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Dupilumab-Induced Ocular Surface Disease: More Than Just Conjunctivitis

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ABSTRACT

Background: Dupilumab, a monoclonal antibody targeting the interleukin-4 receptor α, has significantly improved management of atopic dermatitis (AD). However, a spectrum of ocular complications—termed dupilumab-induced ocular surface disease (DIOSD)—has emerged, encompassing more than just conjunctivitis.

Objective: To comprehensively review DIOSD, highlighting its clinical presentations, mechanisms, risk factors, incidence, and treatment, with emphasis on general clinical practice relevance.

Methods: A narrative review was conducted of primary studies (2015–2025) including case reports, cohort studies, and clinical trials on ocular adverse events in dupilumab-treated AD patients. Review articles were used only in the Introduction.

Results: DIOSD includes conjunctivitis, blepharoconjunctivitis, limbitis, keratitis, dry eye syndrome, and eyelid dermatitis. Incidence varies: 10–11% in trials and 20–38% in real-world settings. Risk factors include severe AD, prior ocular disease, eyelid involvement, high IgE/eosinophils, and older age. Mechanistically, IL-13 blockade leads to conjunctival goblet cell loss and mucin deficiency, with additional Th1/Th17 immune shifts. Most cases respond to lubricants and topical anti-inflammatories; severe cases may require ophthalmologic referral or treatment modification. Dupilumab discontinuation is rarely necessary.

Conclusion: DIOSD is a clinically significant, yet manageable complication of dupilumab in AD. Early recognition, patient education, and collaborative care enable continued use of dupilumab while preserving ocular health.

Keywords: Dupilumab; Atopic Dermatitis; Ocular Surface Disease; Conjunctivitis; Ocular Toxicity

Abbreviations: AD: Atopic Dermatitis; DIOSD: Dupilumab-Induced Ocular Surface Disease; AE: Adverse Events; AKC: Atopic Keratoconjunctivitis; EASI: Eczema Area Severity Index; GPC: Giant Papillary Conjunctivitis; IGA: Investigator Global Assessment; JAK: Janus Kinase; OR: Odds Ratio; RCT: Randomized Controlled Trial; SPK: Superficial Punctate Keratitis

Introduction

Atopic dermatitis (AD) is a prevalent, inflammatory skin condition that involves eczematous rashes, pruritus, and immune dysfunction. It is estimated to affect 20% of children and 10% of adults globally [1]. Dupilumab, a fully human monoclonal antibody, has revolutionized the treatment of moderate-to-severe AD since its FDA approval in 2017. By blocking IL-4Rα and inhibiting IL-4 and IL-13 signaling, dupilumab has been shown to reduce Th2-driven inflammation, restore barrier dysfunction, and alleviate symptoms. Dupilumab has since become a mainstay of treatment for both adult and pediatric AD due to its efficacy and systemic safety profile.

As early as 2017, however, several case reports and case series in AD patients receiving dupilumab revealed an unexpected and new pattern of ocular side effects. In the pivotal Phase 3 AD trials, those treated with dupilumab had higher rates of conjunctivitis compared with the placebo group, which was not observed in Phase 3 asthma and chronic rhinosinusitis with nasal polyps trials [2,3]. This raised the question of whether the ocular manifestations were related to a

unique ocular–cutaneous interaction or an atopic diathesis. As further real-world experience with dupilumab in AD has developed over the past few years, the variety of ocular findings has expanded to include blepharitis, keratitis, and dry eye symptoms that now fall under the umbrella term of dupilumab-induced ocular surface disease (DIOSD) [4,5]. Hypothesized risk factors for DIOSD development include severe baseline AD and the presence of atopic keratoconjunctivitis (AKC) prior to dupilumab initiation [4].

This creates a clinical conundrum because while dupilumab treatment offers skin improvement and enhancement of quality of life for most patients, the associated ocular adverse events (AEs) can have negative effects of their own, including discomfort, visual impairment, and treatment nonadherence. Therefore, for the dermatologist and other prescribing providers, identifying DIOSD early is of the utmost importance to prevent drug discontinuation. It is equally essential for providers to understand the need for interdisciplinary management with an ophthalmologist for the careful monitoring and coordination of treatment and interventions. In this review, we aim to provide a comprehensive overview of the current understanding of dupilumab-associated ocular surface disease and its practical clinical implications. We will cover the range of ocular manifestations, incidence, and risk factors, as well as the latest insights into pathophysiology, including information from immunologic and transcriptomic studies. We will also provide an evidence-based discussion of methods of prevention and treatment. This review will serve as a practical clinical resource for healthcare professionals in the management of DIOSD in patients with AD. We have included a comprehensive range of data from 2015 to 2025 to provide an up-to-date snapshot of the field's current state.

Methods

A narrative review was performed to summarize the clinical presentation, incidence, mechanisms, and management of DIOSD. The purpose of this review is to provide an overview of the rapidly growing evidence describing ocular side effects in AD patients treated with dupilumab. Electronic searches of PubMed, Embase, and Web of Science were performed in January 2015 to May 2025 using the following terms: "dupilumab", "ocular surface disease", "conjunctivitis", "keratitis", "blepharitis", and "ophthalmic side effects" with the addition of "atopic dermatitis". To augment this, consensus statements and treatment guidelines were also searched for pertinent information. In addition, mechanistic studies were evaluated to expand on the pathophysiology and relevance of IL-4/IL-13 inhibition in ocular health. Studies and clinical trials were limited to English-language publications with clinical and/or mechanistic relevance. Editorials, expert opinions, and commentaries were excluded from review. Study types included randomized control trials, post hoc analyses, prospective and retrospective cohort studies, cross-sectional studies, case-control studies, and large or small case series. Single-patient case reports were included if they provided additional details on ophthalmologic evaluation. Mechanistic studies, including in vitro, preclinical, and animal model studies, were also reviewed if they were of translational interest to IL-4/IL-13 blockade and ocular disease manifestations.

Data of interest were extracted from each publication, including the type of ocular involvement, incidence/prevalence (if reported), patient characteristics, and predisposing risk factors such as disease severity at baseline or history of AKC. When available, diagnostic features, including conjunctival hyperemia, punctate keratitis, goblet cell density, and cytokine/chemokine analysis of tears, were also recorded. Therapeutic interventions and management, including ocular surface lubrication and topical anti-inflammatory therapies, were documented, along with any descriptions of treatment resolution and continuation. The quality of each study was not scored or meta-analyzed, and greater emphasis was placed on the description of characterization of patients, objective evaluation (slit lamp exam, Schirmer's test, molecular analysis of tears), and the reporting of outcomes. Reviews and meta-analyses conducted within the study timeframe were used as background references for the current understanding of DIOSD and to identify areas not well represented by newer studies.

Results

Spectrum and Incidence of Ocular Surface Disease with Dupilumab

Dupilumab-induced ocular surface disease demonstrates a complex inflammatory process that affects multiple ocular surface structures rather than being limited to conjunctivitis. Patients who develop ocular symptoms similar to allergic conjunctivitis demonstrate conjunctival hyperemia, tearing, and pruritus but often lack active seasonal allergies or a history of ocular atopy when symptoms first appear [4-6]. The non-standard clinical presentation signals an aberrant pathophysiological process caused by interference in IL-4 and IL-13 signaling pathways, which are essential to ocular immune balance. Achten, et al. [7] demonstrated elevated tear film levels of dupilumab. The research demonstrated increased dupilumab levels in tears and a reduction in goblet cell presence, which together support the notion that drug exposure leads to epithelial damage and destabilizes the mucin layer [7]. The inflammatory profile observed in superficial conjunctival cells from affected patients exhibits similarities to psoriasis, which helps demonstrate that DIOSD involves unique immunologic changes compared to traditional allergic conjunctivitis [8]. Studies of tear samples have shown elevated levels of proinflammatory cytokines IL-8 and TNF-α, supporting the idea of local immune activation beyond systemic atopy [9,10]. More severe cases of DIOSD can develop into blepharoconjunctivitis and limbal inflammation, as well as keratitis and cicatricial changes that persist after treatment is stopped [11,12]. The diverse clinical presentations of DIOSD require early detection followed by interdisciplinary treatment to manage its chronic nature and functional consequences when left untreated.

