



Ocular surface disease in patients with atopic dermatitis treated with dupilumab: a systematic review and meta-analysis

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Abstract

Background. Dupilumab has significantly improved outcomes in patients with moderate-to-severe atopic dermatitis (AD). However, ocular surface disease (OSD), particularly conjunctivitis, has emerged as the most frequently reported adverse event during treatment, with precise risk estimates from randomized controlled trials (RCTs) remaining limited.

Aims. To evaluate the incidence and relative risk of conjunctivitis in patients with moderate-to-severe AD treated with dupilumab compared with placebo.

Methods. A systematic literature review was conducted according to PRISMA guidelines. PubMed was searched from 2016 to 2025. Thirty-five studies met criteria for qualitative synthesis. For quantitative meta-analysis, three phase III randomized, double-blind, placebo-controlled trials (SOLO-1, SOLO-2, and LIBERTY AD CAFÉ) were included. A random-effects model with Restricted Maximum Likelihood estimation was applied. Heterogeneity was assessed using Cochran's Q and the I² statistic.

Results. The pooled analysis demonstrated a significantly increased risk of conjunctivitis in patients receiving dupilumab compared with placebo (RR = 2.90, 95% CI 1.33–6.32), with low heterogeneity (I² = 26.6%). Across trials, ocular events were predominantly mild to moderate and rarely led to permanent treatment discontinuation. Qualitative synthesis confirmed baseline ocular vulnerability in AD populations and variability in reported incidence in real-world settings.

Conclusion. Dupilumab treatment is associated with a nearly threefold increased risk of conjunctivitis compared with placebo. Although most ocular events are manageable, early recognition and ophthalmologic evaluation remain important.

Keywords: atopic dermatitis, dupilumab, ocular surface disease, conjunctivitis, meta-analysis

1. Introduction

Dupilumab, a monoclonal antibody targeting the interleukin-4 receptor α subunit and inhibiting IL-4 and IL-13 signaling, has significantly improved clinical outcomes in patients with moderate to severe atopic dermatitis (AD), particularly in disease control, pruritus reduction, and quality of life. However, ocular surface disease (OSD), which is intrinsically associated with AD due to underlying barrier dysfunction and chronic inflammation, has emerged as the most frequently reported adverse effect during dupilumab therapy. Real-world and prospective studies report OSD in up to 28–37% of dupilumab-treated adults, most commonly presenting as conjunctivitis, blepharoconjunctivitis, or dry eye disease, typically within the first 6 – 10 weeks of treatment and more frequently than in non-dupilumab-treated patients [1–4]. Although the majority of cases are mild to moderate and manageable with topical therapy, rare vision-threatening complications have been described [5]. Despite increasing clinical awareness, reported incidence rates vary substantially across studies, and differences in study design and outcome reporting limit precise risk estimation in AD populations. A focused quantitative synthesis of randomized controlled trial data is therefore warranted. The aim of this study was to evaluate the incidence and relative risk of conjunctivitis and ocular surface disease in patients with moderate-to-severe AD treated with dupilumab compared with placebo.

2. Methods

2.1. Study design for systematic literature review

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The objective was to evaluate the incidence and relative risk (RR) of conjunctivitis and ocular surface disease (OSD) in patients with moderate-to-severe atopic dermatitis (AD) treated with dupilumab. Eligibility criteria were defined using the PICOS framework (Population, Intervention, Comparator, Outcomes, Study design). The predefined search period covered publications from December 2016 to March 2025.

2.2. Search strategy for systematic literature review

A systematic electronic search was performed in PubMed using controlled vocabulary (MeSH terms) and free-text keywords related to atopic dermatitis, dupilumab, conjunctivitis, and ocular surface disease. Only English-language full-text publications were considered. Reference lists of relevant reviews and eligible studies were manually screened to identify additional studies.

2.3. Study selection of qualitative synthesis for systematic literature review

After removal of duplicates, titles and abstracts were screened. Full-text articles were assessed against predefined inclusion and exclusion criteria (Tables 1 and 2). A total of 35 studies met eligibility criteria and underwent structured qualitative synthesis for systematic literature review. These studies were analyzed to characterize baseline ocular vulnerability in AD, report OSD incidence ranges, describe clinical phenotypes, and outline management approaches across different study designs and clinical settings.

