

## REVIEW

# Conjunctivitis in patients with atopic dermatitis treated with dupilumab

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### Abstract

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disorder with high physical and emotional burden. Robust evidence suggests that interleukin (IL)-4 and IL-13 are key cytokines in the immunopathogenesis of AD. New emerging agents include dupilumab, a fully human monoclonal antibody directed against the IL-4 receptor  $\alpha$  subunit that blocks both IL-4 and IL-13 signaling and has shown significant efficacy in patients with moderate-to-severe AD. Dupilumab is approved for the treatment of moderate-to-severe AD, moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma, and chronic rhinosinusitis with nasal polyps. Data from phase 2 and 3 studies have revealed that dupilumab generally has a low rate of adverse events, although an increased incidence of mild-to-moderate conjunctivitis has been reported for dupilumab compared with placebo.

The present paper reviews the data of dupilumab-associated conjunctivitis and risk factors in adults with moderate-to-severe AD and other atopic diseases in dupilumab clinical trials and addresses the characteristics and treatment options available for this clinically highly relevant condition. Additionally, it presents data from ten studies in the real-life setting with dupilumab. Dupilumab-associated conjunctivitis incidence is higher in AD, although most cases are mild-to-moderate and have good response to topical treatment, with no need to suspend dupilumab therapy.

**Keywords:** atopic dermatitis, atopic eczema, conjunctivitis, dupilumab.

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## Background

Atopic dermatitis (AD) is a common, chronic, inflammatory skin condition that affects up to 25% of children and 5% of adults worldwide.<sup>1,2</sup> Patients with AD have an increased risk of developing ocular disorders, such as keratoconus, cataract, glaucoma, and blepharitis, as well as allergic, atopic, and infectious (kerato) conjunctivitis.<sup>3,4</sup>

Topical treatment is usually sufficient to control the disease in the majority of patients, although systemic treatment may be required in some patients due to the severity of the skin disease. Several biologic therapies are currently being developed and evaluated in clinical trials. To date, dupilumab has been the first targeted biologic agent approved in the United States and the European Union for the treatment of moderate-to-severe AD in adults.<sup>5</sup>

Dupilumab is a fully human monoclonal antibody directed against the interleukin 4 receptor  $\alpha$  (IL-4Ra) subunit that blocks both IL-4 and IL-13 signaling, improving both objective signs and subjective symptoms of the disease.<sup>2,6,7</sup> Dupilumab has been shown to be

effective and safe in asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis (EoE), suggesting that IL-4 and IL-13 are pivotal drivers of numerous type 2 inflammatory diseases. Dupilumab has demonstrated rapid improvement in patients with moderate-to-severe AD and a favorable safety profile across all studies; however, an increased incidence of conjunctivitis has been observed in patients receiving dupilumab compared with those treated with placebo.<sup>6,7</sup> Nevertheless, most patients with dupilumab-associated conjunctivitis (DAC) experienced mild disease, while moderate events were less frequent.<sup>2,6</sup>

Although the incidence of ophthalmic complications seems to increase with the disease severity at baseline and in association with other atopic comorbidities, such as asthma and allergic rhinitis, and previous conjunctivitis history, risk factors for the development of DAC remain unclear.<sup>8-10</sup>

## Methods

A narrative review of the literature was written after retrieving relevant articles from the PubMed database (up until January

2020). The search was performed using the following keywords: dupilumab, 'conjunctivitis,' 'atopic dermatitis,' 'real life,' and 'clinical practice' present in the title, abstract, or body. The authors selected papers from this search as the basis for this review. Eleven randomized placebo-controlled trials of dupilumab use in adults with AD, asthma, chronic rhinosinusitis with nasal polyps, and EoE, and one trial in adolescents with AD were evaluated. Data from the three AD 16-week monotherapy studies in adults were grouped together (monotherapy combined group: phase 2b, SOLO 1, and SOLO 2). In addition, ten studies with data from clinical practice were analyzed.

## Incidence of conjunctivitis in dupilumab clinical trials

A greater incidence of conjunctivitis was noticed among dupilumab treatment groups compared with placebo in one phase 2b and four phase 3 AD clinical trials – SOLO1, SOLO2, CHRONOS, and CAFÉ (Table 1).<sup>6,7,11–13</sup>

In the monotherapy combined group (phase 2b, SOLO 1, and SOLO 2; either dupilumab 300 mg weekly [qw], dupilumab 300 mg every 2 weeks [q2w], or placebo qw), 88 patients in the dupilumab group developed conjunctivitis after 16 weeks of treatment with an incidence rate of 8.4% (n=88/1047) *versus* 2.3% (n=12/517) in the placebo group.<sup>6,11</sup>

In the CHRONOS study, the incidence rates of DAC for dupilumab associated with topical corticosteroid (TCS) compared with placebo in association with TCS over the 52-week trial length were 17.9% (n=48/217) and 7.9% (n=25/315), respectively.

