Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience

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Dupilumab was recently approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD), for which current treatment options are limited [1]. Dupilumab binds to the IL-4Rα subunit and blocks the signaling of IL-4 and IL-13, thereby inhibiting the release of proinflammatory cytokines, chemokines, and IgE [2,3]. Although generally well-tolerated, high rates of unspecified conjunctivitis have been reported in patients on dupilumab [2-4].

This multicenter prospective observational study involved 15 secondary care centers as a task force for the Italian Society of Allergy, Asthma, and Clinical Immunology. The aim was to investigate the baseline factors associated with the incidence of dupilumab-induced conjunctivitis. Ninety-six patients with severe AD—defined as an Eczema Area and Severity Index (EASI) score ≥24—and with inadequate response to/intolerance of cyclosporin A (CsA), or medically classified as unsuitable for CsA treatment, were enrolled and treated with a 600-mg loading dose and subsequent biweekly 300-mg injections of dupilumab for 16 weeks. During treatment, the investigators diagnosed, reported, and determined the severity and type of conjunctivitis (conjunctivitis; conjunctivitis, bacterial; conjunctivitis, viral; conjunctivitis, allergic; and

atopic keratoconjunctivitis [Medical Dictionary for Regulatory Activities preferred terms]) at baseline and at weeks 4, 8, 12, and 16. All patients with moderate-to-severe conjunctivitis were referred to an ophthalmologist.

The study protocol was approved by the principal ethics committee, and informed consent was obtained from all patients. To assess the risk of baseline characteristics being associated with a conjunctivitis event, a Cox regression time-to-event analysis was performed. Baseline factors were evaluated individually and in a multivariable model, including age class (≤33 years vs >33 years) and sex. These factors were as follows: clinical scores (EASI, classified as above vs below the 75th percentile; Dermatology Life Quality Index [DLQI], classified as a small effect on quality of life [QoL] below 6, moderate effect on QoL up to 10, very large effect on QoL up to 20 and more than 20; Scoring Atopic Dermatitis [SCORAD], classified as above or below the 75th percentile; Patient-Oriented Eczema Measure [POEM], classified as mild when lower than 8, moderate up to 16, severe up to 24, and very severe more than 24; numerical rating scale [NRS] for sleep and NRS for pruritus, both classified as below and above the 75th percentile), IgE levels (classified as normal up to 100, from 100 to the 75th percentile, below the 75th percentile), eosinophil counts (classified as below or above 350), and family history of allergic conjunctivitis and history of conjunctivitis (both classified as present or not present). A stepwise selection procedure was used to improve the model fit and select variables associated with moderate-to-severe conjunctivitis events; a P value ≤.05 entry model was applied. The final model was adjusted for age class, sex, IgE (≤3637 vs >3637), and history of conjunctivitis. The goodness of fit was evaluated using R2 and the C-index according to Pencina and D'Agostino [5].

Among the 96 patients invited to participate, 24 were diagnosed with conjunctivitis at baseline and were removed from the analysis. Among the remaining 72 patients, 29 (40.3%) were diagnosed with dupilumab-associated conjunctivitis during follow-up. This was mild in 18 patients (62%), moderate in 8 (27.6%), and severe in 3 (10.3%). Mean time to the first dupilumab-associated conjunctival event was 12 weeks (standard error, 0.58).

Cases were managed with topical therapy, as previously described [6]. In 19 cases (65.5%), conjunctivitis had resolved or was resolving by the end of week 16. Nine cases (31%) had not resolved, and 1 case (3.4%) had resolved with sequelae. Dupilumab was discontinued in 1 patient owing to bilateral conjunctivitis and cicatricial ectropion (Table).

