SYSTEMATIC REVIEW

# Dupilumab ocular side effects in patients with atopic dermatitis: a systematic review

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## Abstract

Atopic dermatitis (AD) is a chronic, inflammatory skin disorder that most frequently occurs in children, but it can also affect adults. Even though most AD cases can be managed with topical treatments, moderate-to-severe forms require systemic therapies. Dupilumab is the first human monoclonal antibody approved for the treatment of AD. Its action is through IL-4 receptor alpha subunit inhibition, thus blocking IL-4 and IL-13 signaling pathways. It has been shown to be an effective, well-tolerated therapy for AD, as well as for asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE). However, an increasing incidence of dupilumab-induced ocular surface disease (DIOSD) has been reported in patients treated with dupilumab, as compared to placebo. The aim of this study was to summarize scientific data regarding DIOSD in AD patients treated with dupilumab. A search of PubMed and clinicaltrials.gov databases was performed. There was no limit to study design. All AD cases were moderate-to-severe. DIOSD was either dermatologist-, allergist-, or ophthalmologist-assessed. Evidence shows that DIOSD occurs most frequently in patients with atopic dermatitis and not in other skin conditions, neither in patients with asthma, CRSwNP, nor EoE who are on dupilumab treatment. Further studies are warranted in order to establish a causal relationship between dupilumab and ocular surface disease. Nevertheless, ophthalmological evaluations prior to dupilumab initiation can benefit AD patients with previous ocular pathology or current ocular symptomatology. Also, patch testing for ocular allergic contact dermatitis might be advantageous in patients with a history of allergic conjunctivitis. Furthermore, TARC, IgE, and circulating eosinophils levels might be important biomarkers for a baseline assessment of future candidates to dupilumab treatment. However, TARC measurements should be resumed for research purposes only.

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## Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disorder that most frequently occurs in children, but it can also affect 2–5% of the adult population.[1] Most AD patients can be treated with topical treatments, such as emollients, anti-inflammatory agents, and light therapy. However, moderate-to-severe forms require systemic therapy.[2] Dupilumab is the first human monoclonal antibody FDA and EMA approved for the treatment of AD, starting from 2017.[2] Its action is through IL-4 receptor alpha subunit inhibition, thus blocking IL-4 and IL-13 signaling pathways, which was shown to improve both objective signs and subjective symptoms of AD.[3] Dupilumab was also successfully used in asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic oesophagitis (EoE), which indicates that IL-4 and IL-13 are key pathways for type 2 T helper immune response.[4]

Upon its approval for type II inflammatory diseases, including AD, asthma and CRSwNP,[5] dupilumab efficacy and safety profile were analyzed through different clinical trials and real-life studies. Thus, while it was shown to be an effective,

well-tolerated therapy for AD, an increased incidence of conjunctivitis has been reported in patients treated with dupilumab, as compared to placebo.[6,7] Rates vary greatly, with a pooled proportion of 26.1% in real-world studies,[2] compared to an 8% pooled proportion in randomized controlled trials (RCTs).[8] Conjunctivitis, together with dry eyes, eye pruritus, blepharoconjunctivitis, severe follicular conjunctivitis, limbal nodules, cicatricial ectropion, and keratitis, has been previously included in the umbrella term of dupilumab-induced ocular surface disease (DIOSD).[9,10] Additionally, an increasing number of real-life studies, case series, and case reports describe a large variety of other ocular manifestations observed after dupilumab initiation, and all of these cases are summarized in Tables 3–4 with the purpose of an exhaustive data provision that would enable the reader to draw an informed conclusion. What proportion of these findings is actually caused or exacerbated by dupilumab remains to be further investigated.

However, DIOSD was not reported in patients receiving dupilmab for the treatment of asthma, CRSwNP or EoE, thus suggesting a unique interplay between AD and dupilumab.[11] The aim of this study was to summarize scientific data regarding ocular surface disease in AD patients treated with dupilumab.

## Materials and methods

A systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search of PubMed and clinicaltrials.gov databases was performed using the term *dupilumab* in combination with the following terms: *ocular, eye, conjunctivitis*. Only articles in English were selected. The last search was run on 4$^{th}$ June 2021. There was no limit to study design. We included randomized, controlled clinical trials, real-life studies, case series, and case reports evaluating ocular manifestations in patients diagnosed with atopic dermatitis and treated with dupilumab. The main characteristics of real-life studies are the following: they are conducted in everyday settings; can have an observational, descriptive, or pragmatic design; can be both prospective and retrospective, and they include cohort, case-control, and cross-sectional studies. In contrast to randomized controlled trials, real-life studies do not use inclusion and exclusion criteria, their non-selectivity allowing an objective analysis of a heterogenous and representative population.[12] Although case series and case reports have a smaller value in the medical literature and in evidence-based medicine, they may provide clues about rare manifestations of a disease or a drug.[13] Considering the rather recent approval of dupilumab for AD patients, we believe that pertinent data from all study designs are relevant and should be included in an exhaustive systematic review. Consistent reviews and meta-analyses were selected. Other potentially relevant articles were identified by manually checking the references of the included literature. We selected studies evaluating ocular manifestations in patients diagnosed with atopic dermatitis treated with dupilumab. We excluded articles not available in English, articles for which neither abstract nor full text were available, articles with unavailable full text, and an undetailed abstract.

Independent extraction of articles was performed by two investigators using predefined criteria, and discrepancies were resolved by discussion. Ocular side effects were reviewed by an ophthalmologist and were categorized into mild, moderate, and severe forms. We categorized as mild lighter ocular side effects involving the anterior chamber of the eye (e.g., conjunctivitis, blepharitis); moderate included long-term side effects of the anterior chamber of the eye (e.g., corneal ulcer, keratisis), increased ocular pressure (glaucoma), cataract, and mild side effects requiring long-term medical therapies (more than one week of eyedrops/ oral antibiotics/ steroids); severe side effects were defined as involving the posterior chamber of the eye (e.g., cystoid macular oedema, chorioretinitis), or any side effect which resulted in blindness.