In the SOLO-CONTINUE trial,<sup>12</sup> patients who were good responders to dupilumab in both SOLO trials were re-randomized to more 36 weeks of treatment at their original dosage or longer interval schemes (every 4 weeks [q4w] or every 8 weeks [q8w]) or placebo. Contrary to the other AD studies, no noticeable disparity in conjunctivitis incidence rate was detected between the dupilumab and placebo groups (n=16/338, 4.7%, *versus* n=4/82, 4.9%, respectively). Additionally, in the CHRONOS and SOLO-CONTINUE studies, both dupilumab-dosing schemes presented with identical incidence rates of DAC in the monotherapy group.

The CAFÉ trial reported the highest conjunctivitis rates, with incidence rates of 22.1% (n=48/217) *versus* 11.1% (n=12/108) for dupilumab associated with TCS *versus* placebo plus TCS over the 16-week trial length, respectively.<sup>13</sup> Dupilumab 300 mg q2w plus TCS was associated with higher incidence rates than 300 mg qw plus TCS (n=30/107, 28.0%, *versus* n=18/110, 16.4%, respectively).

While conjunctivitis was a significant adverse event (AE) occurring in patients with AD treated with dupilumab, there was no significant increased risk of DAC in all asthma trials (n=30/2007, 1.5% for dupilumab *versus* n=19/929, 2.0% for placebo) (Table 2).<sup>14–17</sup>

In the chronic rhinosinusitis with nasal polyposis clinical trial, only one patient in the placebo group developed conjunctivitis (3.3%),

while none occurred within dupilumab-treated group (Table 2).<sup>18</sup> Also, in the EoE study, there was no conjunctivitis reported.<sup>19</sup>

LIBERTY AD ADOL was a randomized, double-blind, parallel-group, phase 3 clinical trial conducted at 45 US and Canadian centers and included 251 adolescents (aged ≥12 to <18 years) with moderate-to-severe AD inadequately controlled by topical therapies or for whom topical treatment was not recommended.<sup>20</sup> Patients were randomized (1:1:1) to receive treatment with subcutaneous dupilumab q2w (200 mg, n=43; baseline weight < 60 kg; or 300 mg, n=39; baselineweight = 60 kg) or q4w (300 mg, n=84), or placebo q2w (n=85) during 16 weeks. DAC incidence was higher within dupilumab groups when compared with placebo (q2w, n=8/82, 9.8%; q4w, n=9/84, 10.8%; placebo, n=4/85, 4.7%) (Table 3). These results are consistent with those from dupilumab adult trials in AD.

## Conjunctivitis characteristics in dupilumab clinical trials

Conjunctivitis events were mainly mild to moderate, and almost all recuperated with topical eye drops until the termination of the trial period. Treatment options more frequently prescribed were eye drops of corticosteroids, antibiotics, antihistamines, or mast cell stabilizers. Severe cases were only reported in less than 1% of patients. In the CHRONOS study, one patient receiving dupilumab 300 mg qw plus TCS was suspended due to conjunctivitis, namely keratoconjunctivitis in one eye. Also, in the monotherapy group, another patient receiving dupilumab 300 mg qw interrupted repeatedly due to conjunctivitis.

Differences in new conjunctivitis events between placebo and dupilumab were observed after week 2 in the monotherapy group, after weeks 6–8 in CHRONOS, and after weeks 4–8 in CAFÉ.<sup>21</sup> While new DAC events occurred at a steady rate throughout 16 weeks in the monotherapy group and CAFÉ study, in the CHRONOS trial, new cases seemed to level off around weeks 20–24 and were unusual after week 44.<sup>21</sup> In these AD studies, mean time to first occurrence was identical among dupilumab-dosing schemes.