Additionally, a pediatric series showed that limbitis was present in 62.5% of children who experienced ocular issues from dupilumab treatment [13]. Limbitis typically presents as inflammatory changes at the corneal limbus, resulting in perilimbal redness and focal corneal infiltrates. In adults, the most common ocular condition found in a prospective study of dupilumab users was dry eye disease with superficial punctate keratitis (SPK) [3]. Dupilumab-associated keratitis, particularly SPK, has been documented in children undergoing treatment for AD. This condition often leads to corneal erosions, especially in patients experiencing significant dry eye symptoms [14]. Ulcerative keratitis and corneal melt represent severe corneal sequelae that are infrequent yet documented in extreme cases [15]. Giant papillary conjunctivitis (GPC) manifests as papillary hypertrophy on the tarsal conjunctiva. It shows a high incidence rate among atopic patients, with research revealing 62.5% of affected children showing papillary reactions [13]. DIOSD sometimes presents with periorbital dermatitis, characterized by eczema around the eyes and eyelid edema. Uncommon ocular complications, such as uveitis or cicatricial conjunctival changes, have also been reported in dupilumab-treated patients in case reports [2]. However, the common feature is that these occur in patients already suffering from severe ocular surface disease.

Interestingly, patients with DIOSD often develop multiple eye conditions simultaneously. A retrospective cohort study found that 25% of patients with DIOSD exhibited severe lid and conjunctival inflammation, suggesting blepharoconjunctivitis. A prospective case series showed that 90% of patients treated with dupilumab who presented with eye symptoms displayed concurrent conjunctival inflammation and blepharitis [5].

Incidence Across Studies

The incidence of DIOSD shows substantial variation between clinical trials and real-world research. At the same time, it is evident that a significant minority of AD patients treated with dupilumab develop ocular surface side effects. The SOLO 1 and SOLO 2 Phase III trials for AD identified conjunctivitis as an important AE. Results from a pooled study showed that 10–12% of patients treated with dupilumab for AD experienced conjunctivitis during trials [16], while only 4–5% of placebo-treated patients developed the same condition [2]. Most of these cases displayed mild to moderate severity. However, dupilumab trials targeting non-AD conditions have demonstrated no significant occurrence of conjunctivitis. Fachler, et al. [2] demonstrated the contrast between AD patients and those without confirmed AD in their distinct vulnerability to dupilumab-induced eye effects [2]. Ocular AEs appear more prevalent in real-world settings than in controlled clinical trial environments. Studies conducted at dermatology clinics, which included ophthalmologic examinations, revealed DIOSD incidence rates ranging from 20% to 30%. A single-center prospective study including routine ophthalmologist consultations reported that 34.8% of their adult AD patient cohort treated with dupilumab developed ocular surface complications. Moreover, a Korean multicenter observational study observed that 28.9% of patients receiving dupilumab treatment developed DIOSD [1]. Pradhan, et al. [5] conducted a prospective case series led by ophthalmologists and showed that 28.3% of AD patients developed DIOSD, with nearly all patients experiencing bilateral conjunctivitis along with blepharitis [5].

Retrospective cohorts show a comparable frequency. A retrospective study conducted on adults internationally found that ocular surface disease occurred in approximately 20.6% of patients treated with dupilumab [2]. Children taking dupilumab experience ocular side effects, but these side effects occur at different rates compared to adults [17]. 7.4% of Asian pediatric patients aged 3–17 developed DIOSD, as confirmed by an ophthalmologist in one of the most extensive pediatric studies. The reduced percentage of 7.4% compared to adult rates of ~20–30% may result from study design variations or children's lower natural risk. It is also worth noting that most children received prophylactic artificial tears throughout the study period [13]. An additional pediatric study reported a higher percentage of ocular events but had a smaller sample size, focusing on patients presenting with eye symptoms, which may have increased the observed incidence [14] (Figure 1). The majority of DIOSD cases emerge during the initial months following dupilumab therapy initiation, according to multiple studies (Table 1). Most commonly, ocular symptoms appear anywhere from a few days to over a year and a half after initiation, with most reports indicating an onset time range of 3 to 74 weeks post-dupilumab initiation [5,18]. For example, Pradhan, et al. [5] found that the mean time to onset was 9.2 post-first dupilumab dose, with onset times varying between less than one week and approximately 40 weeks [5]. An Israeli study reported that ocular symptoms typically begin between 2 and 8 weeks after treatment with dupilumab [4].

Table 1: Onset Timing of DIOSD Symptoms Across Studies.

Study (Year)	Patient Population	Reported Onset of Ocular Symptoms
Nahum, et al. [4]	Adults with AD (Israel, retrospective cohort)	2–8 weeks after starting dupilumab; most within 2 months
Pradhan, et al. [5]	Adults with AD (prospective ophthalmology series)	Mean onset ~9.2 weeks; range: <1 to ~40 weeks
Typical range	(Various studies)	Most cases within 3 months; peak onset ~6–8 weeks

Note: "Onset" is measured from the initiation of dupilumab treatment. Close monitoring is recommended during the first 2–3 months of therapy, when most ocular side effects are likely to emerge [4].

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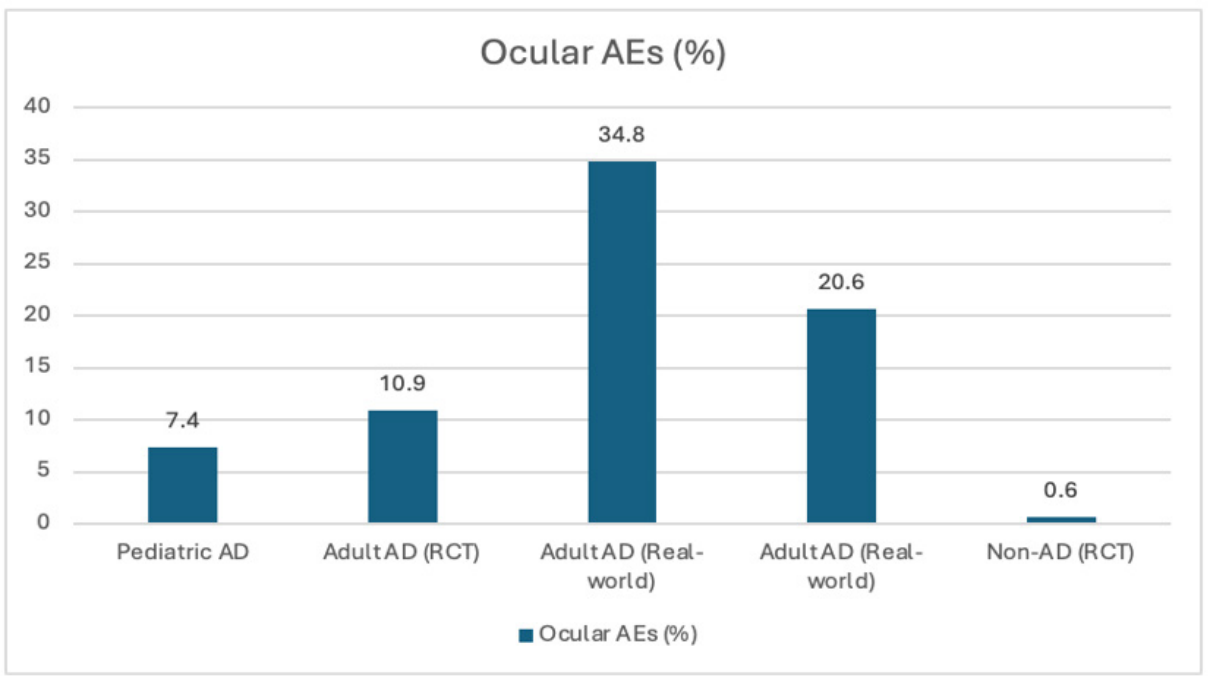


Note: *"Adult AD (RCT)" refers to pooled results from randomized trials in atopic dermatitis [2]. "Adult AD (Real-world)" denotes observational data from dermatology clinics [3,17]. "Pediatric AD" represents a large pediatric cohort [13]. "Non-AD (RCT)" indicates dupilumab trials in other diseases (e.g., asthma) [2], illustrating minimal ocular AEs outside of AD.

