOSD requiring ocular anti-inflammatory therapy *N* = 11
Presence of symptoms		
Redness, *n* (%)	26 (72.2)	11 (100.0)
Tearing, *n* (%)	21 (58.3)	8 (72.7)
Pruritus, *n* (%)	27 (75.0)	11 (100.0)
Pain, *n* (%)	8 (22.2)	3 (27.3)
Photophobia, *n* (%)	4 (11.1)	2 (18.2)
Burning, *n* (%)	13 (36.1)	5 (45.5)
Dry eyes, *n* (%)	4 (11.1)	2 (18.2)
Weeks until onset DAOSD, median (IQR)	13.0 (4.0–27.3)	9.0 (4.0–21.0)
Duration of symptoms (weeks), median (IQR)	24.5 (10.5–50.8)	120.0 (98.0–NA)
Ongoing, *n* (%)	14 (38.9)	9 (81.8)
Ocular characteristics investigated by ophthalmologist, *n* (%)	N/A	8 (72.7)
Blepharitis, *n* (%)	N/A	7 (87.5)
Meibomian gland disfunction, *n* (%)	N/A	6 (75.0)
Tarsal conjunctivitis, *n* (%)	N/A	8 (100.0)
Bulbar conjunctivitis, *n* (%)	N/A	5 (62.5)
Limbitis, *n* (%)	N/A	4 (50.0)[a]
Limbal vascularization, *n* (%)	N/A	4 (50.0)
Punctate corneal lesions, *n* (%)	N/A	3 (37.5)
Hurricane fluorescein staining, *n* (%)	N/A	0 (0.0)
Missing, *n* (%)	N/A	1 (12.5)
UTOPIA-score, median (IQR)	N/A	9.5 (3.0–11.5)
UTOPIA classification, *n* (%)		
UTOPIA score mild, *n* (%)	N/A	3 (37.5)
UTOPIA score moderate, *n* (%)	N/A	0 (0.0)
UTOPA score severe, *n* (%)	N/A	5 (62.5)
Missing[a], *n* (%)	N/A	3 (27.3)

Abbreviations: DAOSD, Dupilumab Associated Ocular Surface Disease; IQR, interquartile range; UTOPIA, Utrecht Ophthalmic Inflammatory and Allergic disease.
[a]Limbitis was diagnosed in two out of three patients in whom ophthalmic characteristics were not assessed by the UTOPIA score.

with the increased awareness of DAOSD over time, may have also contributed to these higher rates. Third, the long follow-up period of this study (median treatment duration of 70.5 weeks) could have contributed to the higher incidence rates, as 13.9% of patients developed DAOSD after 1 year of treatment. Our results underline the importance of awareness of ocular symptoms during dupilumab treatment, especially in (young) paediatric patients, where reporting these symptoms can be challenging and may delay the diagnosis. In addition, since early ocular intervention reduces the severity of DAOSD, timely diagnosis is essential [19].

Among patients who developed DAOSD, the majority (69.4%) had symptoms managed with lubricating eye drops, antihistamine eye drops, and/or tacrolimus ointment for the external eyelids, while a minority (30.6%) required ocular anti-inflammatory therapy to treat persistent symptoms. This contrasts with the real-world study by Ariens et al. in adult patients treated with dupilumab between 2017 and 2019, where the majority (80.6%) of patients with DAOSD required ocular anti-inflammatory therapy [24]. Increased awareness of DAOSD may have led to earlier ocular treatment in our cohort, resulting in less severe disease [19]. Additionally, the prolonged duration