Table 1. Identification of studies via databases and registers for qualitative synthesis

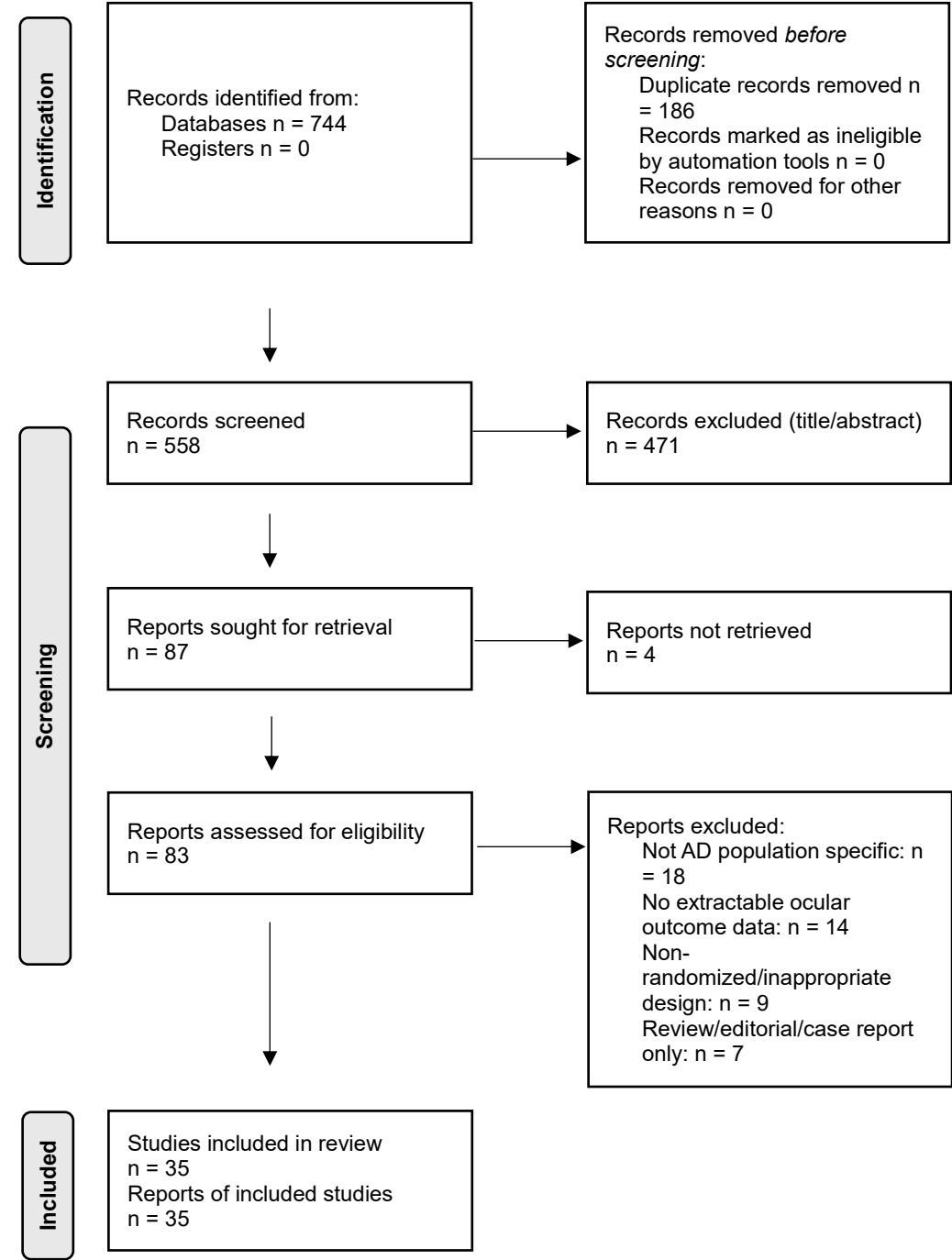


Table 2. Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	• Adolescents or adults with moderate-to-severe atopic dermatitis (AD) • Patients treated for AD indication	• Non-AD indications (e.g., asthma) • Mild AD only • Animal or preclinical studies
Intervention	• Dupilumab administered according to approved dosing regimens	• Studies without dupilumab exposure
Comparators	• Placebo (with or without background topical corticosteroids) • Any comparator (for qualitative synthesis)	• Studies without a comparator arm (for meta-analysis eligibility)
Outcomes	• Reported incidence of conjunctivitis • Ocular surface disease (OSD) • Keratitis or ocular adverse events	• No extractable ocular safety data • Outcomes not reported separately for dupilumab
Study designs	• Phase III randomized, double-blind, placebo-controlled trials (for quantitative synthesis) • Observational and real-world studies (for qualitative synthesis)	• Case reports or small case series • Editorials, narrative reviews, letters, opinions
Timeframe	• Publications from December 2016 to March 2025	• Publications outside predefined timeframe
Language	• English, full-text available	• Non-English full-text unavailable