Limitations of this review lie in study heterogeneity, as well as in confirmation bias in reporting, since DIOSD was either patient-reported, diagnosed by a dermatologist, allergist or by an ophthalmologist. Additionally, previous history of ocular disease was inconstantly documented, follow-up periods were highly variable, and different topical as well as systemic treatments were used in patients with DIOSD, with or without dupilumab discontinuation. Due to study design heterogeneity, we focused our review on objectively summarizing DIOSD rates in AD patients with dupilumab therapy by category: clinical trials, real-life studies including prospective, as well as retrospective studies, case series, and case reports. Pertinent data were selected in the form of number of patients with: AD, DIOSD, previous ocular disease, AD severity, DIOSD severity, dupilumab discontinuation, and ocular pathology diagnosis. AD severity was rated as mild, moderate, or severe according to EASI[14,15] and SCORAD scores.[15]

## Results

A total of 206 articles were initially identified in the literature search, of which 37 were duplicates, and 94 did not meet the inclusion criteria so were consequently excluded (Fig. 1). We selected 15 randomized controlled trials (RCTs), 18 real-life studies, 15 case series, 13 case reports, three reviews, and two meta-analyses. A total of 8456 AD patients on dupilumab therapy were included, of which 5405 from clinical trials, 2883 from real-life studies, 155 from case series, and 13 from case reports. Among them, 840 patients presented DIOSD, 261 had previous ocular involvement, and 53 discontinued dupilumab. All AD cases were moderate-to-severe, as assessed by SCORAD and/ or EASI atopic dermatitis scores. Ocular side effects were either dermatologist-, allergist-, or ophthalmologist-assessed. Following our classification of ocular side effects, 722 were mild forms, 60 were moderate, and seven were severe.

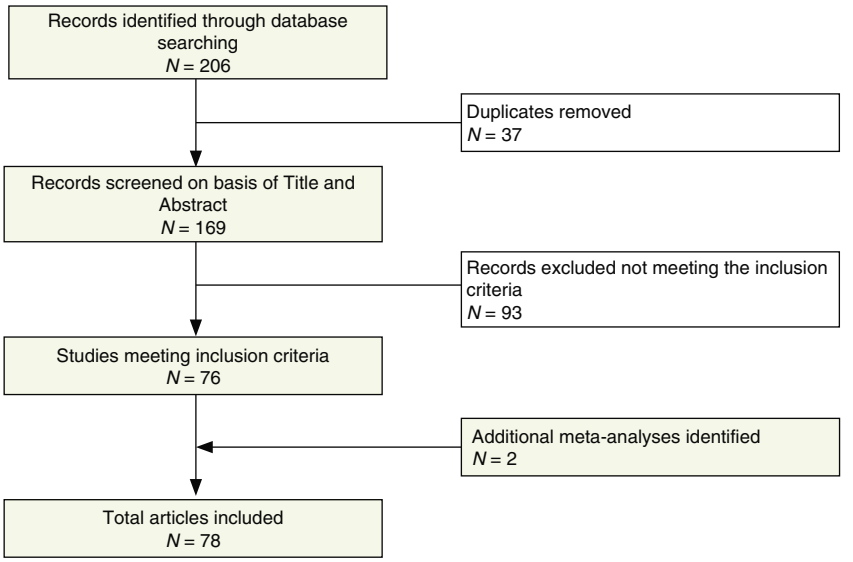


**Figure 1** Literature search and article selection.

## Clinical trials

We found 57 dupilumab clinical trials (CT) conducted on various pathologies: asthma ($n$ = 12), allergic bronchopulmonary aspergillosis ($n$ = 1), atopic dermatitis ($n$ = 23), hand eczema ($n$ = 2), eosinophilic esophagitis ($n$ = 2), nasal polyps ($n$ = 3), localized scleroderma ($n$ = 1), bullous pemphigoid ($n$ = 1), prurigo nodularis ($n$ = 2), chronic obstructive pulmonary disease ($n$ = 2), cold urticaria ($n$ = 1), Netherton's syndrome ($n$ = 1), cholinergic urticaria ($n$ = 1), chronic urticaria ($n$ = 2), seasonal allergic rhinitis ($n$ = 1), numular eczema ($n$ = 1), and chronic sinusitis ($n$ = 1; Table 1).

Among AD clinical trials, DIOSD rates were mentioned in 12 of them[16] (Table 2), ranging from 0.00% (0 of 40 adolescents) to 23.63% (13 of 55 adults). In 283 patients, ocular manifestations appeared after a mean of 18.2 weeks (between 4 and 51 weeks) of dupilumab treatment, and patients were followed-up for AEs for a mean of 27.6 weeks (between 11 and 52 weeks). 10 out of 12 CTs reported DIOSD under the umbrella terms of 'conjunctivitis' or 'allergic conjunctivitis', terms used by the investigators (dermatologists or allergists), who also made the diagnosis. In one CT, the diagnosis of angle closure glaucoma was assigned to only one patient in the placebo group, which indicates a lack of relationship to dupilumab. Another CT reported blepharitis, conjunctivitis, cataract, cystoid macular oedema, and glaucoma. Study protocols did not include ophthalmological assessments, either before, during, or after dupilumab treatment.

Rates of conjunctivitis were higher in AD patients treated with dupilumab than in those receiving placebo, in adult, as well as in adolescent and children clinical trials.[7,11,17–23] Most cases of conjunctivitis were mild-to-moderate forms and responded to topical eye drops with corticosteroids, antibiotics, antihistamines, or mast cell stabilizers without necessitating dupilumab discontinuation.[11] Severe cases were only reported in less than 1% of the patients.[4] Higher baseline AD severity, personal history of conjunctivitis, higher baseline levels of thymus and activation-regulated chemokine (TARC), immunoglobulin E (IgE), and

**Table 1** Dupilumab clinical trials for different medical conditions

| | Total | With results | Ongoing |
|---|---|---|---|
| Asthma | 12 | 6 | 6 |
| Allergic bronchopulmonary aspergillosis | 1 | | 1 |
| Atopic dermatitis | 23 | 9 | 14 |
| Hand eczema | 2 | | 2 |
| Eosinophilic esophagitis | 2 | | 2 |
| Nasal polyps | 3 | 2 | 1 |
| Localized scleroderma | 1 | | 1 |
| Bullous pemphigoid | 1 | | 1 |
| Prurigo nodularis | 2 | | 2 |
| Chronic obstructive pulmonary disease | 2 | | 2 |
| Cold urticaria | 1 | | 1 |
| Netherton's syndrome | 1 | | 1 |
| Cholinergic urticaria | 1 | | 1 |
| Chronic urticaria | 2 | | 2 |
| Seasonal allergic rhinitis | 1 | | 1 |
| Numular eczema | 1 | | 1 |
| Chronic sinusitis | 1 | | 1 |
| **TOTAL** | **57** | **17** | **40** |