Figure 1: Incidence of dupilumab-associated ocular adverse events in different populations.

Together, these studies indicate that close monitoring of patients during the initial stages of dupilumab treatment is necessary to detect any new ocular issues. Most cases of DIOSD receive a mild to moderate severity rating. However, patients rarely experience serious ocular surface problems such as corneal ulcers and vision-threatening inflammation. According to a recent systematic review, less than 5% of DIOSD patients discontinue dupilumab permanently because of severe eye side effects [2]. While non-severe ocular symptoms may not be acutely critical, they can still cause substantial discomfort, which may require adjustments in treatment. For example, dupilumab treatment, in rare cases, has been associated with chronic conjunctival inflammation, which can result in conjunctival scarring and symblepharon formation in a few patients [2]. This demonstrates the importance of proactive management of DIOSD. (Table 2) summarizes the clinical spectrum of DIOSD and highlights differences in incidence across various populations and study types.

Table 2: Clinical Spectrum of DIOSD and Incidence by Population/Study Type.

Population / Study Context	Incidence of DIOSD (ocular AEs)	Common Ocular Manifestations / Notes
Adult AD – RCTs	~10–12% on dupilumab vs ~4–5% placebo [2,16]	Predominantly mild-to-moderate conjunctivitis. Non-AD trials (asthma, CRSwNP) reported ≤1% incidence [2]
Adult AD – Real-World (Observational)	~20–35% in dermatology clinics developed DIOSD in prospective studies (e.g. 28.9% [1] to 34.8% [3]; ~20.6% - multicenter retrospective study [2]	Conjunctivitis often co-occurs with blepharitis, dry eye with punctate keratitis, and limbitis [4]. Most patients exhibit multiple concurrent ocular surface issues rather than isolated conjunctivitis [5].
Pediatric AD – Cohort Studies	~7–8% (e.g., 7.4% in ages 3–17 [13]; higher in selected UK populations [14])	Typically milder than in adults. Limbal inflammation and GPC noted in 62.5% of affected children. Use of prophylactic artificial tears may have mitigated incidence [13].
Non-AD conditions – Trials	~0–1%, similar to placebo [2]	Minimal to no reported ocular events in trials for asthma, CRSwNP, etc. AD is the primary predisposing factor [2,16].

Note: AD = atopic dermatitis; DIOSD = dupilumab-induced ocular surface disease; AEs = adverse events. Pediatric incidence was low in part because most children used prophylactic lubricating eye drops during therapy [13].

Risk Factors for Developing DIOSD

Several AD patients treated with dupilumab do not experience ocular side effects, which has led to extensive research into determining the factors that increase DIOSD risk in particular individuals. Studies demonstrate that patients who experience more severe atopic conditions in the skin, eyes, or systemically face greater risks. Baseline AD severity stands out as one of the most reliable predictors of disease progression. Research shows that patients suffering from severe eczema present a higher risk of developing DIOSD compared to patients with less severe forms of the disease [4,19]. The research by Nahum, et al. [4] showed that patients with moderate AD treated with dupilumab did not develop DIOSD as opposed to patients with severe AD who did develop the condition [4]. Treister, et al. [20] found that each DIOSD case experienced refractory or severe eczema prior to initiating biologic treatment [20]. Five out of nine major studies included in a recent literature review recognized severe AD as a risk factor for DIOSD [19]. Severe AD exhibits a high level of Th2 inflammation and potential allergen sensitization, which may trigger inflammatory responses on the ocular surface when IL-4 and IL-13 levels are altered. The most self-explanatory risk factor for this condition remains a prior history of allergic diseases affecting the eyes. Patients who previously experienced conditions such as AKC, vernal keratoconjunctivitis, allergic conjunctivitis, or other long-term ocular surface disorders tend to demonstrate increased flare-ups when treated with dupilumab.

In a prospective Dutch study by Achten et al. [21], it was found that patients who received dupilumab treatment for AD and developed dry eye syndrome with ocular surface disease were significantly more likely to have a history of the ocular surface disease, such as atopic or allergic conjunctivitis, compared to those without DIOSD [21]. Touhouche, et al. [3] showed that patients with pre-existing dry eye syndrome or keratitis had six times higher odds of developing dupilumab-induced ocular AEs [3]. Nahum's study identified prior AKC as a decisive, independent risk factor for DIOSD [4]. These findings make clinical sense: Patients with past atopic eye inflammation become more susceptible to immune alterations after exposure to an IL-4/IL-13 blockade. Patients with these conditions may experience tear film instability or specific alterations in conjunctival immune cell populations, leading to exaggerated responses. Multiple studies do not agree on this point, with evidence from recent research supporting this divergence. Pradhan et al. [5] and Reddy, et al. [19] found no relationship between a history of allergic conjunctivitis and DIOSD incidence or severity within their research cohort [5,19]. The inconsistency between studies might stem from the different methodologies used for taking patient histories or from varying interpretations of what constitutes a history of an ocular disease.

Medical literature frequently identifies head-and-neck dermatitis together with eyelid eczema as part of AD presentation as a significant risk factor.

Individuals with baseline eczema in the periocular region appear to experience a higher incidence of eye complications associated with dupilumab [19]. Costedoat, et al. [22] discovered that dupilumab-induced blepharoconjunctivitis was independently predicted by head and neck localized AD [22]. The condition likely shows underlying ocular surface inflammation that remains subclinical or demonstrates increased facial skin exposure to treatment-related cytokine changes. In pediatric patients, Yap, et al. [13] documented that every child who developed DIOSD exhibited concurrent head/neck or eyelid eczema exacerbations during dupilumab treatment. The presence of eczema around the eyes can lead to direct ocular surface disruption or show a systemic atopic tendency that affects the eyes [13]. Clinicians should be particularly vigilant in AD patients with significant eyelid involvement: Prophylactic strategies and prompt ophthalmology consultations should be considered for patients starting dupilumab treatment. The risk factors for DIOSD include elevated IgE levels and increased blood eosinophil counts, which are consistent with the theory that an "atopic phenotype" leads to the development of DIOSD. Patients treated with dupilumab who develop ocular side effects usually exhibit significantly high pretreatment total IgE levels or experience temporary increases in eosinophils as caused by dupilumab. Touhouche, et al. [3] found that an IgE level above 1000 kU/L demonstrates an approximate tenth-fold increase in the odds ratio for predicting ocular AEs [3].

Another Japanese research work by Uchida, et al. [23] found that individuals who developed conjunctivitis maintained significantly higher initial serum TARC (Thymus and Activation-Regulated Chemokine, CCL17) and IgE levels compared to those who did not experience conjunctivitis. TARC functions as a Th2 chemokine, and elevated levels show strong type 2 immune activation, which results in rebound inflammation in the eye when Th2 signaling is suddenly blocked. Interestingly, research demonstrated that biomarkers could predict the occurrence of conjunctivitis yet failed to predict its severity [23]. A retrospective study conducted by Li, et al. [24] found that more than 50% of patients had elevated eosinophil counts at baseline. Additionally, over 40% of patients who developed DIOSD also showed elevated eosinophil counts. In both groups, the elevated eosinophil counts were found to be transient. Dupilumab treatment may trigger a rise in blood eosinophils, which, together with their role in atopic conjunctival diseases, may lead to ocular inflammation in certain individuals [24]. The existence of high IgE levels and eosinophilia indicates an atopic immune response that frequently correlates with DIOSD risk. Demographic factors were examined, and age emerged as a significant factor in several analytical studies. Shim, et al. [1] found that age functions as a distinct risk factor for DIOSD, as their model demonstrated that increased age corresponds to a higher risk of DIOSD, which they also incorporated into their prediction scoring system. The researchers believed age-related alterations in the ocular surface, such as baseline tear film deficiencies and meibomian gland dysfunction, could make elderly AD patients more susceptible [1].