Independently of the treatment group, DAC occurred more frequently in patients who had severe AD at baseline, a prior history of conjunctivitis, and low serum levels of dupilumab.<sup>21</sup> Additionally, higher baseline Thymus and activation-regulated chemokine (TARC) and immunoglobulin E (IgE) serum levels and higher baseline circulating eosinophil counts were also observed in patients with conjunctivitis in both groups.<sup>21,22</sup>

Dupilumab efficacy seems to be associated with conjunctivitis incidence. In the monotherapy group, individuals who accomplished high-level effectiveness results, namely an Investigator's Global Assessment (IGA) of 0 or 1 (IGA 0/1) or 75% improvement from baseline in the Eczema Area and Severity Index (EASI-75), had less susceptibility to develop DAC than those who did not achieve those results.<sup>21</sup> However, this trend was merely noted in the dupilumab q2w and placebo groups, in both CHRONOS and CAFÉ trials.

**Table 1. Incidence of conjunctivitis in atopic dermatitis dupilumab trials\* – phase 2b, SOLO 1, SOLO 2, CHRONOS, CAFÉ, and SOLO-CONTINUE.**<sup>6,7,11–13</sup>

Patients with at least 1 event, n (%)	Monotherapy Group**																
	CHRONOS					CAFÉ					SOLO-CONTINUE						
	Dupilumab (combined) (n=1047)	Dupilumab 300mg qw (n=518)	Dupilumab 300mg q2w (n=529)	Placebo (n=517)	Dupilumab + TCS combined (n=217)	Dupilumab 300mg q2w + TCS (n=110)	Dupilumab 300mg q2w + TCS (n=107)	Placebo + TCS (n=315)	Dupilumab + TCS combined (n=217)	Dupilumab 300mg qw + TCS (n=110)	Dupilumab 300mg q2w + TCS (n=107)	Placebo + TCS (n=108)	Dupilumab combined (n=338)	Dupilumab 300mg q1w/q2w (n=167)	Dupilumab 300mg q4w (n=87)	Dupilumab 300mg q8w (n=84)	Placebo (n=82)
Conjunctivitis <sup>§5</sup>	88 (8.4%)	40 (7.7%)	48 (9.1%)	12 (2.3%)	48 (22.1%)	18 (16.4%)	30 (28.0%)	25 (7.9%)	48 (22.1%)	18 (16.4%)	30 (28.0%)	12 (11.1%)	16 (4.7%)	9 (5.4%)	4 (4.6%)	3 (3.6%)	4 (4.9%)

\*These results are expressed in number of patients (percent).

\*\*Include data pooled for phase 2b trial and phase 3 trials SOLO 1 and SOLO 2.

<sup>§1</sup>MEDRA PT.

<sup>§2</sup>Cluster of preferred terms includes conjunctivitis of unspecified cause, allergic, bacterial and viral conjunctivitis, and atopic keratoconjunctivitis.

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; TCS, topical corticosteroid.

**Table 2. Incidence of conjunctivitis in other type 2 disorders dupilumab trials\* – phase 2b (DRI12544); LIBERTY ASTHMA QUEST; LIBERTY ASTHMA VENTURE; and chronic rhinosinusitis with nasal polyposis (ACT12340).**<sup>14–19</sup>

Patients with at least 1 event, n (%)	Phase IIb DRI12544						LIBERTY ASTHMA QUEST			LIBERTY ASTHMA VENTURE			ACT12340			
		Dupilumab (combined) (n=611)	Dupilumab 300mg q2w (n=156)	Dupilumab 200mg q2w (n=148)	Dupilumab 300mg q4w (n=157)	Dupilumab 200mg q4w (n=150)	Placebo (n=158)	1.14 mL/200 mg q2w	2 mL/300 mg q2w	Combined	Placebo (n=107)	Dupilumab 300mg q2w (n=103)	Placebo (n=30)	Dupilumab 300mg q2w (n=30)	Placebo (n=30)	Dupilumab 300mg q4w (n=30)
Conjunctivitis <sup>§5</sup>	7 (1.1%)	0 (0%)	2 (1.4%)	2 (1.3%)	3 (2.0%)	2 (1.3%)	6 (1.9%)	8 (1.3%)	9 (2.8%)	14 (2.2%)	15 (2.4%)	22 (1.7%)	1 (0.9%)	1 (1.0%)	1 (3.3%)	0 (0%)

\*These results are expressed in number of patients (percent).

<sup>§1</sup>MEDRA PT.

<sup>§2</sup>Cluster of preferred terms includes conjunctivitis of unspecified cause, allergic, bacterial and viral conjunctivitis, and atopic keratoconjunctivitis.

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks.