**Table 2** AD clinical trials

| Trial number | Patients enrolled | Patients completed | Dupilumab treatment | AEs Follow-up | DIOSD | DIOSD combined |
|---|---|---|---|---|---|---|
| **NCT02407756** | 78 children and adolescents: 6–18 y; | 78 | 12 weeks | week 20 | **CONJUNCTIVITIS**:<br>2 mg/kg: Adolescents: 0.00%, Children: 0.00%<br>4 mg/kg: Adolescents: 0.00%, Children: 5.26% (1/19)<br>**ALLERGIC CONJUNCTIVITIS:**<br>2 mg/kg: Adolescents: 0.00%, Children: 0.00%<br>4 mg/kg: Adolescents: 0.00%, Children: 5.26% (1/19) | Adolescents: 0.00% (0/40)<br>Children: 5.40% (2/37) |
| **NCT02395133 SOLO-CONTINUE** | 422 adults | 375 | 36 weeks | week 36 | N/A | N/A |
| **NCT03389893** | 72 adults | 71 | 14 weeks | day 28 | **CONJUNCTIVITIS**: Placebo: 11.54% (3/26), dupilumab 300 mg Q2W: 4.35% (2/46) | Placebo: 11.54% (3/26)<br>dupilumab: 4.35% (2/46) |
| **NCT03912259** | 165 adults | 142 | 17 weeks | week 28 | **CONJUNCTIVITIS**:<br>Placebo Q2W: 4.82% (4/83), dupilumab 300 mg Q2W: 9.76% (8/82)<br>**ALLERGIC CONJUNCTIVITIS:**<br>Placebo Q2W: 1.20% (1/83), dupilumab 300 mg Q2W: 8.54% (7/82) | Placebo: 6.02% (5/83)<br>dupilumab: 18.29% (15/82) |
| **NCT01859988** | 380 adults | 277 | 16 weeks | week 32 | **CONJUNCTIVITIS**:<br>Placebo: 0.00% (0/61), dupilumab 300 mg QW: 6.35% (4/63), dupilumab 300 mg Q2W: 1.56% (1/64), dupilumab 200 mg Q2W: 0.00% (0/61), dupilumab 300 mg Q4W: 1.54% (1/65), dupilumab 100 mg Q4W: 0.00% (0/65)<br>**ALLERGIC CONJUNCTIVITIS:**<br>Placebo: 3.28% (2/61), dupilumab 300 mg QW: 4.76% (3/63), dupilumab 300 mg Q2W: 3.13% (2/64), dupilumab 200 mg Q2W: 9.84% (6/61), dupilumab 300 mg Q4W: 4.62% (3/65), dupilumab 100 mg Q4W: 1.54% (1/65) | Placebo: 3.27% (2/61)<br>dupilumab: 5.54% (21/379) |
| **NCT02210780** | 194 adults | 181 | 15 weeks | week 32 | **CONJUNCTIVITIS**: Placebo: 0.00% (0/97), dupilumab 300 mg QW: 8.25% (8/97) | Placebo: 0.00% (0/97)<br>dupilumab: 8.24% (8/97) |
| **NCT02755649**<br>**LIBERTY AD CAFE** | 325 adults | 23 | 16 weeks | week 28 | **CONJUNCTIVITIS**:<br>Placebo QW + TCS: 3.70% (4/108), dupilumab 300 mg Q2W + TCS: 11.21% (12/107), dupilumab 300 mg QW + TCS: 7.27% (8/110)<br>**ALLERGIC CONJUNCTIVITIS:**<br>Placebo QW + TCS: 6.48% (7/108), dupilumab 300 mg Q2W + TCS: 14.95% (10/110), dupilumab 300 mg QW + TCS: 9.09% (16/107) | Placebo: 10.18% (11/108)<br>dupilumab: 21.2% (46/217) |
| **NCT02260986 CHRONOS** | 740 adults | 596 | 51 weeks | week 52 | **BLEPHARITIS**:<br>Placebo QW: 0.95% (3/315), dupilumab 300 mg Q2W: 5.45% (6/110), dupilumab 300 mg QW: 3.49% (13/315)<br>**CONJUNCTIVITIS**:<br>Placebo QW: 6.03% (19/315), dupilumab 300 mg Q2W: 11.82% (13/110), dupilumab 300 mg QW: 17.14% (54/315)<br>**CATARACT**: Placebo: 0.32% (1/315), dupilumab 300 mg Q2W: 0.00% (0/110), dupilumab 300 mg QW: 0.00% (0/315)<br>**CYSTOID MACULAR OEDEMA**: Placebo: 0.00% (0/315), dupilumab 300 mg Q2W: 0.00% (0/110), dupilumab 300 mg QW: 0.32% (1/315)<br>**GLAUCOMA**: Placebo: 0.32% (1/315), dupilumab 300 mg Q2W: 0.00% (0/110), dupilumab 300 mg QW: 0.00% (0/315) | Placebo: 7.61% (24/315)<br>dupilumab: 20% (85/425) |
| **NCT01979016** | 54 adults | 51 | 16 weeks | week 32 | **ALLERGIC CONJUNCTIVITIS:**<br>Placebo QW: 0.00% (0/27), dupilumab 200 mg QW: 7.41% (2/27) | Placebo: 0.00% (0/27)<br>dupilumab: 7.41% (2/27) |

**Table 2** *Continued*

| Trial number | Patients enrolled | Patients completed | Dupilumab treatment | AEs Follow-up | DIOSD | DIOSD combined |
|---|---|---|---|---|---|---|
| **NCT01548404** | 109 adults | 65 | 12 weeks | week 28 | **CONJUNCTIVITIS**: Placebo QW: 3.70% (2/54), dupilumab 300 mg QW: 14.55% (8/55) **ALLERGIC CONJUNCTIVITIS:** Placebo QW: 0.00% (0/54), dupilumab 300 mg QW: 9.09% (5/55); | Placebo: 3.70% (2/54) dupilumab: 23.63% (13/55) |
| **NCT01639040** | 31 adults | 30 | 4 weeks | week 11 | N/A | N/A |
| **NCT03054428 LIBERTY AD ADOL** | 251 adolescents: 12–18 y | 9 | 16 weeks | week 28 | N/A | N/A |
| **NCT03345914** | 367 children and adolescents: 6–12 y | 0 | 16 weeks | week 28 | **CONJUNCTIVITIS**: Placebo + TCS: 2.5% (3/120), dupilumab 300 mg Q4W + TCS: 4.17% (5/120), dupilumab 100 mg or 200 mg Q2W + TCS: 5.74% (7/122) | Placebo: 2.5% (3/120) dupilumab: 4.95% (12/242) |
| **NCT02277743 SOLO 1** | 671 adults | 589 | 16 weeks | week 28 | **ALLERGIC CONJUNCTIVITIS:** Placebo: 1.35% (3/222), dupilumab 300 mg Q2W: 5.24% (12/229), dupilumab 300 mg QW: 3.67% (8/218) | Placebo: 1.35% (3/222) dupilumab: 4.47% (20/447) |
| **NCT02277769 SOLO 2** | 708 adults | 631 | 16 weeks | week 28 | **ANGLE CLOSURE GLAUCOMA**: Placebo: 0.43% (1/234), dupilumab 300 mg Q2W: 0.00% (0/236), dupilumab 300 mg QW: 0.00% (0/237) | Placebo: 0.43% (1/234) dupilumab: 0.00% (0/473) |

circulating eosinophil counts were associated with higher rates of conjunctivitis, regardless of the treatment group (dupilumab or placebo).[11]