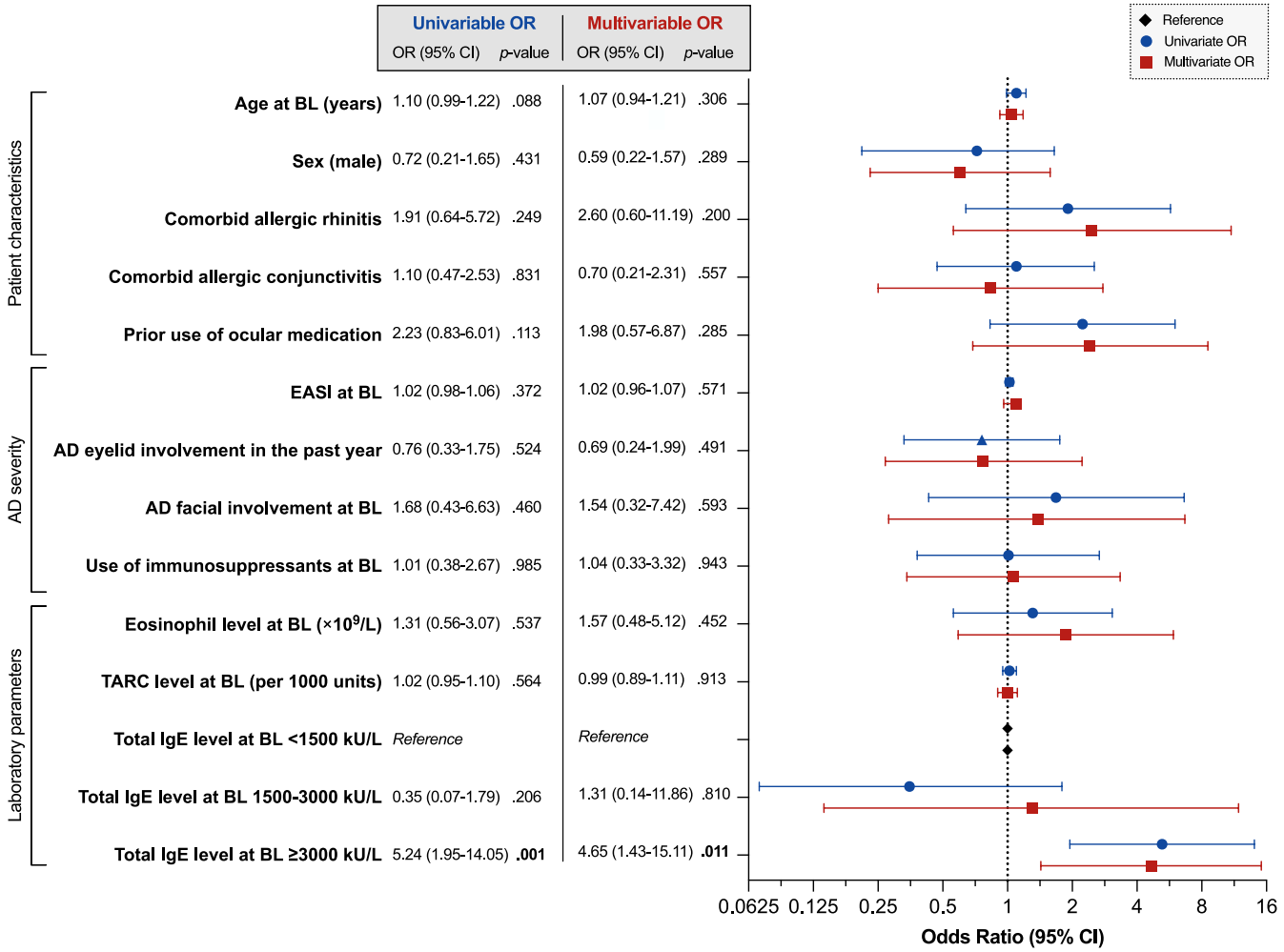
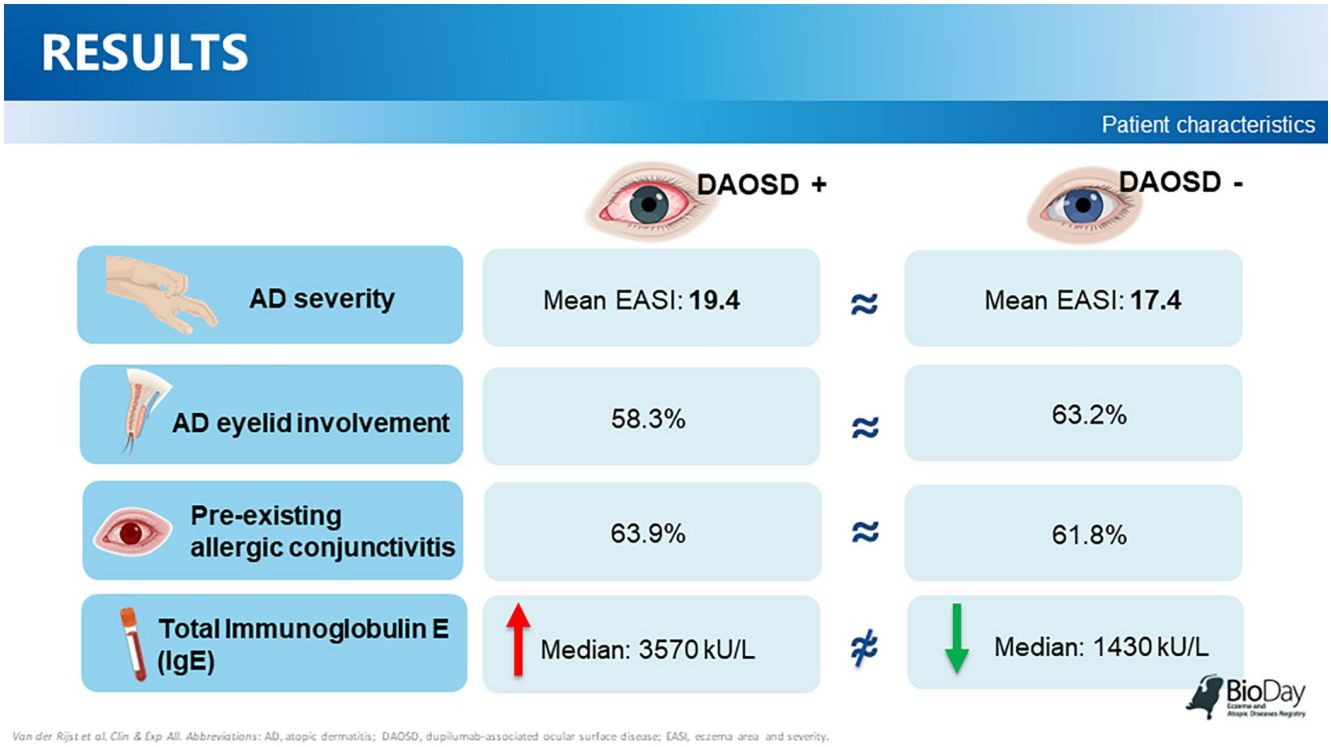