Abbreviations: AD: atopic dermatitis; OSD: ocular surface disease; RCT: randomized controlled trial.

2.4. Study selection for quantitative meta-analysis

A predefined quantitative meta-analysis was restricted to randomized, double-blind, placebo-controlled phase III trials that met strict comparability criteria, including:

- placebo comparator
- extractable conjunctivitis event data
- comparable study duration and outcome definitions.

Three randomized controlled trials (SOLO-1, SOLO-2, and LIBERTY AD CAFÉ) fulfilled these criteria and were included in the quantitative meta-analysis. The restriction of quantitative pooling to phase III randomized trials was predefined to ensure methodological comparability and minimize clinical and design heterogeneity.

2.5. Data Extraction for quantitative meta-analysis

Data were extracted using a predefined structured template and independently verified to ensure accuracy. Extracted variables included

study design, population characteristics, dupilumab dosing regimen, comparator details, and reported ocular outcomes.

For randomized controlled trials included in the meta-analysis, absolute event counts for conjunctivitis in dupilumab and placebo arms were extracted to calculate risk ratios. For the remaining studies, reported incidence rates and effect estimates were recorded for qualitative synthesis.

2.6. Risk of bias assessment for quantitative meta-analysis

The risk of bias of randomized controlled trials included in the meta-analysis was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. The following domains were evaluated: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting.

Each domain was categorized as low risk, some concerns, or high risk of bias. Risk-of-bias assessment was performed, and discrepancies were resolved (Table 3).

Table 3. Risk of bias assessment of included randomized controlled trials

Study	Randomization	Deviations	Missing data	Outcome measurement	Reporting	Overall
SOLO-1	Low	Low	Low	Low	Low	Low
SOLO-2	Low	Low	Low	Low	Low	Low
LIBERTY AD CAFÉ	Low	Low	Low	Low	Low	Low

2.7. Quantitative synthesis

Meta-analysis was performed to estimate the relative risk (RR) of conjunctivitis in dupilumab-treated patients compared with placebo.

Effect sizes were calculated on the logarithmic risk ratio scale (logRR), with corresponding standard errors derived from event count data. A random-effects model was applied to account for potential clinical and methodological heterogeneity. Between-study variance was estimated using the Restricted Maximum Likelihood (REML) method.

Statistical heterogeneity was assessed using Cochran's Q test and quantified using τ , τ^2 , and the I^2 statistic. Results were presented as pooled risk ratios with 95% confidence intervals and visualized using forest plots.

All statistical analyses were performed in R (RStudio) using the "metafor" package. Statistical significance was defined as $p < 0.05$.

2.8. Additional analysis

Due to the limited number of eligible randomized trials, subgroup analyses, network meta-analysis, or indirect comparisons were not performed.

3. Results

3.1. Study selection

A total of 744 records were identified through database searching. After removal of duplicates, 558 records were screened. Of these, 471 were excluded based on title and abstract. Eighty-seven full-text articles were assessed for

eligibility, and 35 studies met criteria for qualitative synthesis.

Three phase III randomized controlled trials (SOLO-1, SOLO-2, and LIBERTY AD CAFÉ) were included in the quantitative meta-analysis

3.2. Qualitative synthesis

3.2.1 Epidemiology and baseline ocular burden

Ocular surface disease (OSD) is a recognized comorbidity of atopic dermatitis (AD), encompassing conjunctivitis, blepharoconjunctivitis, dry eye disease, and keratitis [6]. Epidemiological studies demonstrate a substantial baseline ocular burden in AD irrespective of systemic therapy, with reported lifetime prevalences of conjunctivitis ranging from approximately 31.7% to 66.6% and keratitis from 9% to 10% [7,8]. Clinical manifestations frequently involve eyelid inflammation and meibomian gland dysfunction, reflecting a chronic inflammatory ocular phenotype of AD [9,10].