In a publication by Beck *et al*, 347 AD patients treated with dupilumab were followed-up for 148 weeks. They received dupilumab 300 mg weekly, different from the biweekly regimen approved in adults, and had an exposure-adjusted incidence of conjunctivitis of 16.14 number of events (nE)/100 patient years (PY), which was lower than the 76-week phase of one trial, of 20.8 nE/100 PY and further, lower than in the 52-week phase of the same trial, of 30.60 nE/100 PY.[24] Most ocular events were mild-to-moderate and resolved with topical treatment. Severe conjunctivitis occurred in 26 (1.0%) patients and 14 (0.5%) discontinued dupilumab.[5]

In a meta-analysis by Ou *et al*, the results of eight randomized controlled studies (RCTs) were assessed. The risk of conjunctivitis was 2.64 times higher for AD patients treated with dupilumab than those who were assigned the placebo.[8] However, while conjunctivitis was a significant AE for patients with AD treated with dupilumab, no significant risk of DIOSD was reported in patients with asthma,[25–27] CRSwNP[28] or EoE.[11,29]

## Real-life studies

2883 AD patients under dupilumab therapy were included, 392 (13%) of which developed DIOSD[9,10,30–45] and 37 discontinued dupilumab therapy.[9,30,32–34,37,42–44] 231 out of 392 (58.9%) patients with DIOSD had previous ocular involvement.[9,10,30,31,34–40,42] Most of the cases were diagnosed by an ophthalmologist, 348 were mild, 21 were moderate, and none were severe forms. Topical therapies included artificial tears,[9,10,30,33,35,37,42,44] hyaluronic acid eye drops,[35] corticosteroid eye drops,[9,30,31,33,35,37,42,44] antihistaminic,[10,31,33,42] allergen avoidance according to patch testing,[39] tacrolimus,[10,30,33] antibiotic,[35] and cyclosporine[9,35,42] (Table 3).

## Case series

From the 155 cases presented in the series,[46–60] 12 discontinued dupilumab due to DIOSD severity. Most of the cases were diagnosed by an ophthalmologist (63%),[46–52,54,56,57,60] the rest being assessed by a dermatologist.[53,55,58,59] 87 were mild forms, 32 were moderate, and five were severe. 24 out of 155 patients had previous ocular involvement[47,48,51,52,59,60] and three of them required dupilumab discontinuation.[48,52,60] The rest of the cases improved with topical and/ or systemic treatment. Topical therapies included: artificial tears,[46,50,52,55,57,57,59,60] hyaluronate tear substitute,[52] corticosteroid eye drops,[46–53,55–57,59,60] antihistaminic,[47,49,52,53,56,57,60] tacrolimus,[46–48,50,59,60] antibiotic,[47,50,51,57,59,60] cyclosporine,[49,51–53,56] and surgery[47,50] (Table 4).

## Case reports

There were 13 cases of DIOSD reported in the literature,[61–72] six of which required dupilumab discontinuation due to ocular

**Table 3** AD real-life studies with reported DIOSD

| Publication | AD patients | AD baseline severity | DIOSD Patients | DIOSD after (weeks) | Previous ocular disease | DIOSD | DIOSD severity | Dupilumab discontinuation | DIOSD Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Achten *et al.*[30] | 167, Netherlands | mean EASI 21.7 | 33 | median 33 days | 24/33 allergic conjunctivitis | Tarsal conjunctivitis 28, bulbar conjunctivitis 25, blepharitis 22, corneal punctate 10, Meibomian gland disfunction 9, limbitis 6 | Mild 33 | 3 | Ophthalmologist |
| Armario-Hita *et al.*[31] | 70, Spain | mean EASI 28.1, SCORAD 62.1, | 6 | N/A | 6/6 allergic conjunctivitis | Mild conjunctivitis | Mild 6 | no | Dermatologist |
| Barbé *et al.*[32] | 100, France, Brazil | N/A | 18 | 4 months | N/A | Severe allergic conjunctivitis and blepharitis | Mild 18 | 6 | N/A |
| Bosma *et al.*[45] | 221, The Netherlands | Mean EASI 14.6 | 46 | mean 36 days | N/A | (kerato)conjunctivitis 37, blepharitis 11, sicca complaints 11, epiphora 2, ectropion 3 | Mild 43 Moderate 3 | no | Dermatologist |
| de Wijs *et al.*[33] | 95, The Netherlands | mean EASI 18.6 | 59 | N/A | N/A | keratoconjunctivitis 9, blepharitis 2, sicca 2 | Mild 59 | 5 | Ophthalmologist |
| Faiz *et al.*[34] | 241, France | mean EASI 33.3 | 32 | N/A | 101/241 allergic conjunctivitis | Conjunctivitis | Mild 32 | 10 | Ophthalmologist |
| Fargnoli *et al.*[35] | 109, Italy | mean EASI 33.3 | 12 | N/A | 9/12 allergic conjunctivitis | Conjunctivitis | Mild 12 | no | Dermatologist |
| Igelman *et al.*[36] | 124, USA | N/A | 10 | N/A | 33/124 conjunctivitis | Conjunctivitis | Mild 10 | no | Dermatologist |
| Kreeshan *et al.*[37] | 164, UK | median EASI 23 | 66 | N/A | 1 pre-existing blepharitis | Mild eye symptoms 36, conjunctivitis 25, episcleritis 3, worsening pre-existing blepharitis 1, bacterial conjunctivitis 1 | Mild 63 Moderate 3 | 3 | Dermatologist |
| Nahum *et al.*[10] | 37, Israel | N/A | 16 | as early as 2 weeks after first D administration | 14/ 16 prior keratoconjunctivitis | Transient dry eye sensation 3, chronic dry eye sensation 9 (mild Meibomian gland disease), marked blepharoconjunctivitis 4 (periocular eczema, Meibomian gland disease, thickening and hyperanemia of lid margin to the point of mechanical ectropion) | Mild 16 | no | Ophthalmologist |
| Olesen *et al.*[38] | 43, Denmark | median EASI 24.5 | 7 | N/A | 3/7 conjunctivitis | Conjunctivitis | Mild 7 | no | Dermatologist |

