

Dupilumab-associated conjunctivitis in patients with atopic dermatitis: a multicenter real-life experience

Nettis E¹, Bonzano L², Patella V³, Detoraki C⁴, Trerotoli P⁵, Lombardo C⁶, on behalf of the Italian DADReL study group

¹Allergist and Dermatologist Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari - Aldo Moro, Bari, Italy

²Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

³Division of Allergy and Clinical Immunology, Department of Medicine ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy

⁴Department of Internal Medicine and Clinical Pathology, Azienda Ospedaliera Universitaria Federico II, Naples, Italy

⁵Department of Biomedical Science and Human Oncology, University of Bari - Aldo Moro, Bari, Italy

⁶Division of Dermatology "U.O. Multizonale APSS", Santa Chiara Hospital, Trento, Italy

Italian DADReL (Dupilumab Atopic Dermatitis in Real Life) Study Group: G. Alessandrini (Lecce), E. Bonifazi (Bari), R. Brancaccio (Napoli), G. Calogiuri (Lecce), C. Caruso (Roma), C. Castellano (Bari), M. Congedo (Lecce), A. Damiani (Bari), G. De Feo (Salerno), T. De Pasquale, A. De Paulis (Napoli), M. Di Gioacchino (Chieti), E. Di Leo (Acquaviva delle Fonti), G. D'Ippolito (Brindisi), F. Gaeta (Roma), A. Gatta (Chieti), M.B. Guanti (Modena), S. Guerriero (Bari), M.S. Leto Barone (Palermo), L. Macchia (Bari), A. Paladini (Brindisi), A. Pannofino (Policoro), P. Parronchi (Firenze), G. Pellacani (Modena), S. Pucci (Civitanova Marche), D. Rossi (Bari), O. Rossi (Firenze), L. Salvati (Firenze), G. G. Spadaro (Napoli), M.R. Tagliavanti (Bari), M. Triggiani (Salerno), G.A. Vena (Bari).

Corresponding author:

Laura Bonzano, MD

Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

Largo del Pozzo, 71, 41125 Modena – Italy

E-mail: laurabonzano83@gmail.com

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Dupilumab has recently been approved for the treatment of adult patients with moderate-to-severe Atopic Dermatitis (AD) in which current treatment options are limited [1]. Dupilumab binds to the IL-4R α subunit and blocks the signaling of IL-4 and IL-13, thereby inhibiting the release of pro-inflammatory 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 baseline factors associated with the incidence of dupilumab-associated conjunctivitis. Ninety six patients with severe AD, defined as Eczema Area and Severity Index (EASI) \geq 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, investigators diagnosed, reported and determined the severity and type of any events of conjunctivitis (including conjunctivitis; conjunctivitis, bacterial; conjunctivitis, viral; conjunctivitis, allergic; and atopic keratoconjunctivitis [Medical Dictionary for Regulatory Activities preferred terms]) at baseline and follow up conducted 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 associated with a conjunctivitis event, a Cox regression time-to-event analysis was performed. Each baseline factor, including clinical scores (EASI classified as above *vs* below 75th percentile; Dermatology Life Quality Index [DLQI] classified as 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 lower than 8, moderate up to 16, severe up to 24 and very severe more than 24; numerical rating scale [NRS] for sleep, 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, above the 75th percentile), Eosinophil counts (classified as below or above 350), family history of allergic conjunctivitis and history of conjunctivitis (both classified as present or not present), was evaluated individually and in a multivariable model, including ageclass (≤ 33 y *vs* > 33 y) and sex (M *vs* F). A stepwise selection procedure was used to improve the model fit and select variables associated with moderate-to-severe conjunctivitis events; a p -value ≤ 0.05 entry model was applied. The final model was fitted with ageclass, sex, IgE (≤ 3637 *vs* > 3637) and history of conjunctivitis. The model fit was evaluated by R-square and the C-index by Pencina and D'Agostino [5].

Among the 96 patients approached for study enrolment, 24 subjects were diagnosed with conjunctivitis at baseline, and were removed from the reported analysis. Among the remaining 72 patients, 29 (40.3%) subjects were diagnosed with dupilumab-associated conjunctivitis during follow-up. Reported dupilumab-associated conjunctivitis 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 was recovered/resolved or recovering/resolving by the end of week 16. Nine cases (31%) were not recovered/resolved and one case (3.4%) was recovered/resolved with sequelae. Dupilumab treatment was discontinued for 1 patient due to bilateral conjunctivitis and cicatricial ectropion (Table).

Factors significantly associated with dupilumab-associated conjunctivitis at univariable analysis (detailed in the Supplementary Table) included family history of allergic conjunctivitis (HR: 2.77, 95% CI 1.05 to 7.29), history of conjunctivitis (HR: 21.31, 95% CI 5.03 to 90.26), presence of other atopic conditions (HR: 2.51, 95% CI 1.21 to 5.24), SCORAD score (>76.6 compared to <=76.6; HR: 2.29, 95% CI 1.04 to 5.05), baseline IgE levels (>3637 compared to <=100; HR: 3.15, 95% CI 1.2 to 8.26) and baseline blood eosinophil counts (>350 compared to <=350; HR: 3.99, 95% CI 1.71 to 9.29). The stepwise selection procedure to evaluate multivariable regression remove all predictors except history of conjunctivitis, obviously HR and 95% CI were the same, R-square was 0.39 and C-index resulted 0.53.

Recently, dupilumab-associated conjunctivitis has been reported in up to 50% of AD patients undergoing treatment [5] and 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 were resolved/resolving with patients continuing dupilumab treatment.–In previous studies, severe AD [2,3,6], prior history of conjunctivitis [3,7], atopic AD phenotype [4,7], high baseline IgE levels and eosinophil counts [3], have been suggested as risk factors for dupilumab-associated conjunctivitis.

The current study reinforces these risk factors for the development of dupilumab-associated conjunctivitis, which has a significant value for the clinical settings. 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 dupilumab administration for asthma or nasal polyposis 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]. There are 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 which may potentially result in an irritative conjunctivitis [10,11]. This fact has been confirmed when Dupilumab was withdrawn [12]. The use of artificial tears during dupilumab treatment might reduce the incidence of conjunctivitis/keratitis [6,13].

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

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Conflicts of Interest

The authors declare that they have no conflicts of interests.

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Table. Summary of conjunctivitis events at the onset and during the treatment period in 96 patients

	Conjunctivitis at onset of dupilumab treatment (n=24)	Incidence of conjunctivitis during dupilumab treatment** (n=29)	Prevalence of conjunctivitis during dupilumab treatment (n=53)
Number of conjunctivitis events	24 (25.0%)	29 (40.3%)	53 (55.2%)
Conjunctivitis*	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%)

Data are n (%).

*Conjunctivitis in which the aetiology remained unspecified.

**The incidence was calculated among the 72 patients who were not diagnosed with conjunctivitis at baseline.