**Table 3. Incidence of conjunctivitis in atopic dermatitis dupilumab trial in adolescents\* – LIBERTY AD ADOL (R668-AD-1526).<sup>20</sup>**

Patients with at least 1 event, n (%)	LIBERTY AD ADOL			
	Dupilumab (combined) (n=165)	Dupilumab 300mg q4w (n=83)	Dupilumab 200/300mg q2w (n=82)	Placebo (n=85)
Conjunctivitis <sup>a§</sup>	17 (10.3%)	9 (10.8%)	8 (9.8%)	4 (4.7%)

\*These results are expressed in number of patients (percent).

<sup>a</sup>MEDRA PT.

<sup>§</sup>Cluster of preferred terms includes atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral.

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; q2w, every 2 weeks; q4W, every 4 weeks.

## Real-world data on dupilumab-associated conjunctivitis

Since the approval of dupilumab for the treatment of moderate-to-severe AD in the USA and Europe, several studies have been conducted in real-world clinical practice to compare with dupilumab clinical trials' data.

A real-world retrospective study conducted in Spain evaluated dupilumab treatment outcomes in 27 patients with up to 52 weeks of follow-up.<sup>22</sup> DAC was the most common AE observed, with 5 (16.6%) cases reported. All cases were transitory, and managed positively without dupilumab withdrawal.<sup>22</sup> Another series of 70 patients from Spain reported six cases (8.6%) of mild DAC, all in patients with history of allergic conjunctivitis, without need of dupilumab withdrawal.<sup>23</sup> Faiz and colleagues, in a French multicenter retrospective adult cohort, registered 84 cases (n=84/241, 34.9%) of conjunctivitis corresponding to a significantly higher incidence of DAC.<sup>24</sup> Thirty nine of these patients were consulted by an ophthalmologist, who confirmed conjunctivitis in 32 (82.1%) patients. In this study, the occurrence of DAC was associated with a medical history of allergic conjunctivitis.<sup>24</sup> Another observational cohort study from the Netherlands with 95 patients verified eye symptoms in 59 (62%) patients.<sup>25</sup> Among these 59 patients, 16 were referred to an ophthalmologist who made the diagnosis of DAC in 9 (56%) patients.<sup>25</sup> Wang and colleagues analyzed medical records of 77 AD patients treated with standard dosing of dupilumab and observed the occurrence of six cases of DAC (7.79%), with all cases improving with appropriate ophthalmologic treatment.<sup>26</sup> Another real-world retrospective study conducted in Italy included 109 adult patients, from 39 Italian centers. Conjunctivitis was the most frequently reported side effect, occurring in 12 of the 109 patients (11%).<sup>27</sup> All events were mild and managed to succeed with topical medication. Also, two Canadian hospitals conducted a real-world retrospective review that

included 52 adult patients.<sup>28</sup> In-line with the literature, the most common AE was conjunctivitis, which was reported in four patients (8%). Ribero and colleagues enrolled prospectively 128 adult patients. Fifteen events of DAC were reported (n=15/128, 12%), with the majority being mild in intensity.<sup>29</sup> However, the condition persisted in two patients, despite targeted therapy. The Italian Dupilumab Atopic Dermatitis in Real Life study group, in a 16-week multicenter prospective observational study that involved 15 secondary care centers, reported 29 cases (40.3%) of DAC among the 72 patients included.<sup>30</sup> Most cases (n=18/29, 62%) were mild, while 27.6% (n=8/29) and 10.3% (n=3/29) were moderate and severe, respectively. Also, the first event had a mean time of 12 weeks until its occurrence. Almost two-thirds of patients (n=19/29, 65.5%) have fully recovered or were recovering by the completion of the trial. This study reinforced the following risk factors for the development DAC: family history of allergic conjunctivitis, history of conjunctivitis, presence of other atopic conditions, a SCORAD score of 76.6, baseline IgE levels > 3637, and baseline blood eosinophil counts > 350. However, the principal predictor for the occurrence of DAC was a history of conjunctivitis.<sup>30</sup>

Additionally, Liberman and colleagues reported two cases of DAC occurring in males, 2 weeks and 3 months after starting dupilumab, respectively.<sup>31</sup> Both cases had a rapid resolution with topical steroid drops without the necessity of dupilumab discontinuation. Unfortunately, one of the patients had already developed conjunctival cicatrization in one eye at the time of presentation, highlighting the significance of ophthalmological evaluation in patients treated with dupilumab.