**Table 3** *Continued*

| Publication | AD patients | AD baseline severity | DIOSD Patients | DIOSD after (weeks) | Previous ocular disease | DIOSD | DIOSD severity | Dupilumab discontinuation | DIOSD Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Popiela *et al.*[9] | 28, UK | mean EASI 18.5 | 9 | mean of 6 weeks | AKC 4, HSV keratitis 1, keratoconus 1 | Bilateral conjunctival papillary reaction 6, bilateral conjunctival follicular changes 3, of which: limbal nodules 2, conjunctival cicatrization in the lower fornix 2, cicatrizing ectropion 1, punctal stenosis 1, periocular dermatitis 1 | Moderate 9 | 1 | Ophthalmologist |
| Raffi *et al.*[39] | 48, USA | n/a | 14 | before and after | 14 prior eye involvement | Eyelid dermatitis 13, conjunctivitis 9, blepharitis 10 | Mild 14 | N/A | Dermatologist |
| Ruiz-Villaverde *et al.*[40] | 30, Spain | mean SCORAD 59.4, | 5 | N/A | 10/ 30 conjunctivitis | Conjunctivitis | Mild 5 | no | Dermatologist |
| Schneeweiss *et al.*[41] | 1198, USA | N/A | N/A | N/A | N/A | Conjunctivitis | Mild | N/A | Ophthalmologist |
| Touhouche *et al.*[42] | 46, France | N/A | 16 | 12 weeks | Dry eye disease with keratitis 10, dry eye disease without keratitis 10 | Superficial punctate keratitis 11, conjunctival hyperaemia 9, blepharitis 6, papillae and follicles 6 | Mild 13 Moderate 3 | 2 | Ophthalmologist |
| Waldman *et al.*[43] | 85, USA | N/A | 23 | N/A | N/A | N/A | N/A | 2 | N/A |
| Wang *et al.*[44] | 77, USA | N/A | 20 | N/A | N/A | Dry eyes 8, conjunctivitis 6, keratitis 3, blurry vision 2, HSV 2, blepharitis 2, foreign body sensation 1, hypersensitivity 1 | Mild 17 Moderate 3 | 5 | Ophthalmologist |

discomfort, and the symptomatology subsequently improved. In one case, however, dupilumab frequency of administration was reduced from biweekly to every 4 weeks, in this case, also, with significant ocular improvement.[65] In the other six cases, topical treatment led to symptom remission, along with dupilumab continuous administration. All DIOSD cases were diagnosed by an ophthalmologist and seven cases were mild, five were moderate, and one was a severe form. Six patients had previous ocular disease, either dry eyes[61,72] allergic conjunctivitis,[68] trauma induced corneal flap removal,[67] keratoconus,[66] or repeated episodes of infectious conjunctivitis, keratitis, and cataract.[63] Treatment methods employed were artificial tears,[68,72] hyaluronic acid/carbomer eye drops,[73] autologous serum eyedrops,[67] corticosteroid eyedrops,[62,64–70,73] cyclosporine eye drops,[64,68,72] antibiotic,[66,73] tacrolimus,[73] lifitegrast drops,[72] and surgery[63,69] (Tables 4 and 5).

## Discussion

The pathomechamisms involved in DIOSD are not clearly understood. Several hypotheses have been proposed: reduced conjunctival goblet cell activity with subsequent decreased mucin production and tear film instability, heightened OX40 ligand activity, eosinophilia, and increased Demodex infestation. Voorberg *et al* showed goblet cell scarcity with a median density of 2–4 goblet cells/mm and positive CD4-/ CD8 (predominantly CD4) T-cell infiltrate in a conjunctival biopsy after 16 weeks of dupilumab treatment for AD. After 4 months of dupilumab discontinuation, another biopsy was performed and showed normal goblet cell density and significantly less CD4-/ CD8-positive T cells.[73] This case demonstrates recovery of goblet cell density after dupilumab discontinuation. One hypothesis is that dupilumab blocks IL-4 and IL-13 signaling pathways which leads to reduction of goblet cells and mucin production, subsequent tear film instability, and conjunctival inflammation; however reversible after cessation of IL-4 and IL-13 inhibition.[73,74] This mechanism is further supported by a mice study in which the application of IL-4 and IL-13 to conjunctival goblet cells determined cell proliferation,[66] and by a separate study conducted by Barnett *et al* where mucin 5ac (Muc5AC), a specific marker for goblet cells, was lower in patients with dupilumab as compared to the control group.[75] An increased activity of OX40 ligand in the eye, eosinophilia, and increased Demodex infestation have also been proposed, but these hypotheses has not been demonstrated yet.[59]

Furthermore, Raffi *et al* emphasized the influence of underlying allergic contact dermatitis in DIOSD and the role of allergen avoidance in the remission of ocular pathology.[39] This suggests that previous allergic contact dermatitis may be exacerbated by dupilumab.

Conversely, no significant risk of DIOSD was shown in patients with asthma,[25–27] CRSwNP[28] or EoE.[11,29] Additionally, Waldman *et al* demonstrated that DIOSD occurs at much lower rates in patients with skin diseases other than AD: bullous pemphigoid, chronic actinic dermatitis, chronic idiopathic urticaria, cutaneous T cell lymphoma, dermal hypersensitivity, dermatitis of immunosenescence, dyshidrotic eczema, erythema annulare centrifugum, palmoplantar psoriasis, prurigo nodularis, psoriasiform dermatitis, and Well's syndrome.[43] All this evidence points toward a unique interplay between AD pathomechanisms and dupilumab, which results in various ocular symptomatology. A recent study investigating the association between AD and conjunctivitis showed a fourfold higher risk of conjunctivitis (OR=4.38; 95% CI, 1.39–13.79; $P = 0.012$) and an eightfold higher risk of allergic conjunctivitis (OR=8.03; 95% CI, 1.76–36.58; $P = 0.007$) in patients with AD, as compared to non-AD patients.[76] These findings might support the conclusion that DIOSD is more frequent in patients with atopic dermatitis.

Additionally, Touhouche *et al* reported ocular adverse events in patients with preexisting dry eye disease, keratitis, and eyelid eczema. Furthermore, high levels of baseline IgE and a history of food allergy were significantly associated with DIOSD.[42] Uchida *et al* further linked DIOSD with high baseline levels of TARC and IgE.[58] These findings are further supported by clinical trial data showing that a high baseline AD severity, personal history of conjunctivitis, high baseline levels of TARC, IgE, and circulating eosinophil counts were associated with higher rates of conjunctivitis, regardless of the treatment group (dupilumab or placebo).[11]

On the other hand, exposure-adjusted incidence of conjunctivitis seems to decrease with time: from 30.60 nE/100 PY in a previous 52-week controlled trial, to 20.8 nE/100 PY in the 76-week phase of the same trial,[24] to 16.14 nE/100 PY after 148 weeks of follow-up in another trial.[5] This indicates that DIOSD rates might decrease with time, in patients with continued dupilumab treatment. Furthermore, Pistone *et al* reported no DIOSD in a series of 30 patients treated with dupilumab for 6 months.[55] Indeed, they concomitantly administered artificial tears twice daily, immediately after dupilumab initiation, which might have prevented or delayed the onset of DIOSD. Additionally, Fukuda *et al* showed improvement in two cases of atopic keratoconjunctivitis with giant papillae after dupilumab treatment initiation.[47]

Data from clinical trials and real-life studies are extremely heterogenous. Lower rates, milder forms of DIOSD reported in clinical trials versus real life studies, different follow-up periods, different specialist-reported cases of DIOSD (dermatologist, allergist, ophthalmologist), the lack of ophthalmological assessment before dupilumab initiation in order to establish a baseline for pre-existing ocular pathology, biomarker levels (TARC, IgE and circulating eosinophil counts), as well as patch testing for ocular allergic contact dermatitis make it fairly challenging to make a definitive assessment.