Research in pediatric studies shows that children can develop DIOSD, so age alone does not entirely predict risk, yet adults who are middle-aged or elderly may experience additional risk factors. Research indicates that gender does not show consistent results as both males and females develop DIOSD, with most studies finding no significant differences in incidence rates between genders [5]. There have also been some unexpected or conflicting findings. One investigation showed that having a family history of atopy increased the risk of dupilumab conjunctivitis [25]. However, Nahum, et al. [4] found that this same history provided protection. The inconsistencies identified between studies demonstrate that DIOSD risk arises from multiple factors and may differ among patient groups [4]. The influence of genetic backgrounds and environmental exposures, as indicated through family history, on risk remains unknown. Based on these data findings, scientists have developed practical risk assessment tools. Shim, et al. [1] proposed a risk-scoring system for DIOSD: Researchers assigned point values to three independent predictors – older age, history of conjunctivitis, and baseline EASI (eczema area and severity index) ≥ 28 – and demonstrated that patients with 0 points had approximately 5.8% predicted risk while those scoring the maximum 5 points reached up to 89.6% risk [1]. Risk stratification proves possible, although these tools require validation.

For everyday clinical practice, a reasonable summary is: The highest DIOSD risk groups include patients with severe refractory AD who exhibit high IgE/eosinophils levels and those who have a history of allergic eye disease or active eyelid dermatitis alongside potentially older individuals. Patients taking dupilumab should receive more frequent ophthalmologic monitoring. Selected studies provide supporting evidence summarized in (Table 1), alongside the main risk factors outlined in (Table 3). By identifying these risk factors, clinicians can predict which patients require preventive treatment or early medical action. Patients with AD who suffer from chronic eye allergies and eyelid eczema should have a pre-treatment eye examination before beginning dupilumab while also being ready to apply topical treatments right when symptoms first appear. An adolescent patient who has moderate AD affecting only their limbs faces relatively low risk. Every patient receiving dupilumab treatment faces the risk of DIOSD, which mandates constant vigilance for everyone.

Table 3: Key Risk Factors for Dupilumab-Induced Ocular Surface Disease.

Risk Factor	Evidence from Studies
Severe AD (high EASI/IGA)	Strong predictor across cohorts. DIOSD rare in moderate AD; higher rates in severe cases [4]. Identified in 5/9 studies in 2024 review [19].
History of ocular allergy	Frequent in DIOSD. Prior AKC linked with OR > 20 [4]. 37/152 DIOSD patients had AKC/GPC [19,21]. Not confirmed in one cohort [23].
Head/neck or eyelid eczema	Linked to higher DIOSD risk, especially blepharoconjunctivitis [19]. All pediatric DIOSD cases had head/neck involvement [13], suggesting local predisposition.
High IgE level	IgE > 1000 kU/L associated with OR ~10 [3]. DIOSD patients had higher baseline IgE [23]; reflects Th2-biased immune profile.
Peripheral Eosinophilia	Transient eosinophil rise in 67% of DIOSD cases [17]. Eosinophils observed in conjunctival biopsies [26], supporting inflammatory infiltration.
Older age (adults)	Older age independently associated with DIOSD [1]. Possibly due to baseline dry eye risk or meibomian gland dysfunction.
Atopic comorbidities	Common in DIOSD (e.g., asthma, allergic rhinitis). Family history of atopy inconsistently associated: protective in one study [4], a risk in another [26]. Further study needed.

Note: AD = Atopic Dermatitis; AKC = Atopic keratoconjunctivitis; GPC = Giant papillary conjunctivitis; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment (severity). OR = Odds Ratio.

Pathophysiology and Immunologic Mechanisms

The underlying mechanisms of dupilumab-induced ocular surface disease remain incompletely understood and are the focus of ongoing research. Evidence suggests that DIOSD arises from epithelial alterations in conjunctival goblet cells with reduced mucin secretion, combined with immune dysregulation in the ocular microenvironment secondary to IL-4/IL-13 pathway blockade [2,11]. While dupilumab reduces Th2-driven inflammation systemically and in the skin, paradoxically it can intensify ocular inflammation in predisposed patients [3,16]. Transcriptomic studies have revealed that conjunctival epithelial cells from affected patients display a psoriasis-like gene expression signature, suggesting a shift toward a proinflammatory ocular phenotype [8]. Tear fluid analysis has further demonstrated elevations in proinflammatory mediators, including IL-8 and other chemokines, which likely sustain chronic ocular inflammation [9,10,21]. Clinical and real-world cohorts have also identified systemic predictors of risk, with higher baseline serum IgE and TARC levels correlating with DIOSD development, independent of atopic dermatitis severity [1,19,23]. Collectively, these findings suggest that DIOSD results from a multifactorial interplay between goblet cell dysfunction, mucosal barrier impairment, and paradoxical immune activation driven by IL-4/IL-13 blockade, with systemic immunologic predispositions amplifying local ocular vulnerability [4,12,22] The prevailing suggestion is that dupilumab can lead to goblet cell deficiency and mucin dysfunction.

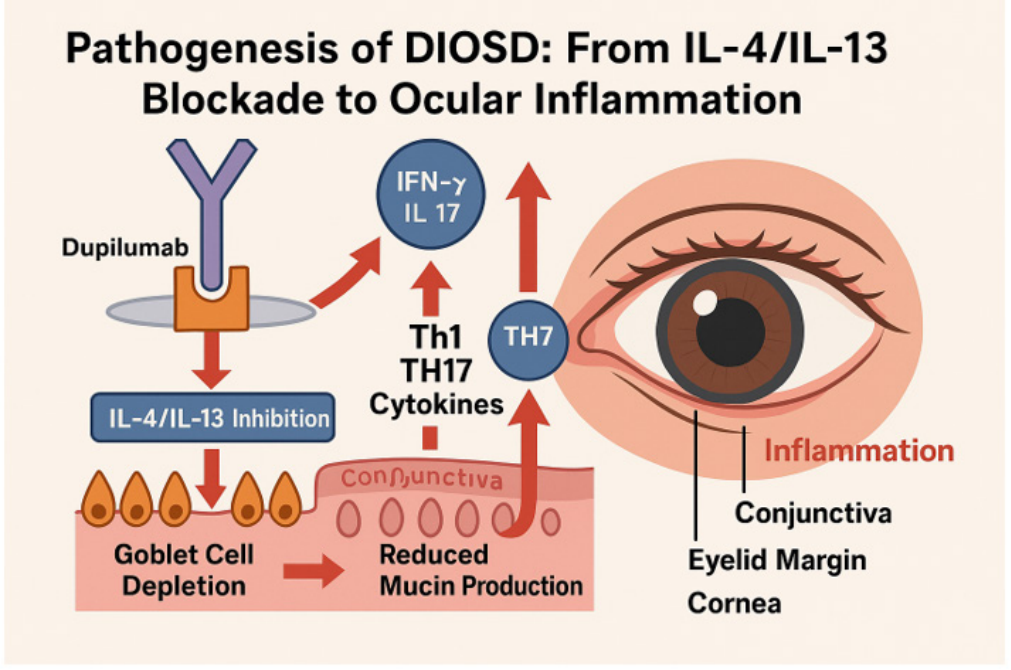
IL-13 is involved in goblet cell biology as it promotes goblet cell multiplication and mucus production in both airway and ocular tissues [25]. Dupilumab inhibits IL-13 activity on conjunctival epithelial cells by blocking IL-4Rα, thereby preventing downstream signaling, rather than physically blocking IL-13 from reaching the tissue. Maudinet, et al. [26] conducted a foundational histopathological study analyzing conjunctival biopsies from atopic dermatitis patients who developed conjunctivitis after dupilumab therapy. Their analysis revealed a marked reduction in conjunctival goblet cells compared with healthy controls, quantified by histological assessment of goblet cell density [26]. Specifically, dupilumab-treated patients demonstrated nearly a tenfold decrease in goblet cell density, with a median of ~3 goblet cells per millimeter versus ~30 goblet cells per millimeter in controls [25]. Goblet cells produce mucins, including MUC5AC, which maintain tear film stability and play a role in immune defense of the ocular surface. With the decrease in the number and density of goblet cells in Dupilumab-treated patients, it is thought that mucin production is reduced, which in turn, destabilizes the tear film, ultimately leading to dry eye conditions [26]. As such, Bakker, et al. [25] found that dupilumab treatment can lead to mucin deficiency in the conjunctiva by blocking IL-13's trophic effect on goblet cells. As a consequence of inadequate ocular lubrication, patients exhibited "irritative conjunctivitis" and dry eye symptoms [25].