FIGURE 2 | Univariable and multivariable odds ratios of risk factors for the development of dupilumab-associated ocular surface disease in paediatric AD patients. Firth's correction was applied in the estimation of the multivariable logistic regression model. The coefficient for TARC represents the change in the outcome per 1000 units (pg/ml) increase in the original laboratory value. Prior use of ocular medication includes ketotifen, cromoglicic acid, and levocabastine. AD, atopic dermatitis; BL, baseline; CI, confidence interval; EASI, Eczema Area and Severity Index; IgE, immunoglobulin E; OR, odds ratio; TARC, thymus- and activation-regulated chemokine.

and/or more chronic form of (eyelid) AD, along with increased pre-existing ocular pathology—both risk factors found in adult patients but less common in paediatric patients—may have contributed to the increased severity observed in adult AD patients [9]. In line, our cohort of paediatric patients with DAOSD requiring ocular anti-inflammatory therapy was more likely to have a history of ocular medication use than those without DAOSD, suggesting that pre-existing ocular pathology may also play a role in the development of more severe DAOSD in the paediatric population.

This study demonstrated comparable rates of DAOSD in patients of different age categories (< 6 years, 30.0%; 6–11 years, 28.6%; 12–17 years, 39.0%) and showed that there was no correlation between age and the development of DAOSD. These results are in line with Kamal et al., reporting no association between the incidence of DAOSD and the concentration of dupilumab in serum in children and adolescents (6–17 years) [34, 35]. In line with this, clinical trials across various age categories demonstrated lower yet comparable incidence rates among age categories, with 12.7% of young children (6 months–6 years), 14.6% of older children (6–11 years), and 8.8% of adolescents (12–17 years) developing DAOSD during 1 year of dupilumab treatment [5–7]. Notably, our study showed that children in all age categories developed DAOSD requiring ocular anti-inflammatory therapy, although sample sizes within each age group were small. Due to the lack of alternative treatment options for DAOSD and/or AD at the time of this study, nine patients were treated with ocular steroids. Although effective, (long-term) steroid use should be limited due to potential ocular complications that may occur, including steroid-induced glaucoma [36–39]. This is especially important for young children (< 6 years), who are at increased risk of developing elevated intraocular pressure [38]. To prevent long-term ocular complications, timely management including steroid-sparing eye treatments and alternative AD therapies should be considered to minimise steroid use for DAOSD in children [32, 36, 38].