Furthermore, because the data are so diverse, an official guideline regarding optimal management and treatment of

**Table 4** AD case series and case reports with DIOSD

| Publication | AD patients | AD baseline severity | DIOSD after | Previous ocular disease | DIOSD | DIOSD severity | Dupilumab discontinuation | DIOSD Diagnosis |
|---|---|---|---|---|---|---|---|---|
| Bohner *et al.*[46] | 29 patients, mean 46 y | N/A | N/A | N/A | Conjunctivitis 18, punctate keratitis 16, papillary reaction 8 | Mild 13 Moderate 16 | No | Ophthalmologist |
| Fukuda *et al.*[47] | M, 25 y | N/A | N/A | Atopic keratoconjunctivitis | Giant papillae with discharge on the upper tarsal conjunctiva; large shield ulcer with plaque on the cornea of the right eye | Severe 1 | No | Ophthalmologist |
| | M, 33 y | N/A | N/A | Atopic keratoconjunctivitis | Giant papillae with hyperemia and discharge on the upper tarsal conjunctiva of both eyes | Moderate 1 | No | Ophthalmologist |
| Ivert *et al.*[48] | 10 patients: mean EASI 20.7 | mean EASI 20.7 | After 5-7 months | All allergic conjunctivitis | Conjunctivitis 7, keratoconjunctivitis 1, keratitis 1, blepharitis 2, HSV reactivation 1 | Mild 10 | 1 | Ophthalmologist |
| Jo *et al.*[49] | 21/ 58 patients | N/A | After avg. 10 weeks | N/A | Conjunctivitis and other OSDs | Mild 21 | 2 | Ophthalmologist |
| Lee *et al.*[50] | M, 34 y | N/A | After 6 months | N/A | Bilateral eyelid dermatitis with edema and hypopigmentation, lagophthalmos, lower eyelid cicatricial ectropion, conjunctival papillae, and obstruction without visible patency of all four puncta | Moderate 1 | 1 | Ophthalmologist |
| | M, 31 y | N/A | After 6 months | No | Bilateral eyelid dermatitis with edema, conjunctival injection, 4 severely stenotic puncta, bilateral mild ectropion | Moderate 1 | No | Ophthalmologist |
| | F, 53 y | N/A | After 4 months | No | Bilateral mild papillary conjunctivitis, meibomian gland dropout, high tear film in both eyes, stenotic puncta on all 4 eyelids | Moderate 1 | No | Ophthalmologist |
| Liberman *et al.*[51] | M, 56 y | N/A | After 2 weeks | No | Conjunctivitis | Moderate 1 | No | Ophthalmologist |
| | M, 19 y | N/A | After 3 months | Mild erythema and itching in both eyes | Blepharoconjunctivitis, symblepharon in the right eye inferonasally | Moderate 1 | No | Ophthalmologist |
| Maudinet *et al.*[52] | 10 cases, mean 36 y | Mean SCORAD 60.4, mean EASI 37 | after mean 3.5 months | Allergic conjunctivitis 6 | 2 clinical patterns of ocular surface diseases: a mild nonspecific conjunctivitis with dry eyes, which improved with warm compresses and artificial tears without any recurrence; and a severe dupilumab-induced follicular conjunctivitis without keratitis | Moderate 10 | 1 | Ophthalmologist |

**Table 4** *Continued*

| Publication | AD patients | AD baseline severity | DIOSD after | Previous ocular disease | DIOSD | DIOSD severity | Dupilumab discontinuation | DIOSD Diagnosis |
|---|---|---|---|---|---|---|---|---|
| Padidam *et al.*[54] | 4 patients | N/A | After | N/A | 1: posterior scleritis or Harada's-type disease; 2: anterior and intermediate uveitis as well as cystoid macular edema in her right eye; 3: placoid chorioretinitis; 4: bilateral cystoid macular edema | Severe 4 | N/A | Ophthalmologist |
| Pistone *et al.*[55] | 30 patients | N/A | N/A | N/A | None | N/A | N/A | Dermatologist |
| Shen *et al.*[56] | M, 44 y | N/A | After 3 weeks | No | Follicular conjunctivitis | Mild 1 | No | Ophthalmologist |
| | F, 43 y | N/A | After 1 month | No | Follicular conjunctivitis; LASIK scars in both corneas | Mild 1 | No | Ophthalmologist |
| Treister *et al.*[57] | 12 patients, mean 30 y | N/A | After mean 15 weeks | No | Conjunctivitis | Mild 12 | 3 | Ophthalmologist |
| Uchida *et al.*[58] | 13 patients | N/A | After mean 5 weeks | N/A | Conjunctivitis | Mild 13 | N/A | Dermatologist |
| Wollenberg *et al.*[59] | 13 patients: 8 severe, 5 moderate AD | N/A | N/A | Conjunctivitis 4 | Conjunctivitis 13, blepharitis 10, limbal edema 5 | Mild 13 | No | Dermatologist |
| Yamane *et al.*[60] | F, 66 y | N/A | After 1 week | Periocular skin thickening and fissures; prior blepharoplasty | Severe periocular dermatitis | Mild 1 | 1 | Ophthalmologist |
| | F, 28 y | N/A | After 5 and a half months | no | Bilateral periocular dermatitis and conjunctivitis | Mild 1 | 1 | Ophthalmologist |
| Barnes *et al.*[61] | M, 61 y | N/A | 2 months | Eyelid erythema, crusting, tearing, intermittent blurred vision. | Bilateral conjunctivitis and severe cicatricial ectropion with punctal stenosis of both lower eyelids. | Moderate 1 | Yes | Ophthalmologist |
| Fukuda *et al.*[62] | W, 35 y | N/A | Several days | no | Bilateral conjunctivitis with papillae and follicular reaction in the upper and lower tarsal conjunctiva; a protruding lesion from the upper fornix in the left eye. | Mild 1 | No | Ophthalmologist |
| Gkalpakiotis *et al.*[63] | M, 45 y | EASI 38.6 | Before | Both eyes: recurrent conjunctivitis and keratitis, complicated cataract extraction, rhegmatogenous retinal detachment, cystoid macular edema | Right eye is blind as a result of steroid-induced glaucoma. | Severe 1 | No | Ophthalmologist |
| Kimura *et al.*[64] | W, 46 y | N/A | After 10 weeks | No | Paradoxical bilateral allergic conjunctivitis, papillary hyperplasia and bilateral blepharitis. | Mild 1 | No | Ophthalmologist |