This underlying mechanism is in contrast to classic allergic conjunctivitis or AKC, where goblet cell numbers rise, and excessive mucus production occurs likely because of persistent Th2 inflammatory responses. Thus, DIOSD represents a distinct pathophysiological entity. The pathophysiology of DIOSD primarily involves mucin deficiency and barrier dysfunction rather than allergen-triggered IgE-mediated allergic responses [25]. The disappearance of goblet cells has become a defining feature with many studies reporting dupilumab-associated conjunctivitis with mucin deficiency [27,28]. The loss of goblet cells in dupilumab-associated conjunctivitis corresponds with immune cell infiltration in conjunctival tissue samples. The main histological pattern in the conjunctival substantia propria consists of predominantly CD4+ T lymphocytes along with eosinophils and other inflammatory cells, which can reach the epithelium [25]. The presence of eosinophils in atopic ocular conditions can create a unique immunopathologic pattern when it occurs with goblet cell depletion, which is not typically seen in classic allergic conjunctivitis [10,29]. Conjunctival T lymphocyte infiltration strongly suggests the existence of an active immune response in these patients. IL-4 and IL-13 tend to mediate Th2 dominant responses. With their action inhibited in Dupilumab-treated patients, questions have arisen as to the drivers of DIOSD. Studies suggest that blocking Th2 pathways can lead to a compensatory immune response, enhancing Th1 and Th17 lymphocyte and cytokine activity.

Immunologic rebalancing permits previously suppressed proinflammatory T-cell subsets to regain activity and instigate tissue inflammation when Th2 dominance is disrupted [8,11,30]. The latest transcription analysis of conjunctival cells from patients reveals a rise in Th1/Th17 gene expression and stress and barrier dysfunction markers, indicating that this immune response hypothesis may be correct and as such, highlights the complex immune interactions in dupilumab-induced ocular surface disease [8,31]. Interestingly, superficial conjunctival cells from dupilumab-treated atopic dermatitis patients who developed ocular AEs demonstrated a transcriptomic profile resembling psoriasis, characterized by upregulation of Th17/Th1 pathways, which contrasts with the Th2-skewed immune environment typically associated with classic atopic disease [8]. Psoriasis is driven by IL-17 and interferon-gamma signaling axes, and this study suggests that dupilumab may, in susceptible individuals, shift ocular immune responses toward this Th17-dominant pattern. Specifically, gene expression revealed increased IL-17 pathway markers such as CCL20 and CXCL8 (IL-8), while Th2-associated chemokines such as CCL26 (eotaxin-3) remained downregulated [8]. The results of this study suggest that a distinct conjunctival immune microenvironment may predispose certain patients to dupilumab-induced ocular surface disease. Aranda, et al. [10] further supported this concept by demonstrating elevated tear proinflammatory cytokines, including IL-8 and TNF-α, in dupilumab-treated patients with conjunctivitis.

This emerging paradigm—that blockade of Th2 signaling can unmask or amplify alternative inflammatory pathways—aligns with clinical observations [10]. Several features of DIOSD, such as blepharitis with meibomian gland dysfunction and punctate keratitis, closely resemble ocular rosacea, a disorder associated with Th17-driven inflammation [25]. In line with this, dupilumab therapy may unmask pathogenic Th17 responses in a subset of patients, as evidenced by additional reports describing chronic blepharitis and rosacea-like ocular manifestations during treatment [11,32]. Bakker, et al. [25] also hypothesized that Demodex mite overgrowth could contribute to this phenomenon through impaired immune surveillance following IL-4/IL-13 inhibition [25]. Although the precise role of Demodex remains uncertain, accumulating evidence suggests that suppression of Th2 pathways may allow compensatory Th1/Th17 activation and associated microbial imbalance along the eyelid margin [30,32]. In summary, the pathophysiology of DIOSD appears to involve two interrelated mechanisms. First, IL-13 blockade disrupts goblet cell differentiation and mucin production, resulting in conjunctival hypoplasia, a thinner mucin layer, and tear film instability that predisposes the ocular surface to injury. Second, inhibition of IL-4/IL-13 signaling may unmask or promote a Th1/Th17 inflammatory program in susceptible individuals, leading to conjunctival inflammation characterized by CD4+ T-cell and eosinophil infiltration, keratitis, and chronic blepharitis [31-34].

These processes likely act in concert: goblet cell loss compromises epithelial barrier integrity, facilitating the activation of stress and cytokine pathways that amplify Th17-driven injury. Notably, in mucosal tissues IL-17 itself can suppress goblet cell differentiation, suggesting the presence of a feed-forward loop that perpetuates ocular surface damage [28,35]. With these immune mechanisms, Dupilumab thereby induces a distinct iatrogenic inflammatory dry eye syndrome—DIOSD—that differs immunologically and histologically from classic allergic conjunctivitis. The latter is mediated by IgE-triggered mast cell degranulation and is typically associated with increased goblet cell numbers, thick mucus discharge, and immediate hypersensitivity signs (Figure 2). In contrast, DIOSD is marked by dry eye symptoms, poor tear film quality, and chronic inflammation with minimal discharge. Clinically, this distinction is essential: antihistamines commonly used in allergic conjunctivitis are often ineffective in DIOSD, and alternative treatments such as lubricants, calcineurin inhibitors, or off-label cyclosporine eye drops may be more beneficial [36]. Despite emerging insights, the full underlying pathogenesis remains incompletely understood. Ongoing research into tear proteomics and conjunctival gene expression may identify key biomarkers and potential genetic or epigenetic susceptibilities—such as polymorphisms in mucin-regulatory or innate immune genes—that explain why only some dupilumab users develop DIOSD [21,37].



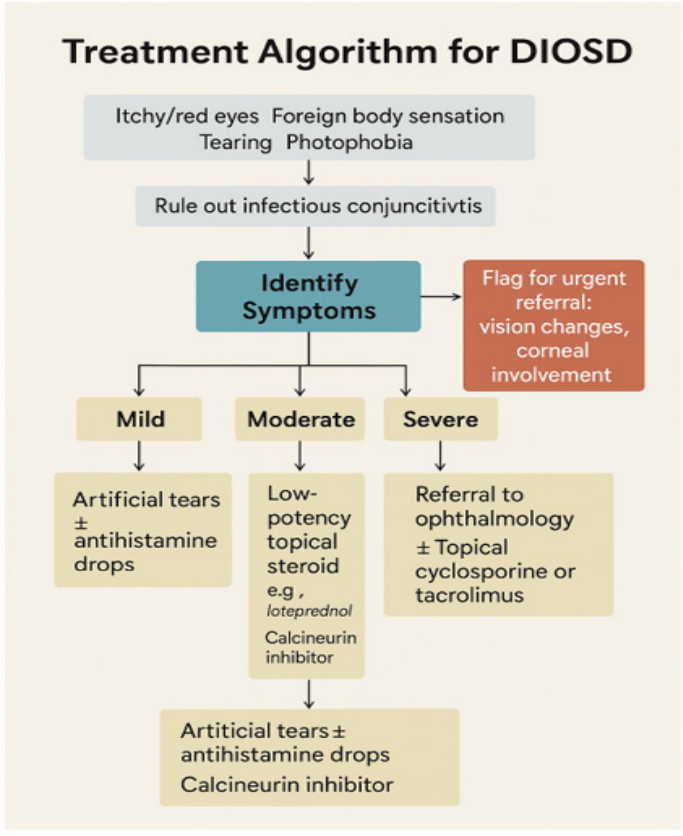
Note: Dupilumab inhibits IL-4/IL-13 signaling, leading to goblet cell depletion and reduced mucin production. This disruption promotes Th1/Th17-mediated inflammation of the conjunctiva, eyelid margin, and cornea, contributing to ocular surface disease.

Figure 2: Pathogenesis of DIOSD.