Interestingly, the real-world study by Berna-Rico et al., which evaluated the incidence of DAOSD in 19 children under 6 years (median age: 4.7 years, range: 3.5–5.4) by assessing adverse



VIDEO 1 | This study aimed to investigate the incidence of dupilumab-associated ocular surface disease, or DAOSD, in paediatric atopic dermatitis patients treated with dupilumab and to identify associated risk factors. This prospective study included patients aged 3–17 years starting dupilumab treatment. They were enrolled in our BioDay registry and were followed using a standardised protocol. Patients who developed DAOSD were initially treated with tacrolimus skin ointment, antihistamine, and/or lubricating eye drops. Patients with persistent symptoms were treated with ocular anti-inflammatory therapy. One hundred four patients were included, with a median follow-up of 70.5 weeks. Almost 35% developed DAOSD, of which 30.6% required ocular anti-inflammatory therapy. The incidence was comparable among age groups. Patients with DAOSD had comparable AD severity, AD eyelid involvement, and pre-existing allergic conjunctivitis at baseline compared to patients without DAOSD. Total IgE levels were, however, higher in patients who developed DAOSD. We found that total IgE levels above 3000 kU/L were independently associated with the development of DAOSD. To conclude, the high incidence of DAOSD underscores the importance of awareness of ocular symptoms during dupilumab treatment in children. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1111/cea.70025

events during follow-up, reported no cases of DAOSD during a median follow-up of 51.3 weeks [40]. The absence of DAOSD may be due to the fact that young children may have difficulty reporting ocular symptoms, resulting in underreporting of incidence rates. Even in adult AD patients, only half of the patients with signs of DAOSD reported symptoms, demonstrating the difficulty of signalling symptoms of DAOSD. In addition, the study by Berna-Rico et al. recommended daily prophylactic use of ectoine and hyaluronic acid eye drops for all patients, which may have led to lower incidence rates, although the preventive effect of ocular treatment could not be determined due to the lack of a control group [40]. To gain more clarity about a potential age-related component in the development of DAOSD and determine the effect of preventive strategies, future research including ophthalmological examination and/or a control group in different age categories is needed.

Our findings indicate that baseline serum total IgE ≥3000 kU/L may be a useful predictor for the development of DAOSD in paediatric patients. Similarly, Uchida et al. identified baseline IgE as a useful predictor for the development of DAOSD in adult AD patients [21]. Moreover, Akinlade et al. reported that higher serum IgE levels were associated with an increased incidence of DAOSD. However, these findings were also observed in the placebo-treated patients [17]. Elevated serum IgE levels may reflect increased allergic predisposition in patients with coexisting allergic conditions [41]. In our study, comorbid allergic rhinitis (OR 2.60) and baseline eosinophil level (OR 1.57), both more prevalent in adult patients developing DAOSD, showed a positive but non-significant association with the development of DAOSD [20, 33]. However, comorbid allergic conjunctivitis (OR 0.70) showed a negative and non-significant association with the development of DAOSD. For further differentiation between ocular and systemic allergic predisposition, tear fluid IgE may be a valuable tool, as it is a more accurate measure of the presence and severity of allergic conjunctivitis than serum total IgE [42]. Moreover, increased IgE levels have been associated with increased AD [17, 43]. Correspondingly, studies in adult patients showed that increased AD severity is associated with the development of DAOSD [17, 20–24]. Although patients with DAOSD in our study tended to have more severe AD at baseline, characteristics reflecting AD severity—EASI and concomitant use of immunosuppressants for AD—were not identified as independently associated predictors for paediatric DAOSD. Since predictive analyses require large numbers of events, future studies with larger cohorts are essential to validate the identified predictors associated with the development of paediatric DAOSD.