**Table 4** *Continued*

| Publication | AD patients | AD baseline severity | DIOSD after | Previous ocular disease | DIOSD | DIOSD severity | Dupilumab discontinuation | DIOSD Diagnosis |
|---|---|---|---|---|---|---|---|---|
| Levine *et al.*[65] | M, 49 y | N/A | After 8 weeks | No | Cicatrizing blepharoconjunctivitis with subepithelial fibrosis and punctal stenosis. | Moderate 1 | No, but D was prolongued to 4 weeks interval administration | Ophthalmologist |
| Li *et al.*[66] | M, 50 y | N/A | After 3 weeks of dupilumab | Left eye: keratoconus, cataract | Moderate-to-severe conjunctival injection; sterile corneal ulcer in the right eye | Moderate 1 | Yes | Ophthalmologist |
| McCarthy *et al.*[53] | F, 26 y | N/A | After 6 weeks | No | Blepharoconjunctivitis | Mild 1 | No | Dermatologist |
| Mehta *et al.*[67] | M, 56 y | N/A | After 1 year | Trauma induced corneal flap removal | Cicatrizing blepharoconjunctivitis and secondary limbal stem cell deficiency, diffuse bilateral symblepharon. | Moderate 1 | Yes | Ophthalmologist |
| Nettis *et al.*[68] | M, 55 y | EASI 25.1 | After 4 weeks | 32 year history of allergic rhinoconjunctivitis | Conjunctivitis, blepharitis, and dry eyes, → cicatricial ectropion of both lower eyelids, severe punctate stenosis | Moderate 1 | Yes | Ophthalmologist |
| Paulose *et al.*[69] | M, 48 y | N/A | After 6 months | No | Bilateral blepharitis, multiple chalazia, dry eye disease, significant papillary conjunctivitis, bilateral superficial punctate keratitis. | Mild 1 | No | Ophthalmologist |
| Vingopoulos *et al.*[70] | F, 22 y | N/A | After 20 weeks | No | Severe blepharoconjunctivitis with macroscopically visible giant papillae in the right lower tarsal conjunctiva. | Mild 1 | No | Ophthalmologist |
| Voorberg *et al.*[73] | W, 36 y | EASI 28.3 | After 8 weeks | No | Bilateral keratoconjunctivitis and periocular eczema. | Mild 1 | Yes | Ophthalmologist |
| Voorberg *et al.*[71] | M, 56 y | N/A | n/a | N/A | Bilateral conjunctivitis with limbal stem cell insufficiency in his right eye. | Mild 1 | Yes | Ophthalmologist |
| Zirwas *et al.*[72] | M, 37 y | N/A | After 3 months | Dry eyes but with no treatment required | Severe conjunctivitis. | Mild 1 | No | Ophthalmologist |

**Table 5** DIOSD treatment in real-life studies, case series, and case reports

| Reference | DIOSD treatment | Dupilumab discontinuation |
|---|---|---|
| Achten *et al.*[30] | Lubricant, corticosteroid, antihistamine and anti-inflammatory eye drops, tacrolimus ointment for external eyelids, and combined anti-inflammatory and antimicrobial eye drops or eye ointment | 3 |
| Armario-Hita *et al.*[31] | Corticosteroid and antihistamine eye drops | No |
| Barbé *et al.*[32] | N/A | 6 |
| Bosma *et al.*[45] | N/A | No |
| de Wijs *et al.*[33] | Artificial tears, corticosteroid and antihistamine eye drops, and tacrolimus 0.03% ointment for external eyelids<br>previous and concomitant systemic immunosuppressive treatment | 5 |
| Faiz *et al.*[34] | Previous systemic immunosuppressive treatment | 10 |
| Fargnoli *et al.*[35] | Artificial tears, hyaluronic acid, corticosteroid, antimicrobial or cyclosporine eye drops<br>Previous systemic immunosuppressive treatment | No |
| Igelman *et al.*[36] | N/A | No |
| Kreeshan *et al.*[37] | Previous and current systemic immunosuppressive treatment<br>Topical treatments | 3 |
| Nahum *et al.*[10] | Preservative-free lubricant drops, antihistamine and mast cell stabilizing eye drops, tacrolimus ointment for external eyelids | No |
| Olesen *et al.*[38] | N/A | No |
| Popiela *et al.*[9] | Lubricant ($n$ = 6), corticosteroid ($n$ = 7), antihistamine ($n$ = 2), cyclosporine ($n$ = 2) and benzalkonium chloride eye drops ($n$ = 2), tacrolimus ointment for external eyelids ($n$ = 1) | 1 |
| Raffi *et al.*[39] | Allergen avoidance | N/A |
| Ruiz-Villaverde *et al.*[40] | Previous systemic immunosuppressive treatment | No |
| Schneeweiss *et al.*[41] | N/A | N/A |
| Touhouche *et al.*[42] | Lubricant ($n$ = 15), antihistamine ($n$ = 6), corticosteroid ($n$ = 5) and cyclosporine eye drops ($n$ = 2), vitamin A ointment ($n$ = 4) | 2 |
| Waldman *et al.*[43] | N/A | 2 |
| Wang *et al.*[44] | Previous and current systemic immunosuppressive treatment<br>lubricant and corticosteroid eye drops | 5 |
| Bohner *et al.*[46] | Topical corticosteroids ($n$ = 23), tacrolimus ($n$ = 6), artificial tears ($n$ = 7) | No |
| Fukuda *et al.*[47] | M, 25 y: eye drops containing tacrolimus, corticosteroid, antihistamine, and antibiotic for 2 months; 3 surgical resections of giant papillae | No |
| | M, 33 y: antihistamine and tacrolimus eyedrops | No |
| Ivert *et al.*[48] | Vaseline eye ointment, artificial tears, tacrolimus eye ointment, oral valaciclovir and antiviral prophylaxis, corticosteroid and antibiotic eye drops, glaucoma treatment | 1 |
| Jo *et al.*[49] | Corticosteroid ($n$ = 11), cyclosporine ($n$ = 3), antihistamine eye drops ($n$ = 4), artificial tears ($n$ = 3), hyaluronic acid ($n$ = 2), antibiotic ($n$ = 1), lifitegrast ($n$ = 1), imidazoline ($n$ = 1) | 2 |
| Lee *et al.*[50] | topical tacrolimus and corticosteroid ophthalmic ointment | 1 |
| Liberman *et al.*[51] | M, 56 y: artificial tears, antihistamine, tetryzoline, tetryzoline eye drops, eyelid wipes | No |
| | M, 19 y: lubricant artificial tears, topical antibiotic, naphazoline/pheniramine, corticosteroid and cyclosporine eye drops | No |
| Maudinet *et al.*[52] | Warms compresses ($n$ = 6), artificial tears ($n$ = 5), trehalose ($n$ = 9), corticosteroid ($n$ = 7), antihistamine ($n$ = 3), cyclosporine eye drops ($n$ = 1), hyaluronic acid ($n$ = 2) | 1 |
| Padidam *et al.*[54] | N/A | N/A |
| Pistone *et al.*[55] | Preventive artificial tears | N/A |
| Shen *et al.*[56] | M, 44 y: corticosteroid, antihistamine, cyclosporine eye drops | No |
| | F, 43 y: corticosteroid, antihistamine, cyclosporine eye drops | No |
| Treister *et al.*[57] | Artificial tears ($n$ = 3), nonsteroidal anti-inflammatory ($n$ = 2), cyclosporine ($n$ = 1), antihistamine eye drops ($n$ = 1), oral antibiotic ($n$ = 3), topical antibiotic ($n$ = 6), corticosteroid eye drops ($n$ = 7), eyelid cleanser ($n$ = 2) | 3 |
| Uchida *et al.*[58] | N/A | N/A |
| Wollenberg *et al.*[59] | Tacrolimus eye ointment 0.03% ($n$ = 4), corticosteroid and antibiotic eye drops ($n$ = 1), corticosteroid eye drops ($n$ = 6) | No |
| Yamane *et al.*[60] | F, 66 y: corticosteroid, antibiotic eye drops and ointment, artificial tears, periocular tacrolimus, oral antibiotic, oral antihistamine | 2 |
| | F, 28 y: antihistamine eyedrops, Vaseline, and corticosteroid eye ointment | |