Management and Treatment Strategies

Effective management of dupilumab-induced ocular surface disease should include a collaborative approach that controls eye inflammation and symptoms while maintaining dupilumab treatment for eczema. The expanding understanding of DIOSD has led to the exploration of various treatments, including prevention measures alongside specific eye treatment options. Dupilumab therapy for patients with DIOSD usually remains uninterrupted as long as sufficient ocular treatments are used. Studies have shown that topical treatments can successfully resolve or improve ocular symptoms, enabling patients to continue their dupilumab therapy for skin disease [15]. Permanent dupilumab discontinuation is typically reserved for patients who do not respond to treatment and their vision becomes endangered [38]. Patients starting dupilumab should be educated about the potential ocular side effects (conjunctival hyperemia, pruritus, ocular dryness, blurred vision) and encouraged to report symptoms early for management [2,3]. Baseline ocular assessment may be considered in patients with known risk factors, such as high baseline IgE or TARC levels, history of ocular disease, or severe AD [1,23]. Documenting the ocular surface status before starting dupilumab can provide a useful reference point for comparison with any later findings. Baseline eye exams may also identify subclinical conditions like mild dry eye, blepharitis, or decreased goblet cell density, which could be treated early with lubricating drops, warm compresses, or lid hygiene, potentially reducing the risk or severity of ocular flares during dupilumab therapy [26,38].

The potential benefits of prophylactic interventions or preventive treatments continue to be debated. Many clinicians administer artificial tears to all AD patients treated with dupilumab before symptoms develop. Stabilizing the tear film can prevent goblet cell stress in patients with dry eye or ocular allergies. However, evidence for routine prophylaxis is limited, with the limited current evidence not supporting universal use of prophylactic lubricant drops [38]. Because artificial tears are safe to use, it makes sense to recommend preservative-free lubricating drops for patients either with existing dry eye conditions or who begin to show early symptoms. It is also sensible to optimize the environment and habits that affect the ocular surface. Patients should avoid smoking and arid settings, take regular screen time breaks, and maintain proper eyelid hygiene (particularly if blepharitis or Demodex is present) (Figure 3).



Note: Clinical approach to managing DIOSD based on symptom severity. After ruling out infection, mild cases are treated with artificial tears ± antihistamines, moderate cases with topical steroids or calcineurin inhibitors, and severe cases warrant ophthalmology referral and immunomodulatory therapy. Urgent referral is indicated for vision changes or corneal involvement.

Figure 3: DIOSD treatment algorithm flowchart.

First-line Treatment of Mild DIOSD

Initial management of mild ocular symptoms, such as slight redness or intermittent dryness, can be handled by a dermatologist or primary care provider. At the same time, patients should have access to an ophthalmologist consultation. Patients typically start treatment with preservative-free artificial tears, which they apply 4–8 times daily to restore tear film volume and alleviate dry eye symptoms [11,33]. Artificial tear substitutes with hyaluronate or other polymers show significant effectiveness in treating discomfort from inflammatory dry eye conditions related to DIOSD [37]. Patients should apply tear gels or ointments at night to provide the necessary moisture for the ocular surface. Applying warm compresses to the eyelids for several minutes twice daily can help release secretions, particularly when blepharitis causes lash crusting or meibomian gland blockages. The Fachler, et al. [2] study recommends gentle lid scrubs with diluted baby shampoo or commercial eyelid cleansers, along with tea tree oil wipes, to treat Demodex and reduce eyelid margin inflammation [2]. Maintaining proper eyelid cleanliness regularly helps restore meibomian gland function and strengthens the tear film's lipid layer [11,32]. DIOSD usually does not involve a classic IgE-mediated allergic reaction; however, patients can experience itching and multiple signs of allergic response. Patients with multiple allergic conjunctivitis symptoms during seasonal outbreaks can benefit from using dual-action anti-allergic eye drops like olopatadine or ketotifen.

These drugs minimize itching and hyperemia, while some patients noted better results when combined with lubricating drops and eyelid care [2,39]. The effectiveness of these treatments diminishes when patients experience chronic inflammation or have lost goblet cells. If supportive care fails to resolve mild conjunctival inflammation, ophthalmologists may recommend soft steroid eye drops, such as loteprednol etabonate 0.25% or fluorometholone, to effectively reduce redness and swelling. Ophthalmic supervision is necessary to monitor steroid-induced intraocular pressure elevation when administering these medications [11,40]. Dermatologists can treat concurrent eyelid eczema using low-strength corticosteroid preparations like hydrocortisone 1% ophthalmic ointment while ensuring that the ointment stays away from the cornea. The treatment method addresses eyelid dermatitis while potentially enhancing general eye comfort [41]. The majority of mild DIOSD cases respond well to treatment with artificial tears and brief topical anti-inflammatory therapy. Several cases will naturally resolve, while others stay mild in severity. Dupilumab treatment continues unchanged during this phase unless ocular symptoms show instability. Recent British consensus guidelines recommend maintaining dupilumab treatment for mild ocular surface disease while monitoring symptoms and escalating treatment if needed [38]. Dermatologists should refer patients to ophthalmologists if their symptoms persist, worsen, or interfere with their vision [37].

Management of Moderate to Severe DIOSD

Patients with ocular symptoms beyond mild severity, such as persistent conjunctival injection or significant discomfort, require ophthalmologist co-management, particularly from a cornea or ocular surface specialist. Moderate DIOSD cases typically require stronger topical anti-inflammatory therapies. Topical corticosteroids of moderate to high potency, such as loteprednol 0.5% or prednisolone acetate 1%, are often prescribed by ophthalmologists to suppress inflammation over several weeks. In particular, notable keratitis or limbitis frequently necessitates this approach. Short courses of corticosteroids have been shown to provide rapid symptom relief, followed by transition to steroid-sparing therapies for long-term control [11,40]. Regular monitoring of intraocular pressure is critical during extended steroid use to avoid steroid-induced glaucoma. Non-steroidal immunomodulators, including tacrolimus and pimecrolimus, are commonly used for periocular skin inflammation and have demonstrated effectiveness when applied off-label for ocular surface inflammation. Tacrolimus ophthalmic ointment has been used successfully to treat dupilumab-associated blepharoconjunctivitis. Nahum, et al. [4] demonstrated that periocular application of 0.03–0.1% tacrolimus ophthalmic ointment was associated with resolution of dupilumab-associated blepharoconjunctivitis within a period of several days in all treated patients [4]. Topical application of tacrolimus to the eyelid margins or conjunctival fornices mitigates local T cell–mediated inflammation without the risks associated with chronic use of corticosteroids.

Transient burning on application is common, but tacrolimus is now a mainstay of chronic management of DIOSD [9,10]. More recently, tacrolimus 0.03% ophthalmic solutions compounded by pharmacies have been reported to have promising efficacy in the management of refractory cases [42]. Cyclosporine A 0.05–0.1% eye drops, such as Restasis or Cequa, are steroid-sparing agents that suppress T-cell activation and are used to treat chronic ocular surface inflammation in DIOSD. These drops require several weeks to take full effect but can help restore goblet cell populations and improve tear production [30,37]. Studies show cyclosporine A is effective in maintaining long-term control and preventing relapse in DIOSD patients. Additionally, lifitegrast, a lymphocyte function–associated antigen-1 antagonist, has been used off-label as another anti-inflammatory treatment option in certain cases [32]. In moderate and severe DIOSD, dry eye management becomes essential. Patients benefit from intensified use of preservative-free artificial tears and overnight lubricating ointments. Some cases may require punctal occlusion to enhance tear retention. In refractory dry eye, autologous serum eye drops may be considered, though data specific to DIOSD remain limited [11]. Systemic therapy is rarely necessary but may be considered in patients with coexisting rosacea-like features or chronic blepharitis. Oral doxycycline, due to its anti-inflammatory and meibomian gland–stabilizing properties,

has been used effectively in such presentations [2,25]. Nonsedating systemic antihistamines may provide symptomatic relief in patients with concurrent allergic rhinitis, although their role is secondary in DIOSD without allergic triggers.