The factors that were significantly associated with dupilumab-induced conjunctivitis in the univariable analysis (Supplementary Table) included family history of allergic conjunctivitis (HR, 2.77; 95%CI, 1.05-7.29), history of conjunctivitis (HR, 21.31; 95%CI, 5.03-90.26), presence of other atopic conditions (HR, 2.51; 95%CI, 1.21-5.24), SCORAD score (>76.6 vs <76.6; HR, 2.29; 95%CI, 1.04-5.05), baseline IgE levels (>3637 vs ≤100; HR, 3.15; 95%CI, 1.2-8.26), and baseline blood eosinophil counts (>350 vs ≤350; HR, 3.99; 95%CI, 1.71-9.29). In the stepwise selection procedure for the multivariable regression, all predictors were removed except history of conjunctivitis; HR and 95%CI remained unchanged, R^2 was 0.39, and the C-index was 0.53.

Dupilumab-associated conjunctivitis was recently reported in up to 50% of AD patients undergoing treatment [5]. The predictors of its incidence are not well known. Over a 16-week observational period, the current study reports a prospectively registered incidence of conjunctivitis in 40.3% of patients without conjunctivitis at baseline. Cases were mostly mild-or-moderate (90%) and had resolved/were resolving in the case of patients continuing treatment. The risk factors for dupilimuab-associated conjunctivitis in previous studies are severe AD [2,3,6], prior history of conjunctivitis [3,7], atopic AD phenotype [4,7], and high baseline IgE levels and eosinophil counts [3] .

The current study reinforces the role of these risk factors in the development of dupilumab-associated conjunctivitis and highlights their value for clinical practice. After accounting for any simultaneous effects of risk factors, the main predictor for the development of dupilumab-associated conjunctivitis was a history of conjunctivitis.

The cause of dupilumab-associated conjunctivitis is still unclear [4,8]. Patients with AD have a greater prevalence of ocular comorbidities than the general population [9], and administration of dupilumab for asthma or nasal polyposis

Table. Summary of Conjunctivitis Events at Initiation of Treatment and During the Treatment Period in 96 Patients

	Conjunctivitis at Initiation of Dupilumab (n=24)	Incidence of Conjunctivitis During Treatment With Dupilumab[a] (n=29)	Prevalence of Conjunctivitis During Treatment With Dupilumab (n=53)
Conjunctivitis event, No. (%)	24 (25.0%)	29 (40.3%)	53 (55.2%)
Conjunctivitis[b]	3 (3.2%)	22 (30.6%)	25 (26.0%)
Allergic conjunctivitis	17 (17.7%)	2 (2.8%)	19 (19.8%)
Atopic keratoconjunctivitis	4 (4.1%)	3 (4.2%)	7 (7.3%)
Bacterial conjunctivitis	0 (0%)	1 (1.4%)	1 (1.0%)
Viral conjunctivitis	0 (0%)	1 (1.4%)	1 (1.0 %)

[a]The incidence was calculated among the 72 patients who were not diagnosed with conjunctivitis at baseline.
[b]Conjunctivitis in which the etiology remained unspecified.

has not been associated with higher rates of conjunctivitis [4]. Some authors hypothesize that both dupilumab- and AD-related mechanisms may be involved and that ocular or immune differences between patients with AD and other type 2 diseases might be considered [3]. Others have suggested that an increased eosinophil count after drug administration, which plays a part in the development of allergic eye disorders, could increase the risk of dupilumab-induced conjunctivitis [4,9]. Recent papers hypothesize that the IL-13 and/or IL-4 blocking effect might lead to reduction of goblet cells and mucin production in a subpopulation of AD patients that may potentially result in irritative conjunctivitis [10,11]. This fact was confirmed when dupilumab was withdrawn [12]. The use of artificial tears during treatment with dupilumab might reduce the incidence of conjunctivitis/keratitis [6,13].

While limited by its relatively small sample size, short follow-up, and a lack of a control group, our study shows that patients with moderate-to-severe AD and a history of conjunctivitis seem to be at greater risk of developing dupilumab-associated conjunctivitis. Identifying associated risk factors at baseline may help to predict the onset of conjunctivitis during treatment with dupilumab. We recommend artificial tears in patients with AD treated with dupilumab to reduce the incidence of conjunctivitis and keratitis.

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