Although the exact pathomechanism of DAOSD remains elusive, dupilumab treatment has been associated with a reduction in the number and function of conjunctival goblet cells in adults with AD, potentially increasing the risk of developing DAOSD [19, 44, 45]. As these effects are currently unknown in paediatric patients, future research is needed to unravel the effects of dupilumab on goblet cells in paediatric patients, although this may be challenging due to the requirement of conjunctival impression cytology or biopsies. Furthermore, Thormann et al. demonstrated that adult AD patients who develop DAOSD exhibit elevated Th2/Th17 inflammatory markers in tear fluid prior to dupilumab treatment, which shift to a Th1/Th17 cytokine profile at DAOSD onset, providing further insight into its pathomechanism [46]. In addition, Achten et al. showed that 90% of adult moderate-to-severe AD patients had signs of OSD at the start of dupilumab treatment, suggesting that pre-existing epithelial barrier dysfunction of the eyelids may play a role in the development of DAOSD [18, 47]. Understanding the prevalence and characteristics of OSD in paediatric patients with moderate-to-severe AD may provide valuable insight into the pathomechanism of DAOSD in this population and guide early and/or preventive intervention.

This study has some limitations. First, ocular characteristics were only investigated in patients developing DAOSD requiring ocular anti-inflammatory therapy, thereby limiting the comparison with less severe forms of DAOSD. Second, it remains challenging to differentiate DAOSD from allergic conjunctivitis, as symptoms may be similar and difficult to report and differentiate in young patients. However, sub-analyses of baseline characteristics in patients developing DAOSD and those without any ocular symptoms (i.e., excluding patients with episodes of allergic conjunctivitis) did not show any differences (data not shown). Third, the lack of a control group, inherent to a registry-based observational cohort study, limited comparative analysis. Fourth, we applied several strategies such as multiple imputation and Firth's correction to correct for potential small sample bias and applied more liberal *p*-values for the interpretation of results. Nevertheless, a bias due to limited statistical power, especially in the multivariable regression, cannot be excluded. Fifth, patients with less than 16 weeks of dupilumab treatment were excluded to ensure sufficient exposure for potential DAOSD development. While this approach may lead to underestimation of DAOSD due to the exclusion of cases that occurred earlier in treatment, none of the patients excluded from this study developed DAOSD.

5 | Conclusion

In conclusion, this long-term, real-world study in paediatric AD patients shows a higher incidence of DAOSD compared to previously published (trial) data, highlighting the importance of awareness of this common side effect. The observed incidence of DAOSD in our paediatric cohort is comparable to rates reported in real-world studies of adult AD patients, although its severity is generally milder. Furthermore, we found that serum IgE may be a useful biomarker for predicting DAOSD. These findings underscore the need for a better understanding of the underlying mechanisms and associated risk factors for DAOSD in paediatric patients, especially in (young) paediatric patients, where reporting ocular symptoms can be challenging and may lead to delayed diagnosis.

Author Contributions

Lisa P. van der Rijst: conceptualization; investigation; methodology; writing – original draft preparation; visualization; writing – review and editing; formal analysis; data curation. **Chantal M. van Luijk:** investigation; methodology; writing – review and editing. **Sara van der Kamp:** conceptualization; writing – original draft preparation. **Nicolaas P. A. Zuithoff:** methodology; formal analysis; writing – review and editing. **Joke H. de Boer:** 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 preparation; methodology; project administration; resources; writing – review and editing; supervision.

Acknowledgements

We would also like to thank Elisabeth S. M. Voskuil-Kerkhof and Michelle B. van Egmond-Ebbeling, both paediatric ophthalmologists, for their contributions in examining paediatric atopic dermatitis patients with ocular symptoms. In addition, we would like to acknowledge all the patients and their parents who participated in the BioDay registry.

Ethics Statement

The study was approved by the institutional Medical Ethics Committee of the University Medical Center Utrecht (METC 18/239).

Consent

All patients provided written informed consent.

Conflicts of Interest

Lisa P. van der Rijst has been a speaker for AbbVie and Novartis; fees were paid directly to the institution. Chantal M. van Luijk declares no conflicts of interest. Sara van der Kamp declares no conflicts of interest. Nicolaas P. A. Zuithoff was involved in studies financed by Eli Lilly; fees were paid directly to the institution. Joke H. de Boer declares no conflicts of interest. Marjolein 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 Pharmaceuticals, and Sanofi; fees were paid directly to the institution. Marlies de Graaf has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Eli Lilly, ALK, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi; fees were paid directly to the institution.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. S. Bylund, L. B. Kobyletzki, M. Svalstedt, and A. Svensson, "Prevalence and Incidence of Atopic Dermatitis: A Systematic Review," *Acta Dermato-Venereologica* 100, no. 12 (2020): adv00160.