Decisions to escalate treatment should be guided by the patient's symptom severity and clinical findings. A structured grading and management approach is provided by the DROSD severity scale, developed in the British expert consensus published by Ardern-Jones, et al. [38]. This framework recommends that dermatologists manage mild cases, initiate treatment and refer non-urgently for moderate cases, and coordinate urgent ophthalmologic intervention for severe cases with corneal involvement. In children under 7 years old, any ocular involvement warrants prompt ophthalmology referral due to the risk of amblyopia and disrupted visual development [38]. One ongoing debate in DIOSD management is whether to discontinue dupilumab upon the emergence of ocular side effects. The general consensus favors continuation when symptoms are manageable, as discontinuation may worsen systemic AD. In the study by Pradhan, et al. [5], none of the 32 DIOSD patients required stopping dupilumab; all responded well to topical treatment, with a drop in OSDI scores from 34 to 10 [5]. Similarly, Yap, et al. [13] reported that only 2 of 16 pediatric cases temporarily suspended dupilumab therapy, and none required permanent discontinuation [13]. These findings underscore the efficacy of integrated ophthalmic care while maintaining dermatologic therapy. Nonetheless, in severe cases where ocular complications threaten vision or severely impact quality of life, temporary suspension or dose skipping may be warranted, especially considering the ~28-day half-life of dupilumab.

If symptoms are unresponsive to aggressive treatment, and corneal ulcers or vision impairment persist, a switch to alternative systemic therapy may be necessary [12,38]. Overall, proactive interdisciplinary care, early identification, and severity-based escalation remain central to optimizing outcomes for patients with moderate to severe DIOSD.

Alternative Therapies for AD if DIOSD is Refractory

The emergence of new treatment alternatives provides hope for the few patients unable to tolerate dupilumab because of intense ocular AEs. Janus kinase (JAK) inhibitors, such as upadacitinib and abrocitinib, function as oral treatments for moderate-to-severe AD without affecting the IL-4/IL-13 pathways, and theoretically, they should have fewer ocular side effects. Patients who experienced conjunctivitis as a side effect of dupilumab treatment showed complete resolution of their eye symptoms after switching to upadacitinib while maintaining control of their eczema (Paganini, et al. 2024). IL-13 targeted therapies, such as tralokinumab (FDA-approved for atopic dermatitis) and lebrikizumab (currently under development), may demonstrate a reduced risk of conjunctivitis. Clinical trials demonstrated that tralokinumab-treated patients developed conjunctivitis at rates of approximately 5–7%. Tralokinumab selectively blocks IL-13 signaling while leaving IL-4–mediated pathways intact, distinguishing its mechanism of action from that of dupilumab, which inhibits both IL-4 and IL-13 through IL-4Rα blockade [43]. This compares favorably with the higher rates seen in dupilumab trials. Patients under treatment with dupilumab who experience DIOSD symptoms showed positive results when switched to tralokinumab [7,44]. IL-4 blockade, which influences IL-13 among other pathways, is likely the primary cause of DIOSD, while selectively targeting IL-13 could help bypass this issue.

The 2024 expert consensus guidance for dupilumab-related ocular issues also applies to patients with tralokinumab or lebrikizumab, as both medications can cause ocular surface disturbances due to IL-13's role in goblet cell maintenance [38]. Patients who cannot tolerate dupilumab should consider changing to a different medication class or a targeted IL-13 inhibitor. Patients with acute DIOSD should be treated accordingly, while those experiencing recurrent or persistent conditions needing continuous ocular therapy should consider switching treatments. Patients need to decide based on their preferences, as some individuals prefer to use eye drops indefinitely to maintain dupilumab treatment. In contrast, others want to avoid potential long-term eye problems.

Follow-up and Monitoring

Patients who experience DIOSD require more frequent follow-up appointments to ensure ocular symptoms are adequately controlled and to prevent disease progression. Patients receiving dupilumab should undergo regular ophthalmologic evaluations every 3–4 months, or more frequently based on the severity of ocular involvement, as determined by their eye care provider [11,37]. In particular, intraocular pressure monitoring is crucial when topical corticosteroids are prescribed, given the risk of steroid-induced glaucoma [40]. Ongoing surveillance allows for early identification of corneal changes, limbal inflammation, and scarring, which can significantly impact visual outcomes if left untreated [33]. Effective communication and coordination between dermatologists and ophthalmologists is essential for optimal patient care. A shared treatment plan should allow dermatologists to manage mild DIOSD, while moderate to severe cases warrant evaluation and co-management by ophthalmology—preferably by a cornea or ocular surface specialist [38]. This collaborative approach ensures that both skin and ocular health are preserved, minimizing the risk of flares in either condition due to suboptimal treatment. With growing clinical experience, most providers now approach DIOSD proactively rather than reactively. Dermatologists frequently incorporate ocular symptom screening tools, such as dry eye questionnaires, into routine follow-up visits for patients receiving dupilumab [15]. In parallel, ophthalmologists at several academic centers have implemented standardized diagnostic and treatment protocols for managing DIOSD, often including tiered escalation strategies for lubrication, anti-inflammatory drops, and immunomodulators [30,31].

This structured and collaborative model of care has allowed many patients to continue benefiting from dupilumab's dermatologic efficacy while simultaneously preserving ocular surface comfort and visual safety. With greater awareness, early recognition, and interdisciplinary cooperation, DIOSD can be managed successfully, allowing for uninterrupted treatment of AD in most cases.

Discussion

Dupilumab treatment offers a fascinating example of a regulatory event in one system that can non-intuitively control immune reactions at a mucosal surface. As a result of the described mechanism, DIOSD has become a unique event that requires collaboration between a dermatologist and an ophthalmologist. Since dupilumab came into use, our understanding of DIOSD has been transformed. Ophthalmologists have been surprised and unprepared for reports of conjunctivitis [20], and even dermatologists initially stopped prescribing the drug to patients with conjunctivitis [16]. In contrast, today there is so much data available that the medical response to eye symptoms becomes one of recognition and reassurance, involving providing patients with early information about their treatment and screening them for risk factors [1,19]. Meanwhile, a modern clinician's approach to management is proactive. Clinical studies have demonstrated that starting dupilumab treatment for patients with AD can result in a quarter of them developing ocular symptoms; however, it is treatable and reversible [3,5]. This is one of the first messages to be communicated to primary care physicians: Do not abandon dupilumab treatment due to possible ocular side effects, as patients' eye health needs to be monitored more actively while on the drug [6]. It is clear to patients with AD that the medication helps them: it improves their ability to control their disease, avoid hospital visits and clinics, and maintain a good quality of life [24,45].

DIOSD is a risk that clinicians are prepared to take and handle on the same level as, for instance, liver checks for methotrexate or blood pressure tests for cyclosporine. The 2024 international consensus is not to withhold dupilumab due to a fear of ocular AEs [38]. Still, we should educate ourselves and our patients on the ways to manage such AEs in case they do occur. One of the most important practical tasks is to develop unified protocols for the diagnosis and treatment of DIOSD to be implemented in clinics. The consensus guidelines provide an example: they require a baseline eye exam for high-risk patients, followed by grading the severity of eye symptoms, and stepwise therapy with established referral criteria and decisions for continuing or stopping medication [38]. Introducing such protocols will simplify care. For instance, in the case of moderate DIOSD, a personalized treatment path can already be developed in advance: start a treatment with steroid drops and tacrolimus ointment without stopping dupilumab and reevaluate the patient's condition after two weeks and consider an ophthalmology referral if symptoms do not improve [4,36]. Forming relationships with ophthalmologists who are familiar with DIOSD has many benefits. The ophthalmic side effects of dupilumab were initially known to only a small group of ophthalmologists; however, they now have clear recognition and representation in scientific articles and medical lectures [11,28], and cooperation in treatment management has also improved naturally. DIOSD now acts as a connecting bridge between different fields of medicine, allowing them to interact with and learn from one another, thereby establishing communication between them.

A wide range of ocular surface disease symptoms and severities presents diagnostic challenges. Crucially, however, ocular redness in individuals treated with dupilumab is not always due to the therapy itself. Infectious conjunctivitis, acute allergic conjunctivitis (due to pollen or other causes), and coincident dry eye disease [18,28] are among the more common differentials that should be considered. In these instances, it is important to consider further evaluation and involve ophthalmology as indicated to help establish a differential diagnosis [3,14]. In general, symptoms and signs associated with DIOSD are a chronic, bilateral process persisting on dupilumab therapy, as opposed to a rapidly occurring postinjection response, which would be more indicative of a rare IgE-mediated reaction to dupilumab [4,16]. Ocular pathologies that occur in atopic dermatitis but are less common than DIOSD (e.g., herpes simplex keratitis, eosinophilic conjunctivitis) should also be considered to ensure that all ocular pathology is not ascribed to dupilumab therapy [11,32,38]. Ultimately, a DIOSD diagnosis is one of exclusion based on history and patterns of signs and symptoms, which may be suggested when ocular signs and symptoms persist during ongoing dupilumab therapy and respond to management of DIOSD [5,12]. The DIOSD research findings prompt intriguing questions regarding the function of Th2 cytokines in maintaining ocular balance. Before dupilumab was developed, IL-4 and IL-13 were primarily blamed for causing allergic diseases [34].