3.2.2 Pathophysiology of dupilumab-associated ocular surface disease

Dupilumab-associated ocular surface disease (DAOSD) likely reflects pre-existing ocular surface vulnerability in atopic dermatitis, amplified by IL-4/IL-13 pathway blockade [11,12]. Functional goblet cell impairment with reduced mucin secretion contributes to tear-film instability, while concomitant meibomian gland dysfunction promotes evaporative dry eye [13].

In parallel, cytokine inhibition induces a local immune shift from Th2-dominant inflammation toward Th1/Th17 pathways, resulting in an atopic keratoconjunctivitis-like phenotype [14–16]. Local ocular exposure to dupilumab may further disrupt epithelial homeostasis [11,17]. Collectively, these mechanisms suggest that DAOSD represents an immune-mediated imbalance of the ocular surface rather than a purely drug-induced adverse event [18,19].

3.2.3 Clinical characteristics, risk factors, and management of DAOSD

DAOSD most commonly develops within the first 4–16 weeks of treatment and presents predominantly as bilateral conjunctivitis, although keratitis and mixed ocular surface phenotypes are also described [20,21]. Typical symptoms include ocular redness, irritation, pruritus, tearing, burning, dryness, and photophobia. Slit-lamp findings frequently reveal bulbar hyperemia, papillary reaction, blepharitis with meibomian gland dysfunction, and superficial punctate keratitis [9,22]. While most cases are mild-to-moderate, chronic or relapsing courses requiring maintenance topical therapy have been reported, and rare vision-threatening complications (e.g., cicatricial changes or corneal involvement) may occur [5].

Identified risk factors include eyelid eczema, pre-existing dry eye with superficial punctate keratitis, high baseline IgE levels, asthma, and facial or head–neck AD involvement [4,5,23]. Baseline ophthalmologic evaluation may improve early detection in high-risk individuals [24]. Management is typically stepwise and allows continuation of dupilumab in most cases. Mild disease can often be controlled with lubricants and topical anti-allergic therapy, whereas moderate-to-severe cases may require topical

corticosteroids with gradual tapering and, in selected cases, topical calcineurin inhibitors [9,21–22]. Permanent discontinuation of treatment due to DAOSD remains uncommon, and most patients maintain dermatologic benefit with appropriate ocular treatment [4,21].

3.2.4 Clinical trials and real-world evidence

Randomized clinical trials consistently demonstrate an increased frequency of DAOSD with dupilumab in AD, with excess risk largely confined to the AD indication [25]. Phase III adult and adolescent AD trials demonstrated higher conjunctivitis rates while maintaining rapid and sustained improvement in skin disease and otherwise comparable safety profiles [26–28]. In adolescents, conjunctivitis was more frequent with dupilumab (10.3% vs. 4.7%), typically mild-to-moderate and rarely leading to discontinuation [29]. Pediatric randomized studies reported conjunctivitis in 5% of dupilumab-treated children, compared with none on placebo [30]. Integrated safety analyses across eight phase III trials confirmed conjunctivitis as a recurrent ocular event cluster [31].

Real-world data confirms excess risks of conjunctivitis and keratitis beyond baseline AD-associated ocular morbidity [3,32]. In a clinically meaningful minority, these manifestations may lead to treatment interruption [2,5,21]. DAOSD remains frequently under-recognized and managed heterogeneously, reflecting gaps in risk stratification, standardized diagnostic criteria, and coordinated dermatology–ophthalmology care pathways [13,25,33–35].

3.3 Quantitative synthesis

Three phase III randomized, double-blind, placebo-controlled trials (SOLO-1, SOLO-2,

and LIBERTY AD CAFÉ) were included in the quantitative meta-analysis. The studies were comparable in terms of design, patient population, and treatment duration (Table 4).

Across all included trials, conjunctivitis events were more frequently observed in patients receiving dupilumab than in those receiving placebo. Although absolute event numbers

varied between studies, the direction of effect was consistent (Table 5).

The clinical presentation of ocular events was generally non-severe, with only occasional moderate cases and rare need for treatment discontinuation. Most cases were successfully managed with supportive or topical ophthalmic therapy, allowing continuation of dupilumab treatment in most patients (Table 6).