2. R. Achten, L. van der Rijst, M. Piena, et al., "Economic and Humanistic Burden in Paediatric Patients With Atopic Dermatitis," *Acta Dermato-Venereologica* 103 (2023): adv00881.

3. S. Weidinger, E. L. Simpson, J. I. Silverberg, et al., "Burden of Atopic Dermatitis in Pediatric Patients: An International Cross-Sectional Study," *British Journal of Dermatology* 190 (2024): 846–857.

4. S. M. Langan, A. D. Irvine, and S. Weidinger, "Atopic Dermatitis," *Lancet* 396, no. 10247 (2020): 345–360.

5. A. Blauvelt, E. Guttman-Yassky, A. S. Paller, et al., "Long-Term Efficacy and Safety of Dupilumab in Adolescents With Moderate-To-Severe Atopic Dermatitis: Results Through Week 52 From a Phase III Open-Label Extension Trial (LIBERTY AD PED-OLE)," *American Journal of Clinical Dermatology* 23, no. 3 (2022): 365–383.

6. A. S. Paller, E. C. Siegfried, E. L. Simpson, et al., "Dupilumab Safety and Efficacy up to 1 Year in Children Aged 6 Months to 5 Years With Atopic Dermatitis: Results From a Phase 3 Open-Label Extension Study," *American Journal of Clinical Dermatology* 25, no. 4 (2024): 655–668, https://doi.org/10.1007/s40257-024-00859-y.

7. M. J. Cork, D. Thaçi, L. F. Eichenfield, et al., "Dupilumab Safety and Efficacy in a Phase III Open-Label Extension Trial in Children 6-11 Years of Age With Severe Atopic Dermatitis," *Dermatology and Therapy* 13, no. 11 (2023): 2697–2719.

8. A. Bohner, C. Topham, J. Strunck, et al., "Dupilumab-Associated Ocular Surface Disease: Clinical Characteristics, Treatment, and Follow-Up," *Cornea* 40, no. 5 (2021): 584–589.

9. R. E. Achten, C. Van Luijk, L. Van der Rijst, et al., "Identification of Risk Factors for Dupilumab-Associated Ocular Surface Disease in Patients With Atopic Dermatitis," *Acta Dermato-Venereologica* 102 (2022): adv00666.

10. S. Igelman, A. O. Kurta, U. Sheikh, et al., "Off-Label Use of Dupilumab for Pediatric Patients With Atopic Dermatitis: A Multicenter Retrospective Review," *Journal of the American Academy of Dermatology* 82, no. 2 (2020): 407–411.

11. L. Stingeni, L. Bianchi, E. Antonelli, et al., "A 52-Week Update of a Multicentre Italian Real-World Experience on Effectiveness and Safety of Dupilumab in Adolescents With Moderate-To-Severe Atopic Dermatitis," *Journal of the European Academy of Dermatology and Venereology* 37, no. 3 (2023): e384–e388, https://doi.org/10.1111/jdv.18648.

12. E. Kamphuis, C. M. Boesjes, L. Loman, et al., "Dupilumab in Daily Practice for the Treatment of Pediatric Atopic Dermatitis: 28-Week Clinical and Biomarker Results From the BioDay Registry," *Pediatric Allergy and Immunology* 33, no. 12 (2022): e13887.

13. A. Lasek, N. Bellon, S. Mallet, et al., "Effectiveness and Safety of Dupilumab in the Treatment of Atopic Dermatitis in Children (6-11 Years): Data From a French Multicentre Retrospective Cohort in Daily Practice," *Journal of the European Academy of Dermatology and Venereology* 36, no. 12 (2022): 2423–2429.

14. R. Achten, D. Bakker, L. Ariens, et al., "Long-Term Follow-Up and Treatment Outcomes of Conjunctivitis During Dupilumab Treatment in Patients With Moderate-To-Severe Atopic Dermatitis," *Journal of Allergy and Clinical Immunology: In Practice* 9, no. 3 (2021): 1389–1392.

15. V. Puangsricharern and S. C. Tseng, "Cytologic Evidence of Corneal Diseases With Limbal Stem Cell Deficiency," *Ophthalmology* 102, no. 10 (1995): 1476–1485.