Compared with the results from clinical trials, the majority of these real-world studies have higher rates of DAC (up to 62%).<sup>22–31</sup> However, when some of the patients were referred to an ophthalmologist, the diagnosis of conjunctivitis was confirmed in a lower percentage, suggesting that there may exist a slight overestimation of DAC by dermatologists.<sup>24</sup> But, the awareness of DAC being a commonly reported AE in AD



patients receiving dupilumab may have influenced apparent increments in reported incidences of DAC over time.

## Discussion

Most AD studies demonstrated that patients receiving dupilumab had higher incidence of DAC (8.6–22.1%) than placebo-treated patients (2.1–11.1%), except for the SOLO-CONTINUE study, with most cases being mild or moderate and resolving with topical eye therapies without need of suspending dupilumab treatment<sup>6,7,11–13</sup> In these trials, conjunctivitis was either patient reported or dermatologist assessed rather than ophthalmologist evaluated. However, in two real-world studies, the incidence of conjunctivitis in real life confirmed by ophthalmologists was higher, specifically 23–25%.<sup>22–33</sup> This difference in conjunctivitis incidence may be due to the fact that DAC was reported by investigators (typically dermatologists or allergists) without any additional workup and ophthalmological referral, which might have led to an underestimation of this AE. In contrast, patients with other atopic comorbidities, such as asthma, chronic rhinosinusitis with nasal polyposis, and EoE, had identical and low incidence rates of conjunctivitis in both treatment groups (0–1.5% for dupilumab *versus* 0–3.3% for placebo).<sup>14–17</sup>

Several factors may be responsible for the increased incidence of DAC, either AD related or dupilumab treatment related. Ocular disorders occur more frequently in AD patients. Additionally, patients with greater baseline AD severity, high levels of TARC and IgE, low serum levels of dupilumab, or a previous history of conjunctivitis had more susceptibility to new conjunctivitis.<sup>21,34</sup> Baseline AD severity and previous conjunctivitis history are presumably independent risk factors for DAC regardless of therapy (dupilumab or placebo), provided that the frequency rises with baseline gravity and previous history in both treatment groups.<sup>21</sup> The CAFÉ study had the highest level of AD severity at baseline, and the greatest rates of previous conjunctivitis history and new conjunctivitis events among all AD trials. An increased awareness of conjunctivitis events after reports of several studies may be the reason for these increments. Treister and colleagues<sup>34</sup> demonstrated that the mean time from treatment initiation to the occurrence of conjunctivitis was 15.8 weeks; however, four patients developed conjunctivitis after 20 weeks, implying that the 16-week end point may have missed cases that occurred posteriorly. However, DAC incidence in the SOLO-CONTINUE study was the lowest, despite patients who achieved a good response to dupilumab in both SOLO studies being re-randomized to maintain dupilumab treatment or placebo for another 36 weeks in this trial.

Increased levels of some biomarkers, namely TARC, IgE, and eosinophils, are associated with higher AD severity.<sup>6,8,31</sup> Therefore, it is not surprising that conjunctivitis was more frequent in patients with more severe AD at baseline and augmented biomarker levels. Also, in patients with both AD and ophthalmic complications, increased levels of IgE were observed.<sup>8,35</sup>

Dupilumab efficacy in AD (IGA 0/1; EASI-75) apparently was associated with lesser conjunctivitis rates than in the monotherapy group. In contrast, this pattern was incongruous in both CHRONOS and CAFÉ studies. As IGA 0/1 and EASI-75 were achieved by fewer patients with baseline severe AD and higher rates of comorbidities and AD biomarker levels are associated with higher disease severity, these risk factors may be interconnected.<sup>21</sup>

Serum concentrations of dupilumab seem to have an inverse relationship with conjunctivitis events, implying that local undertreatment may play a role.<sup>2,6</sup>

The exact pathogenesis of DAC as well as the connection between its diverse pathogenetic mechanisms is presently unknown. Compared with the overall population, prevalence of ocular comorbidities is higher among AD patients. Therefore, pre-existing ophthalmic conditions and a specific interaction between dupilumab and AD may be possibly accountable for this higher rate among dupilumab-treated patients with AD, especially as conjunctivitis events were not increased in other type 2 diseases studies with dupilumab, suggesting a particular mechanism connected to AD, and not an intrinsic effect of dupilumab.<sup>2,15,21</sup>