**Table 5** *Continued*

| Reference | DIOSD treatment | Dupilumab discontinuation |
|---|---|---|
| Barnes *et al.*[61] | No | Yes |
| Fukuda *et al.*[62] | Antihistamine, antibiotic and corticosteroid eye drops | No |
| Gkalpakiotis *et al.*[63] | Previously planned corneal transplantation in the left eye, systemic cyclosporine A and azathioprine | No |
| Kimura *et al.*[64] | Cyclosporine eye drops, corticosteroid ointment | No |
| Levine *et al.*[65] | Corticosteroid eye drops | No |
| Li *et al.*[66] | Previous keratoplasty for keratoconus and cataract surgery, antibiotic, corticosteroid, cyclosporine eye drops, tacrolimus ointment | Yes |
| Mehta *et al.*[67] | Autologous serum, corticosteroid eye drops | Yes |
| McCarthy *et al.*[53] | Antibiotic eye drops, topical tacrolimus, systemic itraconazole | No |
| Nettis *et al.*[68] | Artificial tears, corticosteroid, cyclosporine eye drops, systemic corticosteroids | Yes |
| Paulose *et al.*[69] | Chalazia excision, manual debridement of eyelids margin, eyelid cleanser, one session of Lipiflow treatment, antibiotic, corticosteroid ointment | No |
| Vingopoulos *et al.*[70] | Corticosteroid eyedrops | No |
| Voorberg *et al.*[73] | Tacrolimus 0.1% ointment on the eyelids, hyaluronic acid/carbomer eye drops, fluorometholone, antibiotic eye drops | Yes |
| Voorberg *et al.*[71] | N/A | Yes |
| Zirwas *et al.*[72] | Oral omega 3 supplements, warm compresses, artificial tears, corticosteroid, cyclosporine, lifitegrast eye drops | No |

DIOSD is necessary. Aszodi *et al* recommend that DIOSD patients should be referred to an ophthalmologist in order to rule out an infectious cause.[1] Agnihotri *et al* propose to start with a correct classification of DIOSD, either mild or moderate-to-severe conjunctivitis, and formulate a guide for clinicians: mild forms can be treated with warm compresses, artificial tears, sodium hyaluronate, artificial tears, or antihistamine eye drops, while moderate-to-severe forms necessitate anti-inflammatory, corticosteroid, tacrolimus, cyclosporine, or lifitegrast eye drops.[77] Prophylactic use of artificial tears might be a reasonable suggestion for AD patients starting dupilumab.[77,78] Finally, treatment options should always be individualized and take into account AD, as well as DIOSD severity, possible contraindications, comorbidities, and concomitant systemic therapies.[78]

## Conclusion

In the literature published to date, DIOSD cases were generally investigator-assessed and ophthalmological evaluation prior to dupilumab treatment initiation was rarely performed, which makes the differentiation between dupilumab-induced and dupilumab-exacerbated ocular surface disease highly challenging. Our classification of ocular side effects following dupilumab treatment revealed that the majority of the cases were mild ($n$ = 722), a few were moderate ($n$ = 60), and severe forms were rarely reported ($n$ = 7).

However, evidence shows that ocular surface disease occurs more frequently in patients with atopic dermatitis and not in patients with other skin conditions, neither in patients with asthma, CRSwNP, nor EoE who are on dupilumab treatment, as compared to the placebo control groups. Furthermore, recent evidence has shown a fourfold higher risk of conjunctivitis and an eightfold higher risk of allergic conjunctivitis in patients with AD, as compared to non-AD patients, which might support the conclusion that DIOSD is more frequent in patients with atopic dermatitis. Further studies are warranted in order to establish a causal relationship between dupilumab and ocular surface disease. Nevertheless, we suggest that, for all patients with moderate-to-severe atopic dermatitis, previous ocular pathology or current ocular symptomatology should be investigated during the dermatological evaluation and, when necessary, be referred to an ophthalmologist prior to dupilumab initiation. An early ophthalmological diagnosis would enable the clinician to prescribe adequate treatment in order to minimize, or even prevent ocular symptomatology, thus maintaining a high quality of life and ensuring treatment adherence. Also, patch testing for ocular allergic contact dermatitis performed either before or after dupilumab initiation might be advantageous in patients with a history of allergic conjunctivitis for an accurate recommendation of allergen avoidance, which might lead to significant improvement of ocular symptomatology. Furthermore, TARC, IgE, and circulating eosinophil levels might be important biomarkers for a baseline assessment of future candidates to dupilumab treatment. However, TARC measurements should be resumed for research purposes only due to the low applicability in daily practice and the high costs they entail.

## Data availability statement

The data we included in this manuscript are openly available in a public repository that issues datasets with DOIs.

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** PRISMA 2020 Checklist.