DIOSD has revealed a nuance: Research demonstrates that IL-13 helps preserve goblet cell function and tear film stability in the conjunctiva [25]. This aligns with basic science: research shows that mice lacking IL-13 or IL-4Rα exhibit reduced numbers of conjunctival goblet cells and display spontaneous ocular surface inflammation, regardless of allergen exposure [25]. The signaling pathway of IL-4/13 operates within the intricate immune-endocrine system responsible for safeguarding mucosal surfaces. The systemic drug that interferes with that network triggers unexpected effects in the eye, which is one of the most sensitive mucosal organs. The outcome illustrates the crucial role of immunological processes. IL-13 functions as a harmful agent in AD patients' skin but exhibits protective properties in the conjunctiva. Understanding the roles of cytokines in different organ contexts could lead to new therapies targeting specific organs (for example, topical IL-13 treatments for dry eye might theoretically counteract dupilumab's effects locally, but such treatments do not yet exist). In a minority of patients with DIOSD, Cassagne, et al. [8] found evidence for a Th17-driven psoriasiform immune response. This observation broadens our understanding of the potential contributions

to immune dysregulation that may play a role in atopic disease. The proposed model is that Th2-dominant inflammation, a feature of atopy, likely suppresses or otherwise antagonizes Th17 activation. However, this suppression is relieved when the Th2 pathway is dampened by IL-4/IL-13 blockade, allowing Th17 activity to become the primary driver of inflammation [8,34].

This is compatible with atopic–psoriasis cross-regulation, where atopic and psoriatic disease are thought to be reciprocally suppressing [8,32,46], such that typically either the atopic or psoriatic phenotype is present in an individual, but rarely both simultaneously. Dupilumab may provide an in vivo experiment to support this: When Th2 suppression occurs in predisposed tissue, such as the conjunctiva, it reveals psoriasis-like characteristics. Case reports exist of patients who developed either new-onset psoriasis or psoriasiform eczema while on dupilumab treatment due to what appears to be a similar underlying mechanism [34,46]. Further investigation is required to determine which patients undergo this immunologic switch, utilizing genetic profiling or biomarker assays, such as baseline Th17 cytokine levels, for identification. It is conceivable that we could personalize therapy in the future: We should either practice caution or combine dupilumab with Th17 suppression treatments for patients exhibiting elevated IL-17 levels at baseline.

Future Directions

The next phase of research should target controlled trials specifically for preventive interventions aimed at DIOSD. Randomized studies comparing dupilumab-treated patients who use prophylactic artificial tears with those who do not will establish whether early application of lubrication prevents DIOSD [11,37]. Combined eye drops containing hyaluronate for tear film support and low-dose steroids or immunomodulators for inflammation control offer dual-action benefits for early-stage or high-risk patients [30,36]. It is crucial to conduct longitudinal studies to assess the long-term effects of DIOSD. Healthcare professionals are concerned about potential long-term eye damage, as studies have reported cases of cicatricial conjunctivitis in conjunction with limbal inflammation [8,40]. The effectiveness of optimized management in entirely preventing these outcomes throughout extended dupilumab use remains uncertain. Future research directions should investigate how DIOSD impacts the development process for systemic medications and the changes in medical prescriptions that result. Medical experts treating patients with severe atopic dermatitis who have a significant history of ocular atopy or AKC might prefer the IL-13 inhibitor tralokinumab over dupilumab to minimize the risk of ocular complications [38]. The introduction of lebrikizumab to the market as an additional IL–13–targeted biologic will initiate more studies to compare their ocular safety profiles. Providers may consider JAK inhibitors for patients at high risk of corneal scarring or those with a history of cicatricial disease due to their broad immunomodulatory effects and potential for reduced ocular surface toxicity [2,5].

Prescribing behavior in dermatology is significantly affected by DIOSD's demonstration of off-target effects in non-dermatologic tissues despite drug costs and safety monitoring requirements. DIOSD transformed from an unforeseen AE into a clinically recognized syndrome, complete with diagnostic criteria and treatment guidelines [11,38]. The interconnected immune pathways across organ systems highlight how targeting one organ's immune environment can create effects in secondary tissues. Through joint research efforts by dermatologists and ophthalmologists who have developed DIOSD treatment protocols, patients with AD no longer need to discontinue dupilumab for eye-related symptoms [5,33]. Real-world evidence demonstrates that prompt identification and regimented care lower the risk of serious consequences, including vision damage or discontinuation of medication. Education remains pivotal. Patients exhibit improved assurance and treatment adherence when they understand eye discomfort as a manageable side effect rather than an ambiguous complication [32]. Patients who understand this information become more proactive in reporting symptoms and develop confidence in their care plan. DIOSD research findings could lead to innovative treatments for other diseases affecting the ocular surface.

Research into how IL-13 influences goblet cells and mucin control could help develop potential treatments that aim to restore conjunctival mucosal health through methods like recombinant IL-13 and downstream pathway agonists to maintain tear stability in patients with chronic dry eye, although this remains an untested approach [10,21]. AKC exhibits numerous pathophysiologic similarities with DIOSD and responds to similar immunomodulatory treatments, such as topical tacrolimus or cyclosporine, thereby linking the two conditions through therapeutic approaches [9,30]. Dupilumab's ocular side effects raise clinical concerns, but their impact can be mitigated by robust research efforts combined with educational programs for patients and collaboration across medical disciplines. Healthcare providers will continue to refine methods that provide effective skin treatment while protecting eye health as DIOSD becomes a regular aspect of managing AD. This will enable patients to achieve full benefits from biological therapies with reduced complications.

Conclusion

The dupilumab-induced ocular surface disease represents a complex adverse event that expands knowledge about the systemic effects of biological treatment for atopic dermatitis. DIOSD represents more than basic allergic conjunctivitis, as it encompasses a range of ocular surface inflammation symptoms that involve the loss of conjunctival goblet cells and tear film instability, characterized by a distinctive immunological pattern that may involve Th17-driven inflammation. During the initial stages of dupilumab treatment, patients with AD develop persistent conjunctivitis, which is frequently followed by blepharitis, dry eye, and keratitis. Research advancements and increased awareness over recent years have given clinicians effective management strategies for DIOSD. Identifying risk factors, such as severe ec-

zema, prior atopic eye disease, high IgE, and head and neck dermatitis, enables clinicians to stratify risk and initiate early interventions. Aggressive local treatment protocols, including lubricants and lid hygiene with topical steroids and calcineurin inhibitors adjusted to disease severity, enable sustained dupilumab treatment without breaks. Recent consensus guidelines indicate that interdisciplinary collaboration has formalized an approach that keeps the patient's quality of life at the forefront. Effective treatment requires a combination of eye care and maintaining clear skin.

In practical terms, for the general clinician, the key messages are: All dupilumab-treated AD patients require careful monitoring for ocular side effects while maintaining communication with ophthalmology experts when moderate or severe cases appear.

These preventive steps have transformed the phrase "fears for tears" from a concerning summary of dupilumab into a manageable aspect of AD treatment. Our management will become more effective through ongoing vigilance and research, which may prevent DIOSD entirely or develop targeted therapies for those who develop this condition. Clinicians must stay alert as protectors of their patients' skin and eye health to prevent the dermatological advantages of dupilumab for eczema from being eclipsed by eye-related side effects. In balancing efficacy and safety, knowledge truly is power. Recognizing that dupilumab-related ocular surface disease extends beyond conjunctivitis enables clinicians to respond quickly and effectively, delivering complete care to patients with AD.

Conflicts of Interest

The authors declare no conflicts of interest.

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