16. B. Gu, J. Son, and M. Kim, "Amblyopia and Strabismus by Monocular Corneal Opacity Following Suspected Epidemic Keratoconjunctivitis in Infancy," *Korean Journal of Ophthalmology* 25, no. 4 (2011): 257–261.

17. B. Akinlade, E. Guttman-Yassky, M. de Bruin-Weller, et al., "Conjunctivitis in Dupilumab Clinical Trials," *British Journal of Dermatology* 181, no. 3 (2019): 459–473, https://doi.org/10.1111/bjd.17869.

18. K. Yokoi, N. Yokoi, and S. Kinoshita, "Impairment of Ocular Surface Epithelium Barrier Function in Patients With Atopic Dermatitis," *British Journal of Ophthalmology* 82, no. 7 (1998): 797–800.

19. R. Achten, J. Thijs, M. van der Wal, et al., "Dupilumab-Associated Ocular Surface Disease in Atopic Dermatitis Patients: Clinical Characteristics, Ophthalmic Treatment Response and Conjunctival Goblet Cell Analysis," *Allergy* 78, no. 8 (2023): 2266–2276.

20. A. D. Treister, C. Kraff-Cooper, and P. A. Lio, "Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis," *JAMA Dermatology* 154, no. 10 (2018): 1208–1211.

21. H. Uchida, M. Kamata, M. Nagata, et al., "Conjunctivitis in Patients With Atopic Dermatitis Treated With Dupilumab Is Associated With Higher Baseline Serum Levels of Immunoglobulin E and Thymus and Activation-Regulated Chemokine but Not Clinical Severity in a Real-World Setting," *Journal of the American Academy of Dermatology* 82, no. 5 (2020): 1247–1249.

22. E. Nettis, L. Bonzano, V. Patella, A. Detoraki, P. Trerotoli, and C. Lombardo, "Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience," *Journal of Investigational Allergology & Clinical Immunology* 30, no. 3 (2020): 201–204.

23. A. T. Touhouche, M. Cassagne, E. Bérard, et al., "Incidence and Risk Factors for Dupilumab Associated Ocular Adverse Events: A Real-Life Prospective Study," *Journal of the European Academy of Dermatology and Venereology* 35, no. 1 (2021): 172–179.

24. L. F. M. Ariens, J. van der Schaft, L. S. Spekhorst, et al., "Dupilumab Shows Long-Term Effectiveness in a Large Cohort of Treatment-Refractory Atopic Dermatitis Patients in Daily Practice: 52-Week Results From the Dutch BioDay Registry," *Journal of the American Academy of Dermatology* 84, no. 4 (2021): 1000–1009.

25. L. S. Spekhorst, D. Bakker, J. Drylewicz, et al., "Patient-Centered Dupilumab Dosing Regimen Leads to Successful Dose Reduction in Persistently Controlled Atopic Dermatitis," *Allergy* 77 (2022): 3398–3407.

26. J. M. Hanifin, W. Baghoomian, E. Grinich, Y. A. Leshem, M. Jacobson, and E. L. Simpson, "The Eczema Area and Severity Index-A Practical Guide," *Dermatitis* 33, no. 3 (2022): 187–192.

27. Jr. HF, "Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis," (2015).

28. D. Firth, "Bias Reduction of Maximum Likelihood Estimates," *Biometrika* 80 (1993): 1.

29. J. N. Mandrekar, "Receiver Operating Characteristic Curve in Diagnostic Test Assessment," *Journal of Thoracic Oncology* 5, no. 9 (2010): 1315–1316.

30. L. F. M. Ariens, J. van der Schaft, D. S. Bakker, et al., "Dupilumab Is Very Effective in a Large Cohort of Difficult-To-Treat Adult Atopic Dermatitis Patients: First Clinical and Biomarker Results From the BioDay Registry," *Allergy* 75, no. 1 (2020): 116–126.

31. N. H. Ravn, Z. F. Ahmadzay, T. A. Christensen, et al., "Bidirectional Association Between Atopic Dermatitis, Conjunctivitis, and Other Ocular Surface Diseases: A Systematic Review and Meta-Analysis," *Journal of the American Academy of Dermatology* 85, no. 2 (2021): 453–461.