Table 4. Clinical trial characteristics [36,37]

Study	Design / Duration	Population	Intervention	Comparator	Ocular adverse event reporting
SOLO-1 (2016)	Phase III, randomized, placebo-controlled trial / 16 weeks	Adults with moderate-to-severe atopic dermatitis	Dupilumab 300 mg subcutaneously, weekly or every other week	Placebo	Conjunctivitis
SOLO-2 (2016)	Phase III, randomized, double-blind, placebo-controlled trial / 16 weeks	Adults with moderate-to-severe atopic dermatitis	Dupilumab 300 mg subcutaneously, weekly or every other week	Placebo	Conjunctivitis
LIBERTY AD CAFÉ (2018)	Phase III, randomized, double-blind, placebo-controlled trial / 16 weeks	Adults with moderate-to-severe atopic dermatitis with inadequate response to, intolerance of, or contraindication to ciclosporin A	Dupilumab 300 mg subcutaneously, weekly or every other week, with topical corticosteroids	Placebo with topical corticosteroids	Conjunctivitis

Table 5. Ocular events used for meta-analysis [36,37]

Study	Follow-up	Dupilumab (n)	Conjunctivitis events (n)	Placebo (n)	Conjunctivitis events (n)
SOLO-1 (2016)	16 weeks	447	18	222	2
SOLO-2 (2016)	16 weeks	473	18	234	1
LIBERTY AD CAFÉ (2018)	16 weeks	217	48	108	12

Table 6. Ocular phenotype and management reported in phase III trials [36,37]

Study	Ocular Phenotype Observed	Severity	Management
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SOLO-1 (2016)	Conjunctivitis (predominantly allergic)	Mostly mild-to-moderate; occasional moderate reactions	Treated with supportive ocular therapy; rare need for treatment discontinuation
SOLO-2 (2016)	Conjunctivitis (predominantly allergic)	Mostly mild-to-moderate; occasional moderate reactions	Most events managed conservatively; discontinuation uncommon
LIBERTY AD CAFÉ (2018)	Conjunctivitis, allergic conjunctivitis; broader eye disorders reported	Predominantly mild-to-moderate; severe events rare	Managed with topical ophthalmic therapy; permanent treatment discontinuation uncommon

The heterogeneity analysis demonstrated low between-study variability among the included randomized controlled trials assessing conjunctivitis risk in dupilumab-treated patients (Table 7). Cochran's Q statistic was not statistically significant ($Q = 2.72$, $p = 0.256$), indicating no evidence of substantial heterogeneity across studies. Consistently, the I^2

value was 26.6%, suggesting that only a small proportion of the total variability in effect estimates could be attributed to true differences between trials rather than random error. The estimated between-study variance ($\tau^2 = 0.154$) further supports acceptable consistency among the included studies.

Table 7. Heterogeneity statistics for conjunctivitis risk in dupilumab versus placebo trials

Statistic	Value
Cochran's Q	2.723
Degrees of freedom (df)	2
p-value (Q test)	0.256
I^2 (%)	26.55
τ^2 (between-study variance)	0.154

Abbreviations: Q = Cochran's heterogeneity statistic; df = degrees of freedom; I^2 = percentage of variability due to between-study heterogeneity; τ^2 = between-study variance.

The pooled analysis using a random-effects model showed a significantly increased risk of conjunctivitis in patients receiving dupilumab compared with placebo ($RR = 2.90$, 95% CI 1.33–6.32), as illustrated in the forest plot (Figure 1). At the individual-trial level, all studies demonstrated an increased risk in the same direction, although the magnitude of the

effect varied. The SOLO-1 and SOLO-2 trials reported higher relative risks with wide confidence intervals, reflecting limited precision, whereas the LIBERTY AD CAFÉ trial showed a more moderate but statistically significant increase in conjunctivitis risk. However, the precision of effect estimates is influenced by the limited number of

conjunctivitis events observed in the placebo arms, resulting in wider confidence intervals in some trials.