AD is associated with barrier dysfunction of ocular surface epithelia, including defects in keratinocyte terminal differentiation, keratinocyte lipid production, and tight junctions, leading to augmented transepidermal water loss.<sup>36–40</sup> Barrier impairment is equally detected in the altered mucosal tissues of other type 2 conditions; however, ocular disease is more frequent in AD.<sup>21</sup> The difference in conjunctivitis incidence rates between trials of AD and other type 2 disorders could be in part explained by the presence of distinct barrier anomalies of the conjunctival tissues in AD when compared with the other type 2 diseases.<sup>21</sup>

Various pathogenetic hypotheses have been suggested including: (i) blockage of IL-4 and IL-13 signaling pathways leading to higher activity of ligands, such as OX40L; (ii) increased *Demodex* mites; (iii) eosinophilia, which play a role in the occurrence of allergic eye conditions; (iv) reduced IL-13-related mucus production; (v) disruption of an immune-mediated response of conjunctival associated lymphoid tissue; and (vi) focal scarcity of conjunctival goblet cells.<sup>21,34,39–41</sup> It is possible that multiple mechanisms may play a role, interacting at the same time. Also, the occurrence of DAC in patients with AD and those with other type 2 disorders may be affected by distinct mechanisms. Further elucidation is necessary to better understand the underlying mechanism of the ocular and periocular adverse effects and describe the modifications occurring in the eye at molecular, cellular, and inflammatory levels during these incidents, as well as, throughout and after resolution.

Recently, two types of DAC were observed by ophthalmologists: a mild nonspecific conjunctivitis and keratitis with dry eyes and a more specific dupilumab-induced follicular conjunctivitis and limbitis; most cases were mild or moderate, and the

majority did not have any history of conjunctivitis.<sup>32,33</sup> In the absence of ophthalmologic or microbiologic evaluation of conjunctivitis in all AD trials, it was neither feasible to recognize cases that were concrete or pathognomonic for dupilumab nor to corroborate whether they were infectious, allergic, or idiopathic.<sup>21</sup> Investigators did not collect data on specific clinical characteristics of conjunctivitis, which makes it difficult to compare events between dupilumab and placebo. Additional investigation of the clinical features of DAC is necessary.

Currently, there is no standard treatment to prevent and manage DAC. Eye drops of corticosteroids, antibiotics, and antihistamines or mast cell stabilizers were the most frequent therapies in these trials.<sup>21</sup> Several successful therapeutic approaches used for treatment of DAC without discontinuation of dupilumab were reported and included TCS preparations (e.g. fluorometholone, dexamethasone, hydrocortisone), topical tacrolimus, cyclosporin eye drops, antibiotic plus TCS combination therapies, hyaluronic acid eye drops, and artificial tears.<sup>32,33,42,43</sup> There is a risk of developing glaucoma or cataracts with long-term treatment with topical TCS; therefore, drugs with low penetration into the anterior chamber of the eye, such as fluorometholone, should be preferred. Another therapeutic option is ophthalmic preparations of calcineurin inhibitors, which seem to be a sensible alternative treatment for long term. Additionally, severe conjunctivitis can be treated with eye drops containing cyclosporine, which appear to be an appropriate option.<sup>42</sup> Ocular irritation, a burning sensation, and local pain on application are possible side effects.<sup>44</sup> Both tacrolimus and cyclosporine eye drops constitute off-label use agents. An ophthalmologist should evaluate patients with eye

symptoms in order to properly diagnose DAC and exclude other forms of conjunctivitis, namely bacterial or viral. It would be of interest to add an ophthalmologist to the patient-management team and perform a systematic ophthalmological referral before dupilumab treatment. Maudinet and colleagues<sup>32</sup> reported a 15% decrease in DAC incidence after initiation of standard ophthalmological assessment before dupilumab. Of note, with the use of hydroxychloroquine in autoimmune dermatoses, dermatologists recommend annual eye examinations due to the risk of hydroxychloroquine retinopathy. Patients with AD receiving dupilumab have a comparable risk of ocular complications; thereby, a recommendation for routine eye examinations should be acknowledged.

## Conclusion

Following the approval of dupilumab in the USA and Europe, the proportion of patients treated with this drug will increase in the near future. Therefore, it is extremely important to assess the safety profile of dupilumab and manage its AEs. DAC incidence is higher in AD, and most cases are mild to moderate and have good response to topical treatment with a rapid clinical response, while patients maintain dupilumab. Given AD is a chronic disease, and dupilumab may be used in the long-term, therapeutic approaches for conjunctivitis should include agents with a good safety profile that can be administered long term. Further studies are necessary to characterize clinical phenotypes of DAC and understand its etiology so that strategies for prevention and collaborative care can be created.

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