32. M. R. Ardern-Jones, S. J. Brown, C. Flohr, et al., "An Expert Consensus on Managing Dupilumab-Related Ocular Surface Disorders in People With Atopic Dermatitis 2024," *British Journal of Dermatology* 191, no. 6 (2024): 865–885, https://doi.org/10.1093/bjd/ljae344.

33. M. Katsuta, Y. Ishiuji, H. Matsuzaki, et al., "Transient Increase in Circulating Basophils and Eosinophils in Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis," *Acta Dermato-Venereologica* 101, no. 6 (2021): adv00483.

34. M. A. Kamal, P. Kovalenko, M. P. Kosloski, et al., "The Posology of Dupilumab in Pediatric Patients With Atopic Dermatitis," *Clinical Pharmacology and Therapeutics* 110, no. 5 (2021): 1318–1328.

35. E. Briggs, M. A. Kamal, M. P. Kosloski, et al., "Integrated Exposure-Response of Dupilumab in Children, Adolescents, and Adults With Atopic Dermatitis Using Categorical and Continuous Efficacy Assessments: A Population Analysis," *Pharmaceutical Research* 40, no. 11 (2023): 2653–2666.

36. B. Nuyen, R. N. Weinreb, and S. L. Robbins, "Steroid-Induced Glaucoma in the Pediatric Population," *Journal of AAPOS* 21, no. 1 (2017): 1–6.

37. A. K. Kwok, D. S. Lam, J. S. Ng, D. S. Fan, S. J. Chew, and M. O. Tso, "Ocular-Hypertensive Response to Topical Steroids in Children," *Ophthalmology* 104, no. 12 (1997): 2112–2116.

38. G. Roberti, F. Oddone, L. Agnifili, et al., "Steroid-Induced Glaucoma: Epidemiology, Pathophysiology, and Clinical Management," *Survey of Ophthalmology* 65, no. 4 (2020): 458–472.

39. C. S. Lam, U. M. N. Kalthum, M. D. Norshamsiah, and M. Bastion, "Case Series of Children With Steroid-Induced Glaucoma," *Malaysian Family Physician: the Official Journal of the Academy of Family Physicians of Malaysia* 13, no. 3 (2018): 32–37.

40. E. Berna-Rico, E. Fiz-Benito, J. M. Busto-Leis, G. Servera-Negre, R. de Lucas-Laguna, and M. Feito-Rodriguez, "Effectiveness and Safety of Dupilumab in Children Under 6 Years of Age With Moderate-To-Severe Atopic Dermatitis: A Retrospective Real-World Study," *Dermatology* 240, no. 2 (2024): 337–342.

41. J. Brownell and T. B. Casale, "Anti-IgE Therapy," *Immunology and Allergy Clinics of North America* 24, no. 4 (2004): 551–568.

42. J. Bao, L. Tian, Y. Meng, et al., "Total IgE in Tears Accurately Reflects the Severity and Predicts the Prognosis of Seasonal Allergic Conjunctivitis," *Clinical and Translational Allergy* 12, no. 3 (2022): e12139.

43. Y. Renert-Yuval, J. P. Thyssen, R. Bissonnette, et al., "Biomarkers in Atopic Dermatitis-a Review on Behalf of the International Eczema Council," *Journal of Allergy and Clinical Immunology* 147, no. 4 (2021): 1174–1190.

44. D. S. Bakker, L. F. M. Ariens, C. van Luijk, et al., "Goblet Cell Scarcity and Conjunctival Inflammation During Treatment With Dupilumab in Patients With Atopic Dermatitis," *British Journal of Dermatology* 180, no. 5 (2019): 1248–1249, https://doi.org/10.1111/bjd.17538.

45. B. P. Barnett and N. A. Afshari, "Dupilumab-Associated Mucin Deficiency (DAMD)," *Translational Vision Science & Technology* 9, no. 3 (2020): 29.

46. K. Thormann, A. S. Lüthi, F. Deniau, et al., "Dupilumab-Associated Ocular Surface Disease Is Characterized by a Shift From Th2/Th17 Toward Th1/Th17 Inflammation," *Allergy* 79, no. 4 (2024): 937–948.

47. R. E. Achten, D. S. Bakker, C. M. van Luijk, et al., "Ocular Surface Disease Is Common in Moderate-To-Severe Atopic Dermatitis Patients," *Clinical and Experimental Allergy* 52, no. 6 (2022): 801–805.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.