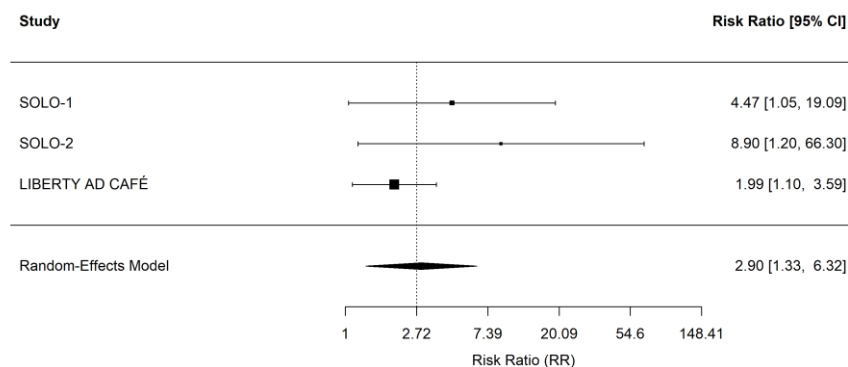


Figure 1. Forest plot of conjunctivitis risk ratios (RR) in dupilumab-treated patients compared with placebo across randomized clinical trials (SOLO-1, SOLO-2, and LIBERTY AD CAFÉ). The pooled estimate was calculated using a random-effects model (REML).

4. Discussion

This systematic review and meta-analysis demonstrate that dupilumab treatment in moderate-to-severe atopic dermatitis is associated with a significantly increased risk of conjunctivitis compared with placebo (RR = 2.90), with low between-study heterogeneity supporting the consistency of this association. These findings indicate that ocular surface disease represents a reproducible safety signal in AD populations receiving IL-4/IL-13 pathway blockade.

The restriction of quantitative synthesis to phase III randomized, double-blind, placebo-controlled trials was predefined to ensure methodological comparability and minimize clinical and design heterogeneity. Although these trials share similar structures, their independent conduct and consistent direction of effect strengthen the robustness of the observed association.

Baseline ocular surface vulnerability is common in AD [6–10], and the increased risk observed with dupilumab likely reflects interaction

between pre-existing inflammatory susceptibility and targeted cytokine inhibition [11–16]. Proposed mechanisms include goblet cell dysfunction, tear film instability, and immune pathway shifts rather than direct pharmacologic toxicity [18,19].

In line with our meta-analytic findings, the inclusion of a representative real-world case provides contextual insight into the clinical relevance of dupilumab-associated ocular surface disease beyond controlled trial settings. A 28-year-old male presented to our Centre of Dermatovenereology with a history of childhood-onset severe atopic dermatitis refractory to topical therapy, phototherapy, cyclosporine, and baricitinib, who was initiated on dupilumab. The dermatologic response was rapid and clinically meaningful, with the SCORAD score decreasing from 64.7 to 29.6 (–35.1 points) and the DLQI score improving from 23 to 14 (–9 points). However, within the first months of therapy, the patient developed ocular surface symptoms characterized by periocular dryness, irritation, and inflammatory

changes consistent with mild-to-moderate conjunctivitis. These manifestations were managed conservatively with topical ophthalmic therapy without discontinuation of dupilumab, while the cutaneous response to dupilumab was maintained. This clinical course mirrors patterns reported in randomized trials and observational cohorts, in which ocular surface disease emerges despite excellent dermatologic control, reinforcing the concept of a disease–drug interaction rather than an isolated adverse event. These findings underscore the importance of early recognition and interdisciplinary management of ocular surface symptoms in dupilumab-treated patients with atopic dermatitis.

Importantly, most ocular events reported in phase III trials were mild to moderate and rarely led to permanent discontinuation of treatment [29–31]. Early recognition of symptoms, patient counseling, and timely ophthalmologic evaluation may allow continuation of effective systemic therapy while minimizing ocular morbidity. Strengths of this study include the restriction to phase III randomized trials and the low heterogeneity across the pooled estimates. Limitations include the small number of eligible RCTs, limited follow-up duration, investigator-reported ocular outcomes, and restriction to a single database.

5. Conclusions

Dupilumab treatment in patients with moderate-to-severe atopic dermatitis is associated with a significantly increased risk of conjunctivitis compared with placebo, with a nearly threefold higher relative risk observed across phase III randomized trials and low between-study heterogeneity. Although most ocular events are mild to moderate and manageable without

treatment discontinuation, ocular surface disease is a clinically relevant complication that may affect patient comfort and adherence. These findings support the concept of a disease–drug interaction, in which underlying atopic ocular susceptibility may be amplified by IL-4/IL-13 pathway blockade rather than reflecting isolated pharmacologic toxicity. Proactive symptom recognition and timely ophthalmologic evaluation may help optimize management while preserving the dermatologic benefits of dupilumab